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ANKARA BİLKENT ŞEHİR HASTANESİ ÇOCUK HASTANESİ

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Turkish Journal of Pediatic Disease
Türkiye Çocuk Hastalıkları Dergisi

ANKARA BİLKENT ŞEHİR HASTANESİ
ÇOCUK HASTANESİ

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

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Türkiye Çocuk Hastalıkları Dergisi TÜBİTAK/ULAKBİM Türk Tıp Dizini, EBSCOhost Research Databases, ve Türkiye Atıf Dizini tarafından indekslenmektedir.

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22 PAP

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

AIMS and SCOPE / AMAÇ ve KAPSAM

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

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

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

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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 pediatrik 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.

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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.

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

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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 articles in each issue, taking into account the acceptance dates. If the articles sent to the reviewers for evaluation are assessed as a 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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2. Drafting the work or revising it critically for important intellectual content; AND

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

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

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

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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.

Authors are required to submit the following:

Copyright Transfer and Acknowledgement of Authorship Form and

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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 Türkiye, 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 Türkiye, 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: It should be at least 20 and at most 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 Türkiye, 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.

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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 Türkiye, 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 parentheses 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.

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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.

If the reference is a journal supplement;

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

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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. Accessed 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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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 Dergisinde yayınlanmak üzere kabul edilmiş makaleler kabul tarihleri dikkate alınarak her sayıda en az 10 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 makale başvurularında DergiPark ile intihal.net ile arasında yapılan işbirliği uyarınca intihal açısından benzerlik raporu istenecektir. Makale gönderim adımlarında yazarlar bilgilendirlecek ve dosya yükleme adımında sistem tarafından rapor hazırlanarak sonuç e-posta ile yazara bildirlecektir. Rapor açıklandığında yazar gönderim işlemini tamamlayabilecektir. Türkiye Çocuk Hastalıkları Dergisi'ne makale gönderebilmek için benzerlik oranı en fazla %20 olmalıdır.

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.

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

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.

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 az 20, en çok 40 olmalıdır.

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.

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

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

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

Kaynak dergi eki ise;

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

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

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

Kaynak kitap ise;

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

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

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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.

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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. Accessed 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.

CONTENTS / İÇİNDEKİLER

Original Articles / *Özgün Araştırmalar*

Case Reports / Olgu Sunumları

Review / Derleme

Evaluation of the Frequency of Asthma Attack and Disease Severity in Children in the COVID-19 Pandemic

COVİD-19 Pandemisinde Çocuklarda Astım Atağı Sıklığı ve Hastalık Şiddetinin Değerlendirilmesi

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ABSTRACT

Objective: As with any lower respiratory tract infection, it is thought that coronavirus disease 2019 (COVID-19) infection may trigger asthma attacks, and the infection may be more severe in patients with asthma. The objective of this study was to establish the incidence of COVID-19 in children with asthma and to assess the disease severity in this patient group.

Material and Methods: We retrospectively analyzed patients who were admitted to the pediatric emergency clinic at our hospital between March and December 2020 with asthma attacks. The patients underwent a real-time polymerase chain reaction (RT-PCR) test to diagnose COVID-19.

Results: The study involved 155 patients, with 85 (54.8%) being male and the median age (IQR) was 122.0 (66.0-163.0) months. The most common symptoms presented by these patients were cough (70.3%), fever (39.4%), and dyspnea (29.7%). Within the patients who required hospitalisation, 18 (81.8%) were diagnosed with moderate attack and 4 (18.2%) with severe attack (p< 0.001). Of the patients who were hospitalised, 10 (45.5%) were partially controlled and 8 (36.4%) were uncontrolled with respect to their medical condition (p<0.001). In the study, COVID-19 was detected in 22 (14.2%) out of 155 patients. According to the diagnosis of COVID-19, there was no difference in the severity of attacks or the requirement for ward hospitalization (p=0.633, p=0.288, respectively).

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Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. Permission was obtained from Ankara City Hospital Clinical Research Ethics Committee (meeting date: 14.10.2020, decision no: E1/1183/2020) for the study.

Contribution of the Authors / Yazarların katkısı*: *KURT F: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***AKÇA H:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, 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 logical interpretation and conclusion of the results. ***ÇAĞLAR AA***: 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, Reviewing the article before submission scientifically besides spelling and grammar. ***METBULUT AP:*** 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. ***BÜYÜK YAYTOKGİL Ş:*** 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. ***BAYHAN Gİ:*** Taking responsibility in necessary literature review for the study. Taking responsibility in the writing of the whole or important parts of the study. ***DİBEK MISIRLIOĞLU E:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in necessary literature review for the study.

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Conclusion: COVID-19 infection does not increase the severity of asthma attacks or the need for hospitalization in children. This information is particularly important in the context of pediatric emergency care for asthma patients during the COVID-19 pandemic.

Key Words: Asthma, COVID-19, Pediatric emergency

ÖZ

Amaç: Her türlü alt solunum yolu enfeksiyonunda olduğu gibi, koronavirus hastalığı 2019 (COVİD-19) enfeksiyonunun da, astım ataklarını tetiklenebileceği ve astımı olan hastalarda enfeksiyonun daha ağır geçebileceği düşünülmektedir. Bu çalışmada COVİD-19 hastalığının astımlı çocuklardaki sıklığının saptanması ve bu hastalardaki hastalık şiddetinin belirlenmesi amaçlanmıştır.

Gereç ve Yöntemler: Hastanemiz çocuk acil kliniğine Mart- Aralık 2020 tarihleri arasında astım atağı ile başvurmuş ve COVİD-19 tanısı için gerçek zamanlı polimeraz zincir reaksiyonu (RT-PCR) testi bakılmış hastalar geriye dönük olarak incelendi.

Bulgular: Çalışmaya alınan 155 hastanın 85'i (%54.8) erkek cinsiyette ve ortanca yaş (IQR), 122.0 (66.0- 163.0)'dı. En sık başvuru şikayetlerinin öksürük (%70.3), ateş (%39.4) ve nefes darlığı (%29.7) olduğu belirlendi. Hastaneye yatışı yapılan hastaların 18'i (%81.8) orta atak, 4'ü (%18.2) ağır atak olarak değerlendirildi (p< 0.001). Yatış yapılan hastaların 10'u (% 45.5) kısmi kontrollü, 8'i (%36.4) kontrolsüzdü (p< 0.001). Çalışmaya alınan 155 hastanın 22'sinde (%14.2) COVİD-19 saptandı. Hastaların COVİD-19 tanısına göre atak şiddetinde ve servis yatış ihtiyacında farklılık saptanmadı (sırasıyla p=0.633, p=0.288).

Sonuç: COVİD-19 enfeksiyonunun çocuklarda astım atak şiddetini ve hastaneye yatış ihtiyacını arttırmadığı saptanmıştır. COVİD-19 pandemisi sırasında astım hastaları için çocuk acil servis değerlendirmesinde bu durum önemlidir.

Anahtar Sözcükler: Astım, COVİD-19, Çocuk acil

INTRODUCTION

Asthma is a prevalent chronic inflammatory lung illness of childhood that features airway obstruction and hypersensitivity responses. Its development is influenced by hereditary and environmental factors. In the United States of America (USA), asthma diagnosis follows over 6 million children, accounting for an 8.4% prevalence, and more than 700.000 children attend the emergency unit every year for asthma-related problems (1,2). Approximately 2%–5% of hospitalizations are attributed to asthma (1).

Asthma is characterized by recurrent episodes of wheezing, coughing, shortness of breath, and chest pain. Patients' complaints usually occur with triggering factors such as cigar smoke, air pollution, cold air, exercise, and infection. This worsening of the disease state is called asthma attacks (3). Because there is impairment in the production of antiviral IFNs (IFN-a/b/l) in airway epithelial cells and leukocytes in asthma patients, viruses with weak virulence, such as rhinovirus and respiratory syncytial virus, which are generally upper respiratory tract infection agents in healthy individuals, cause attacks in asthma patients (4).

COVID-19 is an infection caused by the coronavirus identified as SARS-CoV-2, which causes severe acute respiratory syndrome (4,5). Since the declaration of COVID-19 as a global pandemic in March 2020, it continues to affect both adults and children worldwide. Chronic diseases can increase the risk of severe COVID-19 infection. However, data on whether childhood asthma poses a risk for COVID-19 is not clear, however it is thought that asthma patients with impaired antiviral responses may be at high risk for COVID-19 morbidity and mortality. In this study, we aimed to evaluate SARS-CoV-2 positivity and its effect on attack severity in children admitted to the pediatric emergency department because of an acute asthma attack during the pandemic period.

MATERIALS and METHODS

This study was conducted retrospectively between March 31 and December 31, 2020, in the pediatric emergency department of Ankara City Hospital, Children's Hospital. Cases who presented to the emergency department with asthma attack and who had COVID-19 real-time reverse transcriptase-polymerase chain reaction (RT-PCR) were included in the study.

On 23 March 2020, the World Health Organization published a guideline recommending the use of RT-PCR test in the detection of cases infected with COVID-19 (5). In a short time after SARS-CoV-2 transmission, viral RNA is detected in the upper respiratory tract by RT-PCR method and viral load is high in upper respiratory tract samples within the first week after the onset of symptoms (6). Swab samples taken from the nasopharyngeal and then oropharyngeal regions of patients who came to the emergency department with asthma attacks were placed in transport medium, labelled, request forms and clinical information of the patient were filled and sent to the laboratory by following the cold chain rules and the samples were studied by a special method called RT-PCR free of charge. In the study, only PCR results for COVID-19 were analysed, it is not known whether patients were tested for respiratory viral screening.

Chest radiographs of the patients were taken anteroposteriorly (AP); radiographs with atelectasis and/or hyperinflation, peribronchial thickening and consolidation were interpreted as abnormal (7).

The severity of asthma attacks and asthma control status of the patients were determined according to the Global Initiative for

Asthma (GINA) guideline (3). In the GINA guideline, for asthma control evaluation, the patient was questioned whether the patient had asthma symptoms for more than a few minutes, more than once a week, activity limitation due to asthma, the need for reliever medication more than once a week, and night cough/waking due to asthma in the last 4 weeks. It was considered well-controlled if the patient did not have these symptoms, partially controlled if 1-2 of these symptoms were present, and uncontrolled if 3-4 of these symptoms were present. In the early stages of the COVID-19 pandemic, especially in children with underlying diseases, the isolation of patients with COVID-19 was higher than normal because we did not know how the course would follow in patients with underlying diseases.

Permission was obtained from Ankara City Hospital Clinical Research Ethics Committee (meeting date: 14.10.2020, decision no: E1/1183/2020) for the study.

Statistical Analysis

IBM SPSS Statistics 22.0 (SPSS Inc., Chicago, IL, USA) program was used for statistical evaluation. Frequency distributions were evaluated as numbers and percentages, continuous variables (measurements) were evaluated as median (IQR). The Kolmogrov-Simirnov test was used to determine whether the data were normally distributed. In statistical evaluation, T-test was used for data showing normal distribution and Mann-Whitney U test was used for data not showing normal distribution in the comparison of paired groups. Categorical variables were compared using Chi-square test. The level of significance set was $p<0.050$

RESULTS

During the study period, the number of admissions to the pediatric emergency department was 55.664 and 6070 (10.9%) of the patients were hospitalized and followed up. In this period, the number of patients admitted to the emergency department with asthma attack was 155 (3%) and the hospitalization rate was 23.9%. The number of children diagnosed with COVID-19 in our hospital was 7214. 22 (0.3%) of these patients presented to the emergency department with asthma attacks and non of them has underlying diseases except asthma.

Of the 155 patients included in the study, 85 (54.8%) were male. The median age (IQR) was 122.0 (66.0- 163.0) months and 71 (45.8%) of the patients were younger than 120 months. The most common presenting complaints were cough (70.3%), fever (39.4%) and dyspnoea (29.7%). The most common findings on physical examination were rhonchus (41.3%) and rales (9.0%). 125 (80.6%) had mild, 26 (16.8%) moderate and 4 (2.6%) severe attacks. Thirty-seven (23.9%) of the patients were hospitalized and followed up; 15 (40.5%) of these patients were discharged from the emergency department (median (IQR) emergency department observation time, 3 (2.0- 5.0) hours) and 22 (59.5%) were hospitalized in the pediatric ward (Table I).

Table I: Demographical and clinical characteristics of patients

	n (%)
Age (mo)*	122.0 (66.0- 163.0)
Sex	
Male	85 (54.8)
Female	70 (45.2)
Type of admission to the hospital	
EMS	6 (3.9)
With their own means	149 (96.1)
Time of Emergency department (ED)	
8:00 AM to 4:00 PM	68 (43.9)
4:01PM to 11:59 PM	68 (43.9)
12 midnight to 07:59 AM	19 (12.3)
Complaints	
Cough	109 (70.3)
Fever	61 (39.4)
Dyspnea	46 (29.7)
Nasal discharge	25 (16.1)
Sorethroat	22 (14.2)
Vomiting	16 (10.3)
Diarrhea	12 (7.7)
Headache	11 (7.1)
Wheezing	9 (5.8)
Chest pain	5 (3.2)
Abdominal pain	6 (3.9)
Rash	1 (0.6)
Other	27 (17.4)
Complaint period (hour)*	2 (1-4)
Physical examination findings	
Rhonchus	64 (41.3)
Ral	14 (9.0)
Wheeze	4 (2.6)
Tachypnea	4 (2.6)
Asthma attack severity	
Mild	125 (80.6)
Moderate	26 (16.8)
Severe	4 (2.6)
Hospitalization Rates	
Discharged	118 (76.1)
Hospitalization	37 (23.9)
Emergency Department	37 (100.0)
Pediatric ward	22 (59.5)
Pediatric intensive care unit	2 (5.4)

**median (IQR)*

The distribution of patients according to months was analyzed. The highest rate of presentation with asthma attacks was found in October (20.0%), September (18.1%) and April (16.1%). The rate of COVID-19 positivity in patients presenting with asthma attacks was higher in September (33.3%) and October (27.3%) (Figure 1).

There was no difference between patients with and without COVID-19 infection in terms of lymphocyte count, D-dimer, AST, ALT, BUN, and creatinine values (p= 0.435, p= 0.422, 0.938, 0.550, 0.517, 0.126, respectively). Among patients who

Table II: Labaratory results of the patients

	Total (Mean±SD)	Positive RT-PCR (n=22)	Negative RT-PCR (n=133)	p
WBC (x10^9/L)	9.3±4.0	7.8±4.5	9.5±3.9	0.172
Hemoglobin at presentation (gr/dL)	14.7±1.2	13.8±1.0	14.8±12.9	0.767
Platetelets (x10^9/L)	315.2±86.2	282.2±643.5	321.2±886.6	0.122
ANC x10^9/L	5.4±3.3	4.3±2.8	5.5±3.3	0.206
ALC x10^9/L	9.2±1.7	2.2±2.9	2.7±1.5	0.435
Percentage of eosinophils (mm^3/L)	0.7±1.3	0.7±1.6	0.7±1.2	0.944
ALT (U/L)	25.8±36.0	20.5±18.2	26.6±38.6	0.550
AST (U/L)	26.9±14.2	26.6±12.6	26.9±14.6	0.938
BUN (mg/dL)	24.2±6.2	25.3±6.6	23.9±6.1	0.517
Creatinine (mg/dL)	0.5±0.2	0.6±0.1	0.5±0.1	0.126
CRP (mg/dL)	18.7±48.2	3.6±3.3	21.6±52.1	0.006*
PT	12.2±0.8	12.2±0.5	12.2±0.9	0.914
aPTT (sec)	25.9±3.8	26.5±2.9	25.7±4.1	0.569
INR	1.0±0.08	1.0±0.06	1.0±0.09	0.504
D-dimer	0.8±1.9	1.5±3.8	0.6±0.6	0.422

RT-PCR: *Real-Time Reverse Transcriptase-Polymerase Chain Reaction,* ***WBC:*** *white blood cell,* ***ANC:*** *Absolute Neutrophil Count, ALC: Absolute Lymphocyte Count,* ***ALT:*** *Alanine aminotransferase,* ***AST:*** *aspartat aminotransferase,* ***BUN:*** *blood urea nitrogen,* ***CRP:*** *C-reactive protein,* ***PT:*** *Prothrombin time,* ***aPTT:*** *Partial thromboplastin time,* ***INR:*** *International Normalized Ratio*

Table III: Asthma conditions and hospitalization characteristics.

	Hospitalized patients n (%)	Patients not hospitalized n (%)	p
Asthma attack severity*			< 0.001
Mild	9 (24.3)	116 (98.3)	
Moderate	24 (64.9)	2 (1.7)	
Severe	4 (10.8)	0 (0.0)	
Asthma symptom control*			0.002
Well controled	13 (35.2)	79 (67.0)	
Partly controled	12 (32.4)	24 (20.3)	
Uncontroled	12 (32.4)	15 (12.7)	

column percentage is given

presented to the emergency department with asthma attack, C-reactive protein value was found to be significantly higher in those without COVID-19 infection (p= 0.006) (Table II).

The relationship between asthma control status and hospitalization was evaluated. Of the 37 patients hospitalised, 24 (64.9%) were classified as moderate attack and 4 (10.8%) as severe attack (p< 0.001); 12 (32.4%) of the hospitalized patients were partially controlled and 12 (32.4%) were uncontrolled (p= 0.02) (Table III).

COVID-19 was detected in 22 (14.2%) of 155 patients included in the study, 19 (86.4%) of these patients were evaluated as mild, 3 (13.4%) as moderate attacks, and 3 (16.6%) of the patients were hospitalized in the ward. There was no difference in the severity of attacks and the need for ward hospitalisation according to the COVID-19 diagnosis (p=0.633, p=0.288, respectively) (Table IV). It was determined that the asthma control status of 3 patients who were hospitalized in the ward was partially controlled.

When the imaging modalities performed in patients with and without COVID-19 were evaluated, no difference was found in terms of abnormal X-ray and CT examination (p= 0.630, p=0.243, respectively) (Table IV).

Chest radiographs were performed in 131 (84.5%) patients, and 62 (47.3%) patients had abnormal radiographs. Computed tomography (CT) of the lung was performed in only 5 (3.2%) patients (Table IV).

RT-PCR was positive in only 1 of the patients who underwent chest CT; a 9.5-year-old patient was found to have lobar consolidation on chest radiography and ground-glass opacity in the lower lobe of the right lung on CT examination. This patient was considered to have an intermediate attack and was hospitalized in the ward for 4 days.

Table IV: Clinical Features and Characteristics of Patients Based on Real-Time RT-PCR Results

	Total n (%)	COVID-19 Real-Time RT-PCR Positive n (%)	COVID-19 Real-Time RT-PCR Negative n (%)	p
Asthma attack severity*				0.633
Mild	125(80.6)	19 (86.4)	106 (79.7)	
Moderate	26 (16.8)	3 (13.6)	23 (17.3)	
Severe	4 (2.6)	0 (0.0)	4 (3.0)	
Hospitalisation*				0.288
Yes	37 (23.9)	3 (13.6)	34 (25.6)	
No	118 (76.1)	19 (86.4)	99 (74.4)	
Chest x-ray				0.630
Normal	69 (52.7)	9 (47.4)	60 (53.6)	
Abnormal	62 (47.3)	10 (52.6)	52 (46.4)	
Chest computed tomography				0.243
Normal	0 (0.0)	0	0	
Abnormal	5 (100.0)	1 (20.0)	4 (80.0)	

** column percentage is given*

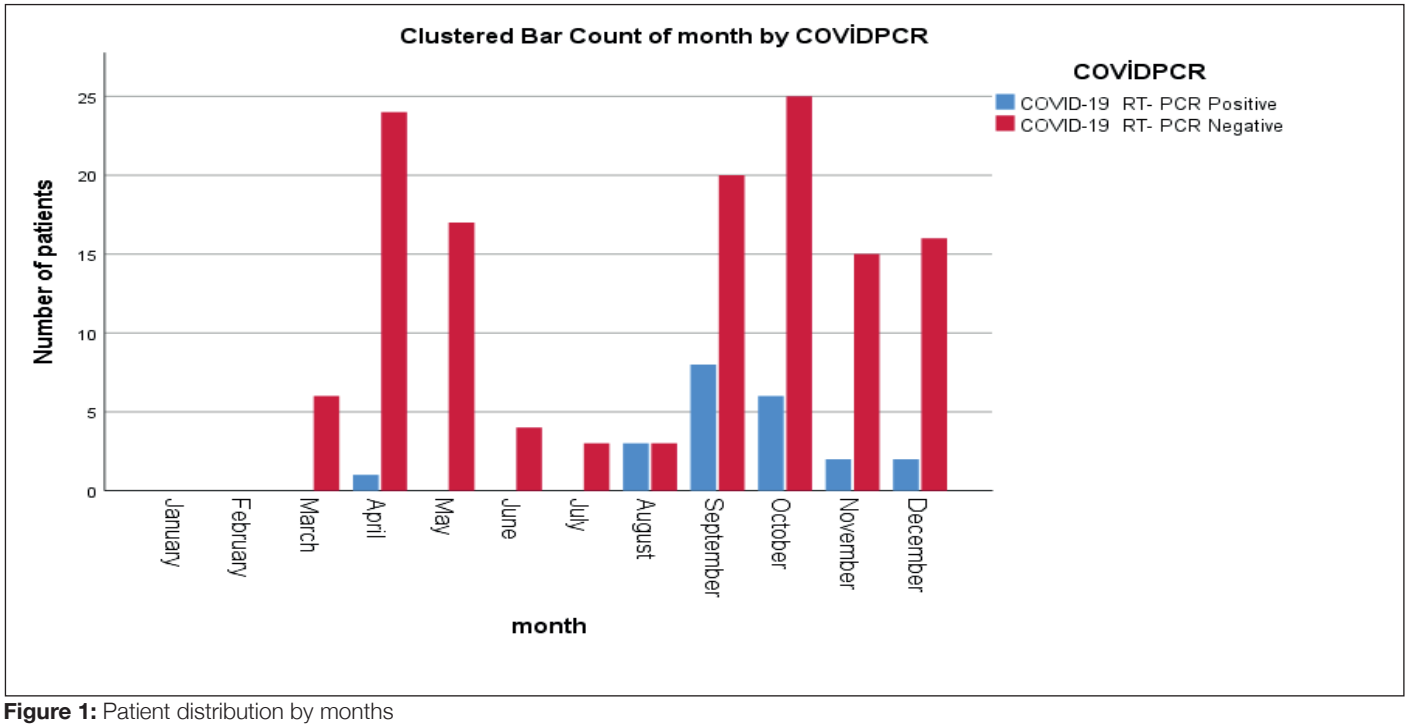

Figure 1: Patient distribution by months

DISCUSSION

Acute asthma attacks are the most important factor determining morbidity/mortality in asthma, which is the most common chronic disease of childhood, and viral infections play a role in most of the attacks. In this study, the rate of patients presenting to the emergency department with asthma attacks was 3% and the hospitalization rate was 23.9%. Of the 155 patients included in the study, COVID-19 was detected in 22 (14.2%), 19 (86.4%) of these patients were evaluated as mild, 3 (13.4%) as moderate attacks, and 3 (16.6%) of the patients were hospitalized in the service. There was no difference in the severity of asthma attacks and the need for ward hospitalization in patients infected with COVID-19.

Asthma attack is a common cause of admission to the pediatric emergency department. Studies have reported that the number of asthma attack admissions was lower than that in the pre-pandemic period (8-10). Similar to previous studies, we found an increase of 13 in emergency department admissions with asthma attacks in the post-pandemic period. The decrease in the hospital admissions with asthma attacks during the pandemic period may be due to quarantine measures for the transmission of respiratory viruses such as rhinovirus and RSV, decreased pollution in the atmosphere, and decreased exposure to outdoor allergens. The use of asthma medication under parental control may also increase medication compliance (10).

Studies have reported that the prevalence of asthma in children and adults diagnosed with COVID-19 was 0-14% and 0.3%–17.9%, respectively (11-13). In two studies conducted in our

country (14,15), the rate of chronic lung disease as a comorbid disease was 0.9% and 1.8% in children with COVID-19 infection, respectively. In our study, similar to these results, we found that the rate of presentation to the emergency department with asthma attack in children diagnosed with COVID-19 was 0.3%.

In the study by Wang L et al. (16), it was reported that especially male gender was a risk factor for hospitalization in adult patients with asthma who had COVID-19 infection. Swann et al. (17) reported that 53.5% of 1612 children with COVID-19 were male and 60.3% were younger than 10 years. Metbulut et al. (11) reported that the mean age of children with COVID-19 enf diagnosed with asthma was 10.5 years and 53.7% were male. Although male gender is not reported as a risk factor for the disease in children, we determined that 53.7% of the cases were male and the median age was 122 months.

COVID-19 symptoms are similar to asthma attack symptoms (2). Jin et al. (18) reported that the most common complaints were fever, cough, chest pain, shortness of breath, and chest pain in both groups in their study in which they evaluated adult patients with (21) and without (100) a diagnosis of asthma with COVID-19. Lu X et al. (19) reported that cough (48.5%) and fever (41.5%) were the most common symptoms in their study in which they evaluated 171 cases with COVID-19 between the ages of 1 day and 15 years. Metbulut et al. (11) reported that 54 (0.87%) of 6.205 children with COVID-19 were diagnosed with asthma; cough, shortness of breath complaints, and hospitalization rate were found to be higher in the asthma group. In our study, we found that cough, fever, and dyspnea were the most common presenting complaints in patients presenting to the emergency department with asthma attack.

Different studies have been conducted on which laboratory parameters should be used to evaluate disease severity in patients with COVID-19. In the study by Jin et al.(18) evaluating adult patients with and without a diagnosis of asthma with COVID-19, leukocytosis was found in the asthma group; no difference was found between the groups in PT, PTT, AST, ALT, urea, and hs-CRP (high sensitivity CRP) values.

Some studies have reported that leukocytosis and increased CRP levels are observed in COVID-19 infection (20, 21). In our study, we found no difference between patients with and without COVID-19 infection in terms of lymphocyte count, D-dimer, AST, ALT, BUN, creatinine, and C-reactive protein values. C-reactive protein level was significantly higher in patients without COVID-19 infection. It can be said that laboratory data vary according to different hospitals and patient groups and have no diagnostic value.

It has not been proven that asthma in children poses a risk of severe COVID-19 (1). Studies have reported that asthma is not a risk factor for morbidity/mortality in pediatric COVID-19 cases (22, 23). In our study, we found no difference in terms of attack severity and the need for ward hospitalization in asthma attack patients with COVID-19. According to these findings, asthma is thought not to affect the course of COVID-19 in children.

Studies have reported that lung radiograph findings were mostly normal in pediatric patients with COVID-19 (24- 27). Consistent with the literature, no difference was found in terms of abnormal chest radiograph examination in our patients with and without COVID-19 (p= 0.630).

There are different data regarding thoracic CT in COVID-19 cases in children. Ma et al. (26) reported that 85% of pediatric patients had abnormal thorax CT findings. In some studies, it was reported that thorax CT examination was normal in asymptomatic and mild clinical stage COVID-19 cases (25, 27). Das et al. (28) reported that although thorax CT can detect specific radiological findings as well as early lung abnormalities, such as ground-glass opacity, it is an appropriate imaging method to evaluate COVID-19-related complications only in symptomatic pediatric patients with COVID-19 pneumonia whose clinic worsens despite treatment. In our study, there was no difference in CT examination between our patients with and without COVID-19 (p=0.243). Because we did not have any patients with a severe clinical condition, the number of patients who underwent CT imaging of the thorax was very low; therefore, there may not have been a difference.

The main limitation of this study is that it is retrospective and single-centre. Since it was retrospective, diagnosis codes and medical records were found to be incomplete and some asthma attack patients could not be included in the study.

In conclusion, the most important factor determining morbidity/mortality in asthma is acute asthma attacks, and viral infections play a role in most of these attacks. It was observed that there was no difference in the severity of asthma attacks and the need for ward hospitalization in COVID-19 infection, and it is thought that asthma is not a risk factor for morbidity/mortality in COVID-19 cases.

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Türkiye Çocuk Hastalıkları Dergisi

Thyroid Functions and Thyroid Lesions in Children with Hodgkin Lymphoma and Central Nervous System Tumors Who Received Radiotherapy to the Head and Neck Region

Baş Boyun Bölgesine Radyoterapi Uygulanan Hodgkin Lenfoma ve Santral Sinir Sistemi Tümörlü Çocuklarda Tiroid Fonksiyonları ve Tiroid Lezyonları

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ABSTRACT

Objective: The aim of this study was to assess thyroid function and lesions after radiotherapy to the head and neck region in children with Hodgkin lymphoma (HL) or central nervous system (CNS) tumors.

Material and Methods: The study included children diagnosed with HL or CNS tumors who were in complete remission at least one year after completion of chemotherapy (CT) and who had all received radiotherapy (RT) to the head and/or neck. All patients were requested to undergo thyroid function tests and thyroid ultrasonography (USG).

Results: A total of 37 patients were included. The mean age was 13.7±3.8 years. The mean follow-up time was 5.09±2.5 years. All patients had CT and RT. Seven (18.9%) patients had subclinical hypothyroidism, and 7 (18.9%) had thyroid USG abnormalities. None of the patients had thyroid malignancy. Age under 10 years at diagnosis, follow-up time of 3 years or more, and an RT dose of 25 Gy or more were found as effective factors for subclinical hypothyroidism development. Only an RT dose of 25 Gy or more was found to be related to thyroid USG abnormalities.

Conclusion: Thyroid function tests and thyroid imaging should be routinely examined in any patient who has been treated for cancer to evaluate thyroid dysfunction regardless of clinical findings and the follow-up of these patients should be lifelong.

Key Words: Brain tumor, Hodgkin lymphoma, Radiotherapy, Thyroid disease

ÖZ

Amaç: Bu çalışmanın amacı Hodgkin lenfoma (HL) veya merkezi sinir sistemi (SSS) tümörlü çocuklarda baş ve boyun bölgesine uygulanan radyoterapi sonrası tiroid fonksiyonunu ve lezyonları değerlendirmektir.

Gereç ve Yöntemler: Çalışmaya HL veya SSS tümörü tanısı alan, kemoterapi (KT) ve baş boyun bölgesine radyoterapi (RT) tamamlanmasından en az bir yıl sonra tam remisyonda olan çocuklar dahil edildi. Tüm hastalardan tiroid fonksiyon testleri ve tiroid ultrasonografisi (USG) istendi.

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

Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. The study protocol was approved with the decision of the Education Planning Board of the Turkish Republic Health Ministry, Ankara Child Health Diseases, Haematology Oncology Training and Research Hospital dated 06.11.2014 and numbered 252. Informed consent was obtained from all the participants.

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

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Bulgular: Çalışmaya toplam 37 hasta dahil edildi. Yaş ortalaması 13.7±3.8'di. Ortalama takip süresi 5.09±2.5 yıldı. Tüm hastalarda BT ve RT mevcuttu. Yedi (%18.9) hastada subklinik hipotiroidi, 7 (%18.9) hastada tiroid USG anormalliği mevcuttu. Hastaların hiçbirinde tiroid malignitesi yoktu. Tanı anında 10 yaşın altında olmak, takip süresinin 3 yıl ve üzerinde olması, RT dozunun 25 Gy veya daha fazla olması subklinik hipotiroidizm gelişimi için etkili faktörler olarak bulundu. Sadece RT dozu 25 Gy veya daha fazlasının tiroid USG anormallikleri ile ilişkili olduğu saptandı.

Sonuç: Kanser tedavisi almış her hastada tiroid fonksiyon bozukluğunu değerlendirmek için klinik bulgulara bakılmaksızın tiroid fonksiyon testleri ve tiroid görüntülemesi rutin olarak incelenmeli ve bu hastaların takipleri ömür boyu yapılmalıdır.

Anahtar Sözcükler: Beyin tümörü, Hodgkin lenfoma, Radyoterapi, Tiroid bozukluğu

INTRODUCTION

With the improvement in the treatment of childhood malignancies, survival rates in childhood cancers have reached 70-80% in recent years. However, due to increased survival rates, there is a marked increase in early and long-term side effects of treatments. Long-term side effects after treatment in childhood malignancies comprise cardiotoxicity, endocrine disorders and neurocognitive impairments (1). Among these, approximately 40% of childhood cancer survivors experience endocrinological side effects (2). Thyroid tissue is one of the most radiosensitive part of human tissue and abnormalities of the thyroid gland following head and neck irradiation have been reported, therefore thyroid functions should be closely monitored in patients receiving RT to head and neck region (3-8).

In the present study, we aimed to assess thyroid functions and lesions after RT to head and neck region in children who were in full remission at least one year after completion of RT and chemotherapy (CT) treatment for Hodgkin Lenfoma (HL) or central nervous system (CNS) tumors.

MATERIAL and METHODS

The study included patients diagnosed with HL or CNS tumors and who have been treated at the Ankara Child Health Diseases, Haematology Oncology Training and Research Hospital and Research Hospital for a period of twelve years. All patients were in full remission at least one year after completion of cancer therapy and all had RT to the head and neck region. The patients with known thyroid disorders before treatment were excluded. Demographic and medical data were obtained from patient files. The study protocol was approved with the decision of the Education Planning Board of the Turkish Republic Health Ministry, Ankara Child Health Diseases, Haematology Oncology Training and Research Hospital dated 06.11.2014 and numbered 252. Informed consent was obtained from all the participants.

Thyroid function studies including thyroid-stimulating hormone (TSH), plasma free thyroxine (fT4), thyroid antibodies [anti-thyroglobulin (TG-Ab) and anti-thyroid peroxidase (TPO-Ab)] were measured in patients. These tests were interpreted according to our hospital's laboratory reference values adjusted for age. Plasma TSH, fT4, and thyroid antibodies levels were measured by electrochemiluminescence immunoassay in a Beckman Coulter dxi 800 device. Overt hypothyroidism was defined as a low fT4 level and an elevated TSH. Subclinical hypothyroidism was defined as a high TSH level with a normal fT4 value. Central hypothyroidism was diagnosed when accompanied by a low serum T4 with low or normal TSH levels. The presence of thyroid antibodies was accepted to indicate autoimmune thyroiditis. Abnormal values were checked at least twice.

Thyroid lesions were assessed with thyroid ultrasonography (USG). Thyroid gland USG was performed with (Toshiba SSA-270-A Powerpace). The terms of hyperechogenicity according to neighboring muscle groups, homogenous echo pattern, having only a few vascular structures, normal anterior-posterior and transverse diameters of the thyroid lobes, and normal thickness of the isthmus according to the age were used to define normal thyroid USG. The thyroid scans other than this definition were accepted as abnormal.

The patients were divided into two groups depending on the diagnosis as HL group and the CNS tumors group. The groups were compared according to sex, mean age, age at diagnosis, duration of follow-up, CT protocols, number of CT cures, RT dosage, RT area, thyroid functions, and thyroid lesions.

Statistical analysis

Statistical analyses were performed using IBM Statiscal Package for the Social Sciences, verison 20.0 (SPSS Inch., Armonk, NY, IBM Corp., USA). Continuous and intermittent numerical variables were defined as mean, standard deviation, minimum and maximum, categorical variables were defined as frequencies and percentages. Kolmogorov Smirnov test was used to detect whether the distribution of intermittent numerical variables was close to normal and homogeneity of the variances was investigated with the Levene test. To compare quantitative data Mann-Whitney U test was used. Qualitative data was compared with the Chi-square test. Statistical significance was considered when the p-value was less than 0.050.

RESULTS

A total of 37 children were included in the study. The total study population consisted of 18 male (48.6%) and 19 female (51.4%). The mean age in the study was 13.7±3.8 years. The mean age at diagnosis was 9±4.2 years. The diagnoses were

Table I: Clinical Characteristics of the HL patients

Sex*	
Male	15 (60)
Female	10 (40)
Stage of the disease*	
I	1 (4)
II	9 (36)
III	10 (40)
IV	5 (20)
Histologic subtype*	
Nodular sclerosis	11 (44)
Mixed cellularity	13 (52)
Lymphocyte rich	1 (4)
Involvement zone*	
Neck	4 (16)
Neck, supradiaphragmatic and infra-diaphragmatic	12 (48)
Neck and supradiaphragmatic	9 (36)
CT protocol*	
ABVD	15 (60)
ABVD-COPP	10 (40)
Current age (yrs)†	13.6±3.7 (7-19.7)
Age at diagnosis (yrs)†	8.6±4.1 (2.9-15.6)
Follow-up time (yrs)†	5.1±2.8 (1.5-11.1)
Number of CT cures†	5.4±2.8 (3-12)
Radiotherapy dosage (Gy) to neck†	23.9±4.9 (15-34)

**n(%), †mean±SD (min-max)*

HL in 25 (67.6%) patients and CNS tumors in 12 (32.4%) patients. The mean follow-up duration was 5.0 ± 2.5 years. All patients had normal thyroid physical examination. Clinical features of the HL and CNS tumor patients are shown in Tables I and II respectively.

Thyroid function abnormalities were detected in 7 (18.9%) patients. All of them had elevated TSH levels and normal fT4 levels. So, these 7 patients were considered as subclinical hypothyroidism. The detailed clinical information of the subclinical hypothyroidism patients is shown in Table III. None of the patients had overt hypothyroidism, central hypothyroidism, and autoimmune thyroid diseases. A comparison of clinic characteristics of subclinical hypothyroidism patients with cases with normal thyroid functions is shown in Table IV. There was no statistically significant difference between the patients with and without subclinical hypothyroidism in terms of gender (p=0.180), age (p=0.277), age at diagnosis (p=0.461), RT dose (p=0.121), number of CT cures (p=0.700), RT area (p=0.254), and CT protocol (p=0.472). The duration of follow-up of patients with subclinical hypothyroidism was longer than that of patients without subclinical hypothyroidism (p=0.003).

Thyroid USG abnormalities were detected in seven (18.9%) patients. four (57.1%) of them were male and three (42.9%) were female. Four (57.1%) of them were diagnosed with HL and three (42.9%) were diagnosed with CNS tumors. The detected USG abnormalities were thyroiditis in three cases, thyroid nodules in three cases, and hypoechoic pattern in one case. Fine needle aspiration biopsy (FNAB) was applied to two of the patients who had nodules, one cytology was a benign follicular nodule and the other one was a hyperplastic adenomatoid nodule. The comparison of clinical characteristics of patients who had thyroid USG abnormalities with cases with normal USG is shown in Table IV.

Table II: Clinical characteristics of the CNS tumor patients

Sex*	
Male	3 (25)
Female	9 (75)
Histologic subtype*	
Medulloblastoma	7 (58.3)
Astrocytoma	3 (25)
Ependymoma	2 (16.7)
CT protocol*	
Cisplatin-Etoposide	10 (83.4)
Carboplastin-Vincristin	1 (8.3)
Temozolomid-Carboplastin-Etoposid	1 (8.3)
Number of patients who RT to the neck region*	2 (16.7)
Number of patients who RT to head region*	12 (100)
Current age (yrs)†	14±4.3 (13.1-21.5)
Age at diagnosis (yrs)†	9.8±4.6 (2.2-17.8)
Follow-up time (yrs)†	5±1.9 (2-8.8)
Number of CT cures†	9.1±1.3 (6-10)
Radiotherapy dosage (Gy) to the neck region†	40.8±10.8 (27-54)
Radiotherapy dosage (Gy) to head region†	36

**n(%), †mean±SD (min-max)*

There was no statistically significant difference between the patients with abnormal thyroid USG and those with normal thyroid scanning in terms of gender (p=0.617), age at diagnosis (p=0.229), duration of follow-up (p=0.130), RT dose (p=0.260), number of CT cures (p=0.072), RT area (p=0.512), and CT protocol (p=0.812), whereas, mean age was higher in patients with thyroid USG abnormalities (p=0.038).

Evaluations of subclinical hypothyroidism patients and patients with thyroid USG abnormalities in terms of possible risk factors are shown in Table V. The age at a diagnosis under 10 years old (p=0.006), follow-up duration of 3 years or more (p=0.010), and RT dose of 25 Gy or more (p=0.014) were related to the development of subclinical hypothyroidism. Only an RT dosage of 25 Gy or more was found to be related to the development of thyroid USG abnormalities (p=0.014).

DISCUSSION

Thyroid disorders that develop due to treatment in cancer patients occur as a consequence of the affected hypothalamus-pituitary-thyroid axis or the thyroid gland. This interaction may be due to CT, RT, or surgery. The risk of thyroid disorder development was found to be 52% and 67% after 20 and 26 years of survival, respectively, in a study including 1787 patients with Hodgkin's lymphoma (9). Demirkaya et al. (10) found thyroid

Table III: Clinical characteristics of the subclinical hypothyroidism patients

Cases	Sex	Age (years)	Diagnosis	CT protocol	Number of CT cures	RT (Gy)	fT4 (ng/dl)	TSH (IU/L)	Thyroid physical examination	Tyroid autoantibodies (TG-Ab, TPO-Ab)	Thyroid USG
1.	M	16	HL	ABVD	6	20	0.7	10.1	Normal	Negative	Nodule
2.	M	18	HL	ABVD	6	30	1.1	7.4	Normal	Negative	Hypoechoic apperance
3.	F	18	HL	ABVD	3	19.8	0.8	7.3	Normal	Negative	Normal
4.	M	16	HL	ABVD-COPP	10	30.6	0.7	6.8	Normal	Negative	Thyroiditits
5.	M	9.1	HL	ABVD	6	26	0.6	9.8	Normal	Negative	Normal
6.	F	9.6	HL	ABVD	3	30.4	0.7	9.2	Normal	Negative	Normal
7.	M	17.8	CNS tumor	Cisplatin-Etoposide	10	36	0.7	9.4	Normal	Negative	Nodule

Table IV: Comparison of clinical characteristics of the patients with subclinical hypothyroidism and USG abnormalities with normals

	Subclinical hypothyroidism	Normal TSH	p	Abnormal USG	Normal USG	p
Current age (yrs)*	14.9±3.8	13.5±3.8	0.277‡	16.3±2	13.2±3.9	0.038‡
Age at diagnosis (yrs)*	8.0±4.8	9.2±4.2	0.461‡	10.5±4.3	8.6±4.2	0.229‡
Follow-up time (yrs)*	7.9±2.6	4.4±2.0	0.003‡	6.7±3.3	4.7±2.2	0.130‡
RT dosage (Gy)*	27.5±5.9	23.8±5.4	0.121‡	27.5±6.8	24.1±5.4	0.260‡
Number of CT cures*	6.2±2.8	6.7±2.7	0.700‡	8.2±2.1	6.2±2.7	0.072‡
Sex†						
Male	5 (27.8)	13 (72.2)	0.180§	4 (22.2)	14 (77.8)	0.617§
Female	2 (10.5)	17 (89.5)		3 (15.7)	16 (82.3)	
RT area†						
Neck	6 (24)	19 (76)	0.254§	4 (16.0)	21 (84.0)	0.512§
Neck±head	1 (8.3)	11 (86.7)		3 (25.0)	9 (75.0)	
CT protocol†						
ABVD	5 (33.3)	10 (66.7)	0.472§	2 (13)	13 (86.7)	0.812§
ABVD-COPP	1 (10.0)	9 (90.0)		2 (20.0)	8 (80.0)	
Cisplatin-Etoposide	1(10.0)	9 (90.0)		3 (30.0)	7 (70.0)	
Carboplastin-Vincristin	0	1 (100.0)		0	1(100)	
Temozolomid-Carboplastin-Etoposide	0	1 (100.0)		0	1(100)	

**: mean±SD, †: n(%), ‡: Mann Whitney U test,§: Chi-square test*

dysfunction in 25.5% of the patients within a mean follow-up duration of 5.54 years. In study of Akca Çağlar et al. (11), 66% of the 79 patients had abnormal thyroid function tests. Eltan et al. (12) found hypothyroidism 12 out of 40 patients (30%) on average 3.1 years after treatment determined. We found a thyroid disorder rate of 25.5% within a mean follow-up duration of 5.09±2.5 years in our study group.

Subclinical hypothyroidism following exposure to radiotherapy has been reported to have a high incidence (13,14). Srikantia et al. (15) detected 5 of 45 (11.1%) patients developed subclinical hypothyroidism following RT in their study. In the study of Demirkaya et al. (10), 78.6% of the patients with abnormal thyroid functions were diagnosed as subclinical and 11.4% as overt hypothyroidism. In our study, the subclinical hypothyroidism rate was higher than in the studies in the literature. All 7 patients with thyroid dysfunction were diagnosed as subclinical hypothyroidism. None of our patients had overt hypothyroidism.

In our study, there was no statistically significant difference between the subclinical hypothyroid patients in terms of gender. Many of studies on cases with RT applied to the thyroid gland as a part of head and neck tumors and HL treatment, the majority of the patients showed that there was no gender effect on thyroid hormone impairment (10,16). Our study was compatible with the literature.

In our study, a statistically significant relationship was found between the development of subclinical hypothyroidism and the diagnosis under the age of 10 years. Paulino et al. (16) found that the risk of hypothyroidism was increased with the reduction of treatment age. Jin et al. (17) conducted a study about thyroid dysfunction in medulloblastoma and primitive neuroectodermal tumor patients and younger age at radiation exposure was found to be significantly associated with an increased risk for permanent thyroid dysfunction. In contrast to these studies, Louis et al. (18) showed that the thyroid dysfunction risk was increased with increased age. However,

Table V: Evaluation of the patients in terms of possible risk factors for thyroid functions and USG abnormalities

	Subclinical Hypothyroidism	Normal TSH	p*	USG Abnormal	USG Normal	p*
Age at diagnosis (yrs)†						
<10	6 (40.0)	9 (60.0)	0.006	4 (26.7)	11 (73.3)	0.32
≥10	1 (4.5)	21 (95.5)		3 (13.6)	19 (86.4)	
Follow-up time (yrs)†						
<3	0	9 (100.0)	0.010	1 (11.1)	8 (88.9)	0.491
≥3	7 (25.0)	21 (75.0)		6 (21.4)	22 (78.6)	
RT dosage (Gy)†						
<25	2 (8.0)	23 (92.0)	0.014	2 (8.0)	23 (92.0)	0.014
≥25	5 (41.7)	7 (58.3)		5 (41.7)	7 (58.3)	

**: Chi-square test, †: n(%),*

in the mentioned study, younger patients had low doses of RT, whereas older patients had higher doses.

The dose of RT and the development of thyroid disorders were correlated in many studies in the literature. In the study comparing the frequency of hypothyroidism in 32 children diagnosed with medulloblastoma and who were treated with 23.4 Gy or 36 Gy craniospinal RT, it was found that the incidence of hypothyroidism did not decrease with the reduction of craniospinal RT dose, and risk was increased in the younger patients and in the patients who had CT (16). In another study that compared thyroid doses of 10, 20, and 30 Gy, the predicted average risk of subclinical hypothyroidism was 12%, 25%, and 44% respectively (19). Laughton et al. (20) found that primary hypothyroidism was found in 54% of those who had a 23.4 Gy dose and 89% of those treated with a 36 Gy or more dose in 88 embryonal tumor patients. In our study, we found that the RT dose of 25 Gy or more was correlated with the development of subclinical hypothyroidism. In contrast, Jin et al. (17) showed that the proportion of patients developing thyroid dysfunction was not significantly different depending on whether patients received less than 23.4 Gy of or more in their study.

In a review evaluating radiation exposure and thyroid lesions; it was estimated that 88% of the thyroid cancers in children are attributable to radiation exposure (21). Crom et al. (22) reported that a nonhomogenous thyroid gland was found in 44% of patients when they investigated thyroid abnormalities with USG in 96 childhood cancer survivor patients who had RT to the head and neck region. In the same study, thyroid nodules were detected in 22 (23%) of 96 patients, 6 patients with cold nodules had FNAB and only one had papillary carcinoma (22).

Somerville et al. (23) conducted a study with 142 patients who survived childhood cancers and found cancer in only 6 of 78 patients who received direct thyroid gland RT but found thyroid cancer in 12 of 65 patients who did not directly have RT to the thyroid gland but received radiation therapy such as cranial RT. Krawczuk-Rybak et al. (24) found an ultrasonographic abnormality (hypoechoic appearance, heterogeneous appearance, solid nodule) in 9.7% of 31 patients who underwent RT to the neck, upper mediastinum, and cranial region. Baran et.al. (25) performed thyroid USG screening in childhood cancer survivors following RT, 150 of 306 (49%) patients had thyroid nodules. In their cohort, the number of CNS tumor and HL diagnoses was 94. In our study, 18.9% of the patients had thyroid USG abnormalities that were consistent with the literature. The risk of developing benign or malignant thyroid disease after RT is controversial.

As a result, today, successful results are obtained in the treatment of childhood cancers, however late side effects become a serious problem. Side effects of cancer treatment can be seen immediately, as well as, can be seen after 20 years. Early intervention to side effects will positively affect the social and physical life of the patients and will reduce morbidity.

Serum thyroid hormone and thyroid antibodies should be routinely examined in any patient who has been treated for cancer to evaluate thyroid dysfunction regardless of clinical findings. Regular thyroid imaging is required from patients especially those who had RT to the head and neck region or directly to the thyroid gland and the follow-up of these patients should be lifelong.

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Evaluation of the Effect of Fluid and Electrolyte Therapy on Electrolytes and Acidosis Resolution Time in Diabetic Ketoacidosis

Diyabetik Ketoasidoz Hastalarında Sıvı ve Elektrolit Tedavisinin Elektrolit Düzeyleri ve Asidoz Düzelme Süresine Etkisi

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ABSTRACT

Objective: Fluid replacement and insulin infusion are the cornerstones of treatment of diabetic ketoacidosis, but the optimal volume, rate of infusion, and electrolyte content of fluid replacement have been controversial. The aim of this study was to investigate the effects of treatment on pH, bicarbonate (HCO_3), anion gap, chloride, and potassium levels as well as time to resolution of acidosis in children with diabetic ketoacidosis.

Material and Methods: Ninety-six episodes with diabetic ketoacidosis between January 2015-December 2017 were evaluated.

Results: The mean resolution time of acidosis was 13.4±7.1 hours. Anion gap was returned to normal in 68 (70.8%) episodes at the 4th hour of treatment with a mean of 11±4.2 mmol/L. Episodes with potassium phosphate (KPO_4) replacement resulted in a faster increase in pH and a significantly shorter resolution time of acidosis (p<0.001). Acidosis persisted at the 16th hour of treatment in episodes with lower pH, lower serum bicarbonate (HCO_3) and higher white blood cell (WBC) counts on admission (p<0.001, p=0.003 p=0.033, respectively). Hyperchloremia (Cl/Na ratio > 0.79) was observed in 97% of cases after 8 hours of treatment.

Conclusion: Although the value of the anion gap in predicting acidosis is controversial, severe DKA episodes and high white blood cell count at admission; potassium replacement with high amounts of chloride and KCl containing fluids given during treatment have been associated with a longer recovery time of acidosis.

Key Words: Acidosis, Diabetic ketoacidosis, Hypopotassemia, Pediatric, Type 1 Diabetes

ÖZ

Amaç: Sıvı replasmanı ve insülin infüzyonu Diyabetik Ketoasidoz DKA tedavisinin temel taşlarıdır, ancak sıvı replasmanının optimal hacmi, infüzyon hızı ve elektrolit içeriği hala tartışmalı olan bir konudur. Bu çalışmanın amacı, diyabetik ketoasidozlu çocuklarda tedavinin pH, bikarbonat (HCO_3), anyon açığı, klorür ve potasyum düzeyleri üzerindeki etkilerinin yanı sıra asidozun düzelme süresini araştırmaktı.

Gereç ve Yöntemler: Ocak 2015-Aralık 2017 tarihleri arasında diyabetik ketoasidoz tanısı ile takip edilen 93 hasta (toplam 96 DKA atağı) retrospektif olarak değerlendirildi.

Bulgular: Asidozun ortalama düzelme süresi 13.4±7.1 saatti. Anyon açığı 68 (%70.8) atakta tedavinin 4. saatinde ortalama 11±4.2 mmol/L ile normale döndü. Potasyum fosfat (KPO_4) replasmanı yapılan hastalarda pH artışı daha hızlı ve asidoz düzelme süresi daha kısa olarak saptandı (p<0.001). Başvuruda daha düşük pH, daha düşük serum bikarbonat (HCO^3) ve daha yüksek beyaz küre sayısı olan ataklarda tedavinin 16. saatinde asidozun devam ettiği görüldü (sırasıyla p<0.001, p=0.003 p=0.033). Hiperkloremi (Cl/Na oranı > 0.79) tedavinin 8. saatinde atakların %97'sinde tespit edildi.

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Sonuç: Asidozu yansıtmada anyon açığının değeri tartışmalı olarak bulunsa da, DKA ataklarının ağır derecede olması ve hastaneye yatışta beyaz kürenin yüksek olması; tedavi sırasında verilen yüksek miktarda klorür ve KCl içeren sıvı ile potasyum replasmanı asidozun daha uzun sürede düzelmesi ile ilişkilendirilmiştir.

Anahtar Sözcükler: Asidoz, Diyabetik ketoasidoz, Hipopotasemi, Pediatri, Tip 1 diyabet

INTRODUCTION

The autoimmune destruction of the pancreatic beta cells that produce insulin is the cause of type 1 diabetes mellitus (1). Diabetic ketoacidosis (DKA) is one of the most life-threatening complications of type 1 diabetes mellitus (T1D). Its frequency at the onset of T1D ranges from 15% to 70% (2).

Insufficient insulin and elevated counter-regulatory hormones result in gluconeogenesis, glycogenolysis, lipolysis, and muscle proteolysis, which leads to hyperglycemia, hyperosmolality, and ketoacidosis. Hyperglycemia causes glycosuria, which leads to osmotic diuresis and significant loss of fluid and electrolytes. The fundamental components of managing DKA involve replacing fluids and electrolytes, administering insulin therapy, and closely monitoring the patient's progress using current laboratory tools (2,3).

Despite a comprehensive randomized controlled trial, it was determined that the rate of administration and sodium chloride (NaCl) content of intravenous (IV) fluids did not have a significant impact on neurological outcomes in children with DKA (4). However, there is still ongoing discussion regarding the ideal volume, infusion rate, and sodium content for IV fluid replacement in these patients (3,5). Normal saline (0.9%) has traditionally been the preferred fluid for treating DKA. However, it can lead to an increase in chloride levels and the development of hyperchloremic metabolic acidosis due to the excessive administration of fluids rich in chloride during DKA treatment (6-9). Hyperchloremia affects the duration of acidosis, making it difficult to monitor the patient (10).

Serum potassium levels are usually normal or slightly elevated at DKA presentation due to the shift of potassium ions from the intracellular to extracellular space. Urinary potassium loss can occur due to osmotic diuresis, increased levels of aldosterone in response to reduced blood volume, and the excretion of ketoacids. Hypokalemia is an expected finding due to the intracellular entry of potassium during DKA treatment (11, 12).

Glycosuria-induced osmotic diuresis also causes phosphate deficiency in children. However, the serum phosphate concentration is usually normal or even slightly elevated initially, as both metabolic acidosis and insulin deficiency result in the movement of phosphate from the extracellular space. The levels of phosphate decrease during the therapy of DKA due to the reversal of this transcellular shift.

We aimed to investigate the effect of treatment with DKA on alterations of pH, HCO_3, anion gap, chloride, and potassium levels, as well as the time to resolution of acidosis in children with DKA. This study will be among the rare studies on this subject, adding data to the literature and providing new ideas about future studies.

MATERIALS and METHODS

This retrospective study was performed at the emergency department of Dr. Sami Ulus Training and Research Hospital between January 1, 2015, and December 31, 2017. Children below 18 years of age diagnosed with DKA due to T1D were included. Patients with comorbidities that could lead to diagnostic confusion, patients who were referred to our institution after initial presentation at another hospital, and children who did not meet the diagnostic criteria for DKA were excluded from the study. Patients who subsequently had another episode of diabetic ketoacidosis during the study period were also enrolled in the study. The analysis of the results was based on the number of episodes of DKA. Ninety-three children were included in the study, with a total of 96 episodes of DKA.

University of Health Sciences, Ankara Pediatrics Hematology Oncology Hospital Clinical Research Ethics Committee approved the study (ID: 2018-058). Written informed consent was obtained from the parents or guardians of all enrolled patients.

Patients' data were obtained from the hospital registration system. Age at diagnosis, gender, clinical findings (nausea, vomiting, abdominal pain, tachypnea, altered consciousness, fever, polyuria, polydipsia, weight loss), degree of dehydration, and severity of DKA were recorded.

The biochemical criteria for diagnosis of DKA were based on hyperglycemia (blood glucose >200 mg/dL [11 mmol/L]), metabolic acidosis (venous pH <7.3 or serum bicarbonate <15 mEq/L [15 mmol/L]) and ketosis (presence of ketones in the blood [>3 mmol/L beta-hydroxybutyrate] or urine ["moderate or large" urine ketones]). Ketoacidosis was categorized into three stages of severity. DKA was classified as: mild (pH: 7.2-7.3, HCO_3: 10-15 mmol/L), moderate (pH 7.1- 7.2, HCO_3: 5-10 mmol/L) and severe (pH < 7.1, HCO_3 <5-10 mmol/L) (9).

All initial laboratory parameters, including pH, serum bicarbonate (HCO^3), blood glucose level, serum sodium (Na) (corrected sodium level not calculated), potassium (K), chloride (Cl), phosphorus (P), creatinine, blood urea nitrogen (BUN), HbA1c, white blood cell (WBC), urine and blood ketone levels, were recorded.

The normal range of potassium levels is between 3.5-5.0 mEq/L. Lower than 3.5 mEq/L was defined as hypokalemia and higher than 5 mEq/L was defined as hyperkalemia (13).

Serial measurements of blood glucose, HCO_3, pH, and electrolytes were taken upon arrival and at certain time intervals (4-8-12-16-20-24 and 36 hours) after the start of treatment. Acidosis was considered resolute if the pH levels were above 7.30 and/or the HCO_3 levels were over 15 mmol/L. The time of first oral intake (based on fluid withdrawal time) and initial insulin dose were recorded.

The total amount of fluid (in milliliters [mL]), sodium, chloride and potassium (as potassium chloride [KCl] or potassium phosphate [KPO_4]) (in milliequivalent [mEq]) administered at the 1st, 8th, 16th, 24th and 36th hours of treatment were calculated. The total amount of fluid and chloride were divided by body weights to find the fluid and chloride levels per kg. The chloride level was also expressed as the amount of chloride contained in 100 mL of fluid. The potassium content per 1000 mL of fluid in the first 8, 16, and 24 hours of treatment was calculated by subtracting the loading fluid given in the first hour.

Anion gap (Na - [Cl+HCO3]) and serum osmolarity (2x [plasma Na] + plasma glucose/18 [mmol/L] + BUN/2.8 [mmol/L]) levels of the patients were calculated with the formula in the SPSS program. A Cl/Na ratio > 0.79 was defined as hyperchloremia (8).

The statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc., Armonk, NY, IBM Corp., USA) software version 20.0. Of the continuous variables, those with a normal distribution were expressed as mean and standard deviation (SD). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Categorical variables were expressed as numbers and percentages. The significance of the difference between the median or mean of the two groups was evaluated with the Mann Whitney-U Test for data that were not normally distributed, and the Student t-Test for normal distributions. The significance of the difference between the two groups in categorical variables was evaluated with the Chi-Square test. $p<0.050$ was considered statistically significant.

RESULTS

The study included a cohort of 93 patients diagnosed with DKA. Out of these patients, three experienced a recurrence of DKA during the trial. Hence, a grand total of 96 separate episodes of DKA were examined.

Out of the total number of patients, 50 (53.8%) were male and 43 (46.2%) were female (male-to-female ratio=1.16:1). The mean age was 8.33±4.9 years at the onset of the disease. Of the 96 DKA episodes, 78 (81.3%) were at the time of the initial diagnosis of T1D. The most common symptoms were polyuria (76%) and polydipsia (76%). Forty-five (46.9%) episodes were classified as severe DKA. The demographic and clinical characteristics were shown in Table I.

Table I: Demographic and clinical characteristics of patients presenting with diabetic ketoacidosis

Gender, male* (n=93)	50 (53.8)
Age at diagnosis (year)†	8.33±4.9
New diagnosis* (n=96)	78 (81.3)
Degree of dehydration* (n=96)	
Severe	13 (13.5)
Moderate	83 (86.5)
Clinical Findings*(n=96)	
Polyuria-polydipsia	73 (76)
Nausea-vomiting	47 (49)
Weight loss	43 (44.8)
Tachypnea	39 (40.6)
Consciousness change	24 (25)
Abdominal pain	22 (22.9)
Fever	13 (13.5)
DKA severity* (n=96)	
Mild DKA	19 (19.8)
Moderate DKA	32 (33.3)
Severe DKA	45 (46.9)

:** *n(%),* **†:** *(mean±SD),* ***DKA: *Diabetic ketoacidosis*

The laboratory parameters at the time of admission and the subsequent changes that occurred within a few hours are shown in Table II.

Insulin therapy was started at a dose of 0.05 IU/kg in 4 (4.1%) episodes, 0.1 IU/kg in 90 (93.8%) episodes, and 0.15 IU/kg in 2 (2.1%) episodes.

The mean amount of fluid administered at the first hour was 13.1±5.02 mL/kg. The total fluid administered was calculated as 39.6±10.1 mL/kg at the 8th hour, 71.5±18.9 mL/kg at the 16th hour and 100±28.8 mL/kg at the 24th hour. The mean duration of fluid therapy was 17.9±7.1 hours. The longest transition time to oral intake was 52 hours in one patient.

Potassium level at admission was <3.5 mmol/L in 8 (8.3%) episodes, 3.5-5.5 mmol/L in 77 (80.2%) episodes, and >5.5 mmol/L in 9 (9.4%) episodes. During follow-up, potassium levels decreased to <3.5 mmol/L in 43 (44.8%) episodes. The total amount of potassium given at the 24th hour was 90±53.3 mEq. In patients who were normokalemic at the time of diagnosis, the mean amount of potassium given at 8, 16 and 24 hours was 31.4±10.5, 35.5±10.4 and 38.2±15.2 mEq/L, respectively, while in hyperkalemic patients, the mean amount of potassium in the fluid within 24 hours was 18.4±9.3 mEq/L. KPO_4-containing fluid was given in 60 (62.5%) episodes (only KPO_4 in 3 episodes, KCl+KPO_4 in 57 episodes) and only KCl containing fluid was given in 36 (37.5%) episodes. The initial pH in episodes given KPO_4 for potassium replacement was significantly lower than episodes given KCl ($p<0.001$). In the subgroup analysis of the changes at 8th, 16th and 24th hours according to initial serum pH and HCO_3 values, it was observed that the pH increase was rapid, and the resolution of acidosis took shorter time in KPO_4-treated patients compared to KCl-treated patients ($p<0.001$) (Table III).

Table II: The laboratory parameters of diabetic ketoacidosis patients at admission and their changes according to hours

	At admission	4th hour	8th hour	12th hour	16th hour	20th hour	24th hour
pH*	7.07±0.14	7.19±0.09	7.25±0.07	7.27±0.06	7.30±0.05	7.31±0.06	7.34±0.05
HCO3* (mmol/L)	8.4±3	11±3.2	13.4±3.3	14.1±2.2	15±2.3	15.9±2.5	17.2±3.5
Glucose* (mg/dL)	476±137	263±118	226±93	208±70	214±74	216±76	224±99
Anion gap* (mmol/L)	19.7±5.5	11±4.2	7.9±4.2	6.7±2.7	6.2±3.3	11.4±23	6.7±2.6
Sodium* (mmol/L)	133±6	136±5	136±6	137±5	137±4	137±4	137±4
Potassium* (mmol/L)	4.46±0.8	4.12±0.88	3.81±0.62	3.58±0.57	3.65±0.57	3.38±0.59	3.37±0.47
Chloride* (mmol/L)	105±7	113±6	115±6	115±6	117±5	115±5	112±6
Phosphorus* (mg/dL)	3.8±1.1	2.8±1	2.7±1.1	2.9±1.2	2.9±1.2	3.3±1.2	2.9±1.2
Creatinine* (mg/dL)	0.89±0.31	0.8±0.25	0.73±0.19	0.65±0.2	0.63±0.22	0.61±0.21	0.56±0.11
Osmolality* (mOsm/kg)	305.7±13.6	299±14.6	296.4±11.5	297.8±14.4	299.5±10.2	297.5±9.5	296.5±9.5

***:** *Mean ± SD*

Table III: Acidosis recovery time and pH changes over hours in patients with and without potassium phosphate

	KPO_4	n	mean	SD	p
pH at admission	-	36	7.153	.105	<0.001*
	+	60	7.026	.137	
pH change in the first 4 hours	-	34	.097	.083	0.029*
	+	55	.142	.097	
pH change in the first 8 hours	-	27	.151	.113	0.026†
	+	53	.210	.110	
pH change in the first 16 hours	-	16	.196	.101	0.003†
	+	44	.296	.115	
pH change in the first 24 hours	-	5	.226	.114	0.011†
	+	16	.415	.134	
Acidosis resolution time (hours)	-	59	15.42	6.76	<0.001*
	+	35	10.23	6.61	<0.001*
Oral intake time (hours)	-	36	14.53	6.23	<0.001*
	+	60	20.02	6.99	<0.001*

***:** *Student t Test,* **†:** *Mann Whitney-U Test,* ***KPO_4:** potassium phosphate,* ***SD:** Standard deviation,* ***+ :** Fluid containing with KPO_4,* ***- :** KPO_4 free fluid*

Table IV: The factors affecting the time to resolution of acidosis at 16 hours

	Acidosis at the 16th hour	n	mean	SD	p*
pH	-	68	7.105	.133	<0.001
	+	28	6.998	.127	
HCO3 (mmol/L)	-	67	8.96	3.15	0.003
	+	27	7.01	1.93	
WBC (10^9/L)	-	68	14.8	7.9	<0.001
	+	28	22.9	11.6	
Total amount of chloride given in 100 mL of fluid in 16 hours	-	39	11.86	1.61	0.031
	+	28	12.62	1.00	

***:** *Student t Test,* ***SD:** Standard deviation,* ***HCO_3:** sodium bicarbonate,* ***WBC:** white blood cell,* ***+ :** Those who continue to have acidosis at the 16th hour,* ***- :** Those whose acidosis does not persist at 16th hours*

The mean chloride level at the time of admission was 105±7 mmol/L. The mean Cl/Na ratio was 0.78 at the time of diagnosis. It was > 0.79 after 8 hours of treatment in 93 (96.8%) episodes. It increased to a maximum of 145 mmol/L and an average of 116.6 mmol/L at the 16th hour of treatment. The mean total amount of chloride given within 16 hours was 8.64±2.16 mEq/kg and 11.6±3.2 mEq/kg within 24 hours.

The mean anion gap on admission was 19.7±5.5 mmol/L. The anion gap was returned to normal in 68 (70.8%) episodes after 4 hours of therapy, with a mean value of 11±4.2 mmol/L.

The mean correction time for acidosis was 13.4±7.1 hours (6.67±3.6 hours in mild, 11±6 hours in moderate, and 18±5.7 hours in severe DKA cases). A statistically significant difference was observed in the average resolution time of acidosis between the severity levels of ketoacidosis (p<0.001). The acidosis was corrected in 69 (71.9%) episodes at the 16th hour of admission. Acidosis persisted at the 16th hour of treatment in episodes with lower pH, lower HCO_3 and higher WBC values on admission (p<0.001, p=0.003, p<0.001, respectively) (Table IV). Patients with acidosis lasting longer than 16 hours had lower pH on admission (p=0.039).

It was determined that the WBC count at the time of admission was significantly related to the resolution time of acidosis (p<0.001). The mean white blood cell count at admission was 14.8x10^9/L in those whose acidosis resolved at 16 hours and 22.9 x10^9/L in those whose acidosis did not resolve at 16 hours.

DISCUSSION

In this study, the relationship between fluid-electrolyte therapy and the alterations in chloride and potassium levels and the resolution time from acidosis in 96 episodes of diabetic ketoacidosis due to T1D were evaluated.

In this study, acidosis was resolved in 69 (71.9%) episodes at the 16th hour of admission and the mean resolution time of acidosis was below 14 hours. A statistically significant difference was observed in the average resolution time of acidosis between the severity levels of ketoacidosis The duration of acidosis in this study is reasonable, as nearly half of the episodes were severe. These findings correlate with the results of previous studies conducted on children with DKA. In a study by von Oettingen

et al. (14), mean resolution time of acidosis was reported to be 8.4 hours, where it reached 14.5 hours in severe cases. In a study by Mrozik et al. (15), the mean resolution time of acidosis was reported to be 17.1 hours in severe episodes and 10.5 hours in milder episodes. The differences between mean acidosis resolution times in the literature may have been related to the varieties in DKA episode severity, subsets of patients enrolled in the study, fluid infusion rates and proposed DKA protocols (14).

The clinical significance of hyperchloremia in DKA is currently being studied. In the study of Taylor D. et al. (8), the rate of hyperchloremia was 6% at the beginning of treatment and 94% at the 20th hour, and they stated that chloride increased rapidly in the first 4 hours and became the dominant component for acidosis at the end of the 20th hour. In this study, the rate of hyperchloremia (Cl/Na ratio > 0.79) after 8 hours of treatment was nearly 97%. Additionally, episodes with persistent acidosis after 16 hours of treatment received a higher total dose of chloride throughout the first 16 hours of treatment. Also, no significant correlation was found between the amount of chloride given during treatment and the resolution time for acidosis. This may be due to the fact that hyperchloremia was observed in 97% of patients at the 8th hour of treatment and a similar treatment protocol was administered to each patient. More information about the link between chloride and the length of acidosis will be gained from prospective multicenter studies that use different types of fluids that contain chloride as part of the treatment.

The value of the anion gap in reflecting acidosis during DKA treatment was discussed and its role in reflecting acidosis was found controversial because of its correlation with increased chloride levels during DKA treatment (8). Hyperchloremic metabolic acidosis can happen when the kidneys get rid of more ketones than chloride ions in people with DKA or when a lot of NaCl is infused during treatment for DKA (16,17). Von Oettingen JE et al. (14) reported that the dominant component of acidosis after 12 hours was chloride, which caused masking in calculations based on the anion gap level. In the study of Mrozik RN et al. (15), it was reported that secondary hyperchloremic metabolic acidosis occurred in 58% of patients and there was a difference of >6 hours between HCO_3 and anion gap level in the acidosis resolution time calculations. In this study, the anion gap returned to normal in nearly 70% of episodes at 4th hour of treatment, whereas the resolution time of acidosis was above 13 hours. This indicates that the anion gap level did not reflect the resolution time of acidosis as reported in the literature.

In the DKA protocol, it is recommended to add 40 mEq/L potassium to fluid therapy in cases of a potassium level <5.5 mmol/L at the time of diagnosis (9). Peeters E. et al. (18) found that over 25% of the patients had a potassium level below 3.5 mEq/L when they were given a treatment with a potassium amount of 20 mEq/L. In a study by Naeem MA et al. (19), potassium levels were found to be 4.03±0.66 mmol/L and 3.84±0.59 mmol/L, respectively, at the 6th and 12th hours of treatment, in which 40 mEq/L potassium was given according to the ISPAD protocol. In another study, it was found that 8.8% of people who had replacement fluid with 40 mEq/L of potassium still had hypokalemia (20). In our study, the potassium levels gradually declined to values lower than 3 mmol/L after the 4th hour of treatment, resulting in hypokalemia in around 45% of the cases. This may be due to the detection of potassium levels below 40 mEq/L at the 8th and 16th hours. To prevent hypokalemia, it has been proposed to initiate insulin infusion one hour after beginning fluid replacement, as the reduction in serum potassium level is most noticeable within the first two hours of treatment (20). The causes of hypokalemia were demonstrated to be urinary potassium excretion due to insulin infusion and osmotic diuresis. A study found that administering insulin at a rate of 0.05 U/kg/hour reduced the occurrence of hypokalemia, with no significant changes in resolving acidosis and ketosis compared to an insulin infusion rate of 0.1 U/kg/hour (21). The insulin infusion rate was 0.1 U/kg/hour in nearly 95% of episodes, which was thought to be another reason for the high rate of hypokalemia in our study. It is essential to administer a 40 mEq/L dosage of potassium when the potassium level is below 5.5 mmol/L after the diagnosis of DKA. Additionally, considering a lower-dose insulin infusion may be an option to prevent hypokalemia.

The study investigating the relationship between KPO_4 supplementation and pH change was not found in the literature. This study will be a guide for systematic studies that will investigate the relationship between KPO_4 replacement and pH change. It will consider the movement of potassium and phosphate out of the cell during acidosis, their movement into the cell with the effects of rehydration and insulin, and the acidification effect caused by chloride when given with KCl, leading to hyperchloremia (21).

Markers of oxidative stress (WBC, platelets, and MPV) were associated with increased severity of DKA. Sehgal M. et al. (22) reported that both leukocytosis and thrombocytosis were associated with severe metabolic acidosis. Karavanaki K. et al. (23) reported a significantly higher WBC value in patients with moderate or severe DKA compared to those with mild DKA. In this study, it was determined that the number of WBC on admission was associated with the resolution time of acidosis. This condition is thought to be associated with high levels of H^+ can be associated with the production and release of leukocytes, systemic inflammation, oxidative stress response, or the severity of dehydration, as previously stated in the literature (24,25).

One of the limitations of this study was its retrospective nature. The data from a single center did not reflect the universe, so it would have been better if it was a multi-center prospective study. All episodes were managed according to the same treatment protocol, so the relationship between treatment differences could not be clearly demonstrated. Nevertheless, the data of this study is valuable because it is the data of the

busiest third-level emergency department in our country. It is among the rare studies on this subject, adding data to the literature and providing new ideas about future studies.

CONSLUSION

Episodes of DKA characterized by a severe degree and higher WBC upon hospital admission, along with a high administration of chloride during therapy and potassium replacement using fluid containing KCl, were found to be associated with a longer time for the resolution of acidosis. The value of the anion gap in reflecting acidosis was found to be controversial. To explore the association between the length of acidosis and various chloride-containing liquids or the addition of KPO_4 and pH change, it is important to conduct multicenter, thorough prospective research.

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Early Period Assessment of the Nutritional Status of Child Patients in the Earthquake Zone

Deprem Bölgesindeki Çocuk Hastaların Beslenme Durumunun Erken Dönem Değerlendirmesi

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ABSTRACT

Objective: The objective of this study was to investigate the impact of earthquakes on the nutritional status and infection rates of children in the early stages of post-earthquake recovery.

Material and Methods: Following the earthquakes on February 6, 2023, 80 out of 504 patients who presented to the pediatric examination tent in Hatay province were included in the study. Reasons for patient visits and weight loss compared to pre-earthquake measurements were examined.

Results: A total of 80 patients were examined across three different age groups [1 month-5 years (29 patients), 5-10 years (34 patients), and 10-18 years (17 patients)]. In all three age groups, a statistically significant decline was observed in body weights, weight percentiles, and age-specific standard deviations when compared to their pre-earthquake measurements ($p<0.001$). Besides, frequently occurring illnesses were respiratory tract infections (51.25%) and acute gastroenteritis (38.75%).

Conclusion: Ensuring appropriate and adequate nutrition for children in the aftermath of a disaster is of critical importance for sustaining normal growth and preventing of diseases. Therefore, emergency plans should include expert pediatricians and prioritize children.

Key Words: Children, Disaster, Earthquake, Nutrition

ÖZ

Amaç: Bu çalışmanın amacı, deprem sonrası iyileşmenin erken evrelerinde depremlerin çocukların beslenme durumu ve enfeksiyon oranları üzerindeki etkisini araştırmaktır.

Gereç ve Yöntemler: 2023 yılı 6 Şubat'taki depremler sonrasında, Hatay ilindeki çocuk muayene çadırına başvuran 504 hastadan 80'i çalışmaya dahil edilmiştir. Hastaların ziyaret nedenleri ve deprem öncesi ölçümlere göre kilo kayıpları incelenmiştir.

Bulgular: Toplam 80 hasta, üç farklı yaş grubunda incelenmiştir [1 ay-5 yaş (29 hasta), 5-10 yaş (34 hasta) ve 10-18 yaş (17 hasta)]. Üç yaş grubunda da, deprem öncesi ölçümlerle karşılaştırıldığında, vücut ağırlıklarında, ağırlık persentillerinde ve yaşa özgü standart sapmalarda istatistiksel olarak anlamlı bir düşüş gözlemlenmiştir ($p<0.001$). Ayrıca, sık görülen hastalıklar solunum yolu enfeksiyonları (%51.25) ve akut gastroenterit (%38.75)'di.

Sonuç: Felaket sonrası çocuklar için uygun ve yeterli beslenmenin sağlanması, normal büyümenin sürdürülmesi ve hastalıkların önlenmesi için kritik öneme sahiptir. Bu nedenle, acil durum planları uzman çocuk doktorlarını içermeli ve çocuklara öncelik vermelidir.

Anahtar Sözcükler: Çocuklar, Deprem, Felaket, Beslenme

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INTRODUCTION

Disasters can pose significant challenges to both the psychological and physical health of children. It is well-documented that earthquakes have adverse effects on child nutrition (1). Rapid alterations in living conditions can lead to difficulties in food accessibility, issues in water supply, anorexia, changes in dietary habits, and psychological factors, all of which constitute serious risks in terms of infections and malnutrition (2,3). Existing data indicate that children are the most vulnerable individuals during periods of catastrophe (1). Children who experience weight loss possess a compromised immune system, making them more susceptible to infections in the short term and developmental delays in the long term (4).

On February 6, 2023, two devastating earthquakes with magnitudes of 7.8 and 7.5, according to the Richter scale, struck the province of Kahramanmaraş in Turkey. Approximately 14 days subsequent to these events, which directly impacted an estimated 9.1 million individuals, an additional two earthquakes emanated from the province of Hatay (5). Following these seismic occurrences, the living conditions in the affected regions significantly deteriorated. Access to potable water and appropriate food supplies emerged as the most pressing concerns in these locales.

The objective of our study was to investigate the nutritional status and incidence of infections among children in the immediate aftermath of the earthquake.

MATERIALS ans METHODS

Study Design and Background

Our study was conducted with patients who presented to the Pediatric Emergency tent, which was established as a medical endpoint in the yard of Hatay Mustafa Kemal University Hospital, between the dates of February 26, 2023, and March 7, 2023. Prior to this, pediatric healthcare services in the region were primarily provided by general practitioners, and only a trauma tent was available. On the 20th day following the Kahramanmaraş earthquakes and the 6th day following the Hatay earthquakes, a new tent was established with the assistance of three pediatricians and three pediatric nurses, thereby initiating professional pediatric services. Due to limited resources, all records were manually maintained by the attending physicians and nurses. Facilities for vital sign measurement were available; however, laboratory capabilities were lacking. The established tent offered outpatient services and provided short-term intravenous, oxygen, and inhaler therapies on a day-to-day basis.

Data Collection and Population

Of the 504 patients who presented, 80 were included in the study who had a hospital visit in the month preceding the earthquake, had their body weight measured during that visit, and whose measured values were distinctly remembered by their caregivers. Patients younger than one month, those who had not visited any healthcare facility in the last month, and those who had visited but whose body weight measurements were not distinctly remembered by the caregivers were excluded from the study. In order to attain accurate information related to the patients, individuals whose both parents had deceased were excluded from the study. Body weights measured during healthcare visits in the month prior to the study were queried from caregivers and noted, and their body weights at the time of presentation were recorded.

Statistical Analysis and Ethical Approval

For the purpose of data analysis, IBM Corp.'s Statistical Package for the Social Sciences (SPSS Inc., Armonk, NY, IBM Corp., USA), Version 23.0, was employed. Comprehensive descriptive statistical measures, encompassing both frequencies and arithmetic means, were calculated for all variables under study. The expression of results varied depending on the parametric nature of the data and included mean accompanied by standard deviation, median values, and ranges from the minimum to the maximum values, as well as numerical counts represented as percentages. In non-parametric data, Wilcoxon signed-rank test was used for paired group comparison, and Kruskal-Wallis test was used for three independent group comparison. The Chi-Square test was utilized for the comparison of quantitative variables. A p-value threshold of less than 0.050 was established as the benchmark for determining statistical significance.

This study was conducted in conformity with the principles of the Declaration of Helsinki and approved by the Republic of Turkey Ministry of Health, the Ethics Committee of Ankara Bilkent City Hospital Ethics Committee, and the Institutional Review Board of the Children's Hospital of Ankara Bilkent City Hospital.

RESULTS

A total of 80 patients were included in the study. The average age of the patients was 6.75±4.15 years. Of the participants, 48 (60%) were male, and 32 (40%) were female. In 62 of the patients (77.5%), the primary caregiver was the mother, whereas in 18 (22.5%) of the cases, the father was the caregiver. It was observed that in all instances where the father was the primary caregiver, the mother was deceased.

Weight loss was observed in 67 patients (83.8%), while an increase in body weight was detected in 13 patients (16.3%). The pre- and post-earthquake body weights, weight percentiles, and age-specific standard deviation scores for body weight of the patients are presented in Table I. A comparison of these three parameters across all age groups before and after the earthquake revealed statistically significant

Table I : Patients' pre- and post-earthquake body weights, weight percentiles, and age-specific body weight standard deviation scores.

Age	Mean±SD	p*
All Ages (n:80)		
Remembered Wt. (kg)	25.01±13.55	<0.001
Measured Wt. (kg)	24.17±13.79	
Remembered Wt. Percentile	48.71±33.36	<0.001
Measured Wt. Percentile	39.55±32.74	
Remembered Wt. SDS	-0.07±1.19	<0.001
Measured Wt. SDS	-0.41±1.21	
1 month-5 years (n:29)		
Remembered Wt. (kg)	14.44±3.50	<0.001
Measured Wt. (kg)	13.54±3.31	
Remembered Wt. Percentile	53.92±30.09	<0.001
Measured Wt. Percentile	40.26±29.88	
Remembered Wt. SDS	0.16±1.03	<0.001
Measured Wt. SDS	-0.33±1.04	
5 years-10 years (n:34)		
Remembered Wt. (kg)	23.77±6.85	<0.001
Measured Wt. (kg)	22.92±7.43	
Remembered Wt. Percentile	51.47±34.14	<0.001
Measured Wt. Percentile	42.84±33.71	
Remembered Wt. SDS	-0.03±1.19	<0.001
Measured Wt. SDS	-0.34±1.22	
10 years-18 years (n:17)		
Remembered Wt. (kg)	45.52±11.64	<0.001
Measured Wt. (kg)	44.80±12.11	
Remembered Wt. Percentile	34.29±34.92	<0.001
Measured Wt. Percentile	31.79±36.03	
Remembered Wt. SDS	-0.57±1.35	<0.001
Measured Wt. SDS	-0.69±1.47	

*****Wilcoxon signed-rank test*

declines post-earthquake (p<0.001 for each parameter). Patients were categorized into three age groups: 1 month to 5 years, 5 years to 10 years, and 10 years to 18 years. The first group comprised 29 patients, the second group 34, and the third group 17. When each group was separately analyzed, statistically significant declines in all three parameters were observed post-earthquake (p<0.001 for each). No significant relationship was found between the caregiver and the loss of body weight (p=0.484).

Changes in body weight post-earthquake were examined for patients who were underweight prior to the earthquake as compared to those who had normal body weight (Table II). Patients with body weight below the 10th percentile were considered underweight. No statistically significant differences were observed. However, the percentile decline in the underweight patient group was 63.2%, whereas in patients with normal body weight before the earthquake, the percentile decline was 82%. No significant relationship was identified between age groups in terms of body weight loss (p=0.965).

The diagnoses established post-medical evaluation are summarized in Table III. Acute gastroenteritis and respiratory tract infections constituted 90% of the conditions observed in the patients included in the study. Notably, no clinical cases

Table II: Relationship Between Pre-Earthquake Body Weight and Subsequent Body Weight Loss

Body Weight	Current Weight (Percentile)			Total*
	Decreased*	Increased*	Unchanged*	
Pre- Earthquake				
Underweight	12 (63.2)	4 (21.1)	3 (15.8)	19 (100)
Normal	50 (82)	9 (14.8)	2 (3.3)	61 (100)
Total	62 (77.5)	13 (16.3)	5 (6.3)	80 (100)

***** *n(%)*

Table III: Diagnoses and distribution of the patients included in the study

	n (%)
Acute Gastroenteritis	31 (38.75)
Upper Respiratory Tract Infection	28 (35)
Lower Respiritory Tract Infection	13 (16.25)
Dermatitis / Scabies / Cellulitis	7 (8.75)
Wound Site Infection	1 (1.25)
Total	80 (100)

of cholera or dysentery were encountered among patients diagnosed with acute gastroenteritis.

In cases presenting with acute gastroenteritis who were suitable for home-based treatment and had oral intake, guideline-based recommendations were implemented, and packaged oral rehydration solution (ORS) and zinc treatment were initiated (6). One patient, despite intravenous fluid resuscitation, continued to exhibit hypotensive symptoms and was thus airlifted to a higher-level medical facility for further care.

For patients with lower respiratory tract infections, oxygen therapy was initiated in the tent, and intravenous hydration was provided. Oral amoxicillin treatment was started. Patients who had the facility for inhaler treatment were discharged under control conditions to their living areas. Children with a cough lasting longer than two weeks were referred to a higher-level center for X-ray examinations (6). Three patients who did not show clinical improvement or showed deterioration at the follow-up examination were referred to a higher-level center by road.

Treatment opportunities for scabies patients were limited due to conditions, but topical treatment was available.

For outpatient visits, the provision of medical treatment was facilitated by a mobile pharmacy. Patients were invited for repeated follow-ups during their treatment process.

DISCUSSION

Studies focusing on child nutrition in the immediate aftermath of disasters are exceedingly limited. The worsening of living conditions following a disaster and the escalation of medical care needs make the feasibility of academic studies challenging.

In this regard, we believe that this study, conducted in a limited timeframe following the earthquake and concerning child nutrition, offers valuable guidance.

The prioritization of trauma patients in the disaster region and the provision of healthcare predominantly by non-pediatric physicians resulted in disruptions in the monitoring of pediatric patients. Expert pediatricians evaluated each presenting case not only in terms of the immediate illness but also considered nutritional, psycho-social, and mental health aspects, in accordance with existing guidelines. This holistic approach was crucial for minimizing ongoing adversities and mitigating the emergence of new issues. This is especially pertinent given that child mortalities in disaster situations frequently occur not during the disaster itself but in the aftermath (7).

Weight-for-age is not an ideal index for screening or for assessing nutritional emergencies. However, it can be useful for tracking individual children over time, monitoring a child's development, or identifying a declining trend (6). In our study, we also used percentiles and standard deviations to evaluate the applicability of the weight-for-age parameter.

In the extant literature, there are publications that highlight the significance of infant nutrition during periods of disaster. Furthermore, the World Health Organization (WHO) has been formulating updated guidelines on this subject for an extended period of time. According to prior guidelines by the WHO, a study indicated that infants who are not breastfed have a six-fold higher risk of succumbing to infectious diseases within the first two months of life compared to those who are breastfed (8). Subsequent research over the years has consistently demonstrated that insufficient breast milk intake during times of disaster results in markedly adverse long-term outcomes (9).

In the earthquake-stricken regions, conditions were often not conducive for breastfeeding, complicating the prospects of exclusive breast milk feeding. Factors such as the psychological state of the mother, lack of privacy, and maternal malnutrition could precipitate declines in breast milk production and subsequent cessation of breastfeeding. On the other hand, the provision of formula milk and bottles to families with infants as a preventive measure can also negatively impact the continuation of breastfeeding (10). Moreover, there are publications indicating an association between unregulated formula distribution and the increased prevalence of diarrhea among infants (11). In such situations, ensuring that formula feeding is administered in the appropriate quantities and at the correct times becomes critically important (2).

During the 23rd to 30th day post-earthquake period in our study, there were no issues in accessing clean food. However, various factors can render weight loss inevitable even if clean food is accessible in the early phases. Publications exist that demonstrate a positive correlation between home damage, the sense of security, levels of post-traumatic stress disorder, and household size with skipping meals and reducing portion sizes after the earthquake (12). Failure to maintain a balanced diet post-disaster could be one reason for weight loss in children over the age of two. In the immediate aftermath of a disaster, most of the relief aid consists of basic food items. Also, it is often not feasible to purchase a variety of foods in the early stages. While this situation usually rectifies itself in later stages, the risk of growth stunting in children persists until such rectification occurs (13).

To address the need for psychological support, a specialized psychologist was appointed to the pediatric tent. Patients in need were evaluated during their examination in the tent and subsequently in their living areas.

Conversely, there exists literature indicating that children from economically disadvantaged backgrounds are more prone to nutritional deficiencies in the pre-disaster period (12). While our study did not yield statistically significant results on this aspect, we observed greater weight loss in patients who were in the normal percentile compared to those who were in the lower percentile prior to the earthquake. This could suggest that, during disaster periods, all children may be at risk, irrespective of their body weight and socioeconomic status.

In light of publications related to pre-disaster food supplies, emergency plans prioritizing children could circumvent many nutrition-related challenges in both the short and long term (14).

Disaster zones are high-risk areas for infectious diseases due to disrupted infrastructure, difficulties in accessing clean water and food, and crowded living conditions. All 80 patients included in our study presented with infectious diseases, with acute gastroenteritis being the most prevalent. This aligns with the study by Farfel et al. (15), which found a rate of 45% for gastroenteritis among infectious diseases. All patients were questioned about the camp they were living in from the perspective of potential outbreaks. Fortunately, no outbreaks occurred in the region in the early period.

The proportion of patients diagnosed with pneumonia was also consistent with the study by Farfel et al. (15). Guha-Sapir et al.'s (3) evaluation following the 2004 Indonesia tsunami also identified gastroenteritis and pneumonia as the two most frequent infections.

Of the patients included in the study, only 4 can be considered a success of the medical endpoint application for referral to an advanced center. On the other hand during patient transfers, social challenges emerged, such as the death of a parent or the family's desire to stay together. In such situations, increasing social resources is as important as providing psychological support.

Malnutrition and crowded living conditions make children susceptible to infections. Some of these infections (for example: measles, meningitis, polio) can be prevented with vaccines. Therefore, the rapid vaccination of children in disaster areas should also be part of emergency plans (2). Another

operational challenge in disaster-stricken areas pertains to the preservation of cold-chain-requiring medications such as vaccines and insulin. A refrigerator had been procured at the medical endpoint to meet the tetanus vaccine needs of trauma patients, but families were referred to higher-level centers for routine vaccinations. Given the potential for electricity-related issues, this aspect should be taken into consideration in post-disaster healthcare organization plans.

Limitations

Our study has several limitations. Firstly, the study was conducted in a specific region within a province affected by an earthquake. Patient diversity may vary in other regions. On the other hand, some of the patients who presented may have experienced weight loss due to illness. However, given that infectious diseases are highly likely in areas affected by earthquakes, such conditions may be considered typical under the present circumstances. Another limitations are the small sample size of the study and its single-center design and the absence of a control group due to the prevailing disaster conditions.

CONCLUSION

In order to minimize the detrimental impact of natural disasters on pediatric nutrition, emergency response plans should be designed with a comprehensive understanding of the potential healthcare needs of children. The expeditious dispatch of specialized pediatric medical teams to affected regions is paramount for both preventive medicine and effective management of pediatric illnesses.

Ensuring adequate and varied nutrition for children in the aftermath of disasters is essential for maintaining normal growth and developmental trajectories, as well as for mitigating the onset of diseases. Therefore, access to age-appropriate nutritional supplements is significant importance during such calamities. Moreover, safeguarding the integrity of the food supply chain, facilitating water accessibility, and maintaining hygienic conditions are critical factors in sustaining adequate nutrition. These aspects should be clearly delineated in post-disaster emergency planning frameworks.

Our study contributes an experiential narrative regarding pediatric care following a disaster. Conducting early post-disaster studies with broader populations will contribute to the development of emergency action plans.

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Reflections of Children Victims of the Turkey Earthquake on February 6, 2023 to a Pediatric Emergency Department Far Away

6 Şubat 2023 Türkiye Depremlerinde Mağdur Olan Çocukların Uzaktaki Bir Çocuk Acil Servise Yansımaları

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ABSTRACT

Objective: After the earthquake, which was called the 'Disaster of the Century', which affected 11 provinces in our country on February 06, 2023 we presented the reflection of the grievances of children who were not trapped under the rubble in a pediatric emergency clinic 700 km away from the region. This study was aimed to evaluate the pediatric 'earthquake victims' patients, who were not trapped under the rubble, applied to the pediatric emergency department (PED) of a tertiary care children's hospital.

Material and Methods: Between 7 February 2023 and 22 February 2023, the data of pediatric 'earthquake victims' who applied in the first 15 days after the earthquake to the PED of our hospital and were not trapped under the rubble, evaluated retrospectively. The admission times of the patients were divided into three groups as early, mid-term and late admissions. The age, gender, nationality, complaint and clinical characteristics of the patients, the province where they were exposed to the earthquake, the time from the moment of the earthquake to the application, the mode of transportation to the hospital diagnosis and treatments were recorded.

Results: The study included 719 earthquake victim children. Median age of patients was 49 months (IQR 16 – 105), 387 were male (53.8%). According to age classification, infancy (n=131; 18.2%), early childhood (n=192; 26.7%) and middle childhood (n=207; 28.8%) were the most frequent admissions. The first admission to our hospital after the earthquake was 19 hours later. Thirty five (4.8%) patients were applied due to accidents during the earthquake. The leading diagnoses of the patients applied were upper respiratory tract infection (URTI) (33.9%), acute gastroenteritis (14.4%) and otitis media (11.2%). Six hundred and sixty (91.8%) patients were discharged from the emergency department, 59 (8.2%) were hospitalized.

Conclusion: In the first days, while secondary accidents were at the forefront of the earthquake, in the following days, infections followed. Children are the most vulnerable group in disasters. For this reason, good planning should be done to deal with secondary accidents, infectious diseases and special medical conditions that may occur during the 'healing' period after disasters.

Key Words: Disaster, Earthquake, Emergency, Pediatric

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ÖZ

Amaç: Bu çalışmada üçüncü basamak bir çocuk acil servisine başvuran, enkaz altında kalmayan pediatrik 'deprem mağduru' hastaların değerlendirilmesi amaçlandı.

Gereç ve Yöntemler: 7 Şubat 2023 ile 22 Şubat 2023 tarihleri arasında hastanemize depremden sonraki ilk 15 gün içinde başvuran ve enkaz altında kalmayan pediatrik 'deprem mağdurlarının' verileri geriye dönük olarak değerlendirildi. Hastaların başvuru süreleri erken, orta ve geç başvurular olmak üzere üç gruba ayrıldı. Hastaların yaşı, cinsiyeti, uyruğu, şikâyeti ve klinik özellikleri, depreme maruz kaldıkları il, deprem anından başvuruya kadar geçen süre, hastaneye ulaşım şekli, tanı ve tedavileri kaydedildi.

Bulgular: Araştırmaya 719 depremzede çocuk katıldı. Hastaların ortalama yaşı 49 aydı (IQR 16 – 105), 387'si erkekti (%53.8). Yaş sınıflamasına göre infant (n=131; %18.2), oyun çocukluğu (n=192; %26.7) ve okul çocukluğu (n=207; %28.8) en sık başvuru yapılan yaş grubuydu. Depremden sonra hastanemize ilk başvuru 19 saat sonra gerçekleşti. Otuz beş (%4.8) hasta deprem sırasındaki kazalar nedeniyle başvurdu. Başvuran hastaların önde gelen tanıları üst solunum yolu enfeksiyonu (ÜSYE) (%33.9), akut gastroenterit (%14.4) ve orta kulak iltihabı (%11.2)'di. Hastaların 660'ı (%91.8) acil servisten taburcu edildi, 59'u (%8.2) hastaneye yatırıldı.

Sonuç: Depremin ilk günlerinde ikincil kazalar ön plana çıkarken, ilerleyen günlerde enfeksiyonlar takip etti. Afetlerde en savunmasız grup çocuklardır. Bu nedenle afet sonrası 'iyileşme' döneminde oluşabilecek ikincil kazalar, bulaşıcı hastalıklar ve özel tıbbi durumlarla başa çıkmak için iyi planlama yapılmalıdır.

Anahtar Sözcükler: Deprem, Felaket, Acil durum, Çocuk

INTRODUCTION

Disasters are events that negatively affect the health care system by causing mortality and serious morbidity. Türkiye is a country where natural disasters are frequently experienced due to its geological structure and climatic characteristics (1). In our country, which has witnessed high earthquakes throughout its history, on 06.02.2023, at 04:17 and 13:24 Turkish time, two earthquakes occurred with a magnitude of Mw 7.7 and 7.6 on the Richter scale, with the epicenters in Pazarcık (Kahramanmaraş) and Elbistan (Kahramanmaraş) (2). These two earthquakes, which occurred nine hours apart, affected 11 provinces in a wide area and attracted the attention of the whole world as the "Disaster of the Century". According to the official figures, more than forty-seven thousand people died and many were injured due to this disaster (3). Approximately 15 million people, 1.7 million of whom were foreign nationals, were victims of the earthquake and about 5 million of them were children (4,5). Children are the most vulnerable group in disasters.

After the first interventions of the earthquake victims who were rescued from the rubble were carried out in the nearest health institutions, the transfer of the patients to the surrounding provinces was ensured safely. After the earthquake, the people whose houses and workplaces were destroyed started to migrate to the surrounding provinces. Children who are exposed to earthquakes may have physical injuries due to being under the rubble, psychosocial factors should not be ignored after the earthquake as well. Factors such as exposure to cold weather due to the destruction of their homes, inadequate nutrition, increase in infectious diseases and inability to access clean drinking water can be cited among the non-traumatic effects of the earthquake on children (6). While there are many studies on trauma management in children under the rubble, studies evaluating the victimization caused by the earthquake are limited.

Our hospital is a tertiary pediatric hospital in Ankara, the Turkish capital, and approximately 700 km away from the earthquake zone. In this study, it was aimed to evaluate the pediatric 'earthquake victims' patients, who were not trapped under the rubble, applied to the pediatric emergency department (PED) of our Hospital.

MATERIALS and METHODS

Between 7 February 2023 and 22 February 2023, the data of pediatric 'earthquake victims' who applied to the PED of our hospital and were not trapped under the rubble, evaluated retrospectively. In the first 15 days after the earthquake, all patients aged 0-18 years who were not trapped under the rubble and who applied to the PED of our hospital were included. The age, gender, nationality, complaint and clinical characteristics of the patients, the province where they were exposed to the earthquake, the time from the moment of the earthquake to the application, the mode of transportation to the hospital (ambulance, own means), diagnosis and treatments were recorded. Cases of children who were trapped under the rubble were excluded from the study. Patients were grouped according to age using a standard classification (7). The admission times of the patients were divided into three groups as early, mid-term and late admissions (admission on days 0-5, between 6-10 days, between 11-15 days). Admission diagnoses were evaluated according to groups.

The study was approved by the local ethics committee with reference number Ankara Etlik City Hospital-EK1-2023-021.

Statistical analysis

Data analysis was performed using IBM statistical package for social sciences version 22 for Windows (SPSS Inc., Armonk, NY, IBM Corp., USA). Descriptive statistics were presented with frequency, percentage, mean, standard deviation, median, minimum (min) and maximum (max) or interquartile range (IQR)] values.

RESULTS

The study included 719 earthquake victim children. Median age of patients was 49 months (IQR 16 – 105), 387 were male (53.8%). According to age classification, infancy n=131 (18.2%), early childhood n=192 (26.7%) and middle childhood n=207 (28.8%) were the most frequent admissions (Table I). The main earthquake-affected provinces were Kahramanmaraş (n=216, 30%) and Hatay (n=197, 27.4%). While 698 children (97.1%) came with their own means, accompanied by a companion, 21 children (2.9%) were transferred from the earthquake zone by emergency ambulance.

The first admission to our hospital after the earthquake was 19 hours later. The median time from the earthquake exposure of the patients to the admission to our hospital was 9 days (min-max: 1day-15 days). 109 (15.2%) patients applied between 0-5 days, 439 (61.1%) patients applied between 6-10 days, and 171 (23.8%) patients applied between 11-15 days.

Thirty five (4.8%) patients were applied due to accidents (burns, falling objects while escaping, etc.) during the earthquake. The leading diagnoses of the patients applied in the first 5 days were upper respiratory tract infection (URTI) (24.3%), soft tissue injury (17.1%) and health check-up (13.5%); in the second 5 days URTI (37.1%), acute gastroenteritis (AGE) (14.4%) and acute otitis media (13.5%), in the third 5 days URTI (31.9%) and AGE (16.2%). The diagnoses of the patients according to the application days are given in Table II. Twenty (2.7%) patients applied for the treatment of chronic diseases such as intravenous immunoglobulin therapy, erythrocyte suspension transfusion, diabetes mellitus and epilepsy. Forty-two (5.8%) children applied for health check-up. Five (0.6%) patients applied with psychiatric problems that started due to the earthquake.

Six hundred and sixty (91.8%) patients were discharged from the emergency department, 59 (8.2%) were hospitalized. Three (0.4%) brothers received hyperbaric oxygen therapy due to carbon monoxide intoxication. One patient with a diagnosis of sickle cell anemia was applied because of cold-induced vaso occlusive crisis and received a transfusion of erythrocyte suspension. Three (0.4%) technology-dependent such as home mechanical ventilation patients were applied to the palliative care service for social reasons and followed up. One patient (0.1%) applied to get their glasses again because they were broken during the earthquake. Two patients (0.2%) were applied due to stray dog bites and were vaccinated against rabies.

All patients were consulted to the social services for identity check, accompaniment and post-medical care accommodation needs for patient safety during emergency service applications, and after the follow-up, they were discharged after taking the necessary measures in line with the functioning of the Ministry of Family and Social Policies in our country. 5 (0.6%) of the patients were consulted to child and adolescent mental health clinicians for psychiatric support.

Table I: Demographic characteristics of the patients and the provinces they were exposed to earthquakes

Age*	
Neonatal (Birth – 27 day)	39 (5.4)
Infancy (28 day – 12 month)	131 (18.2)
Toddler (13 month – 2 year)	54 (7.5)
Early Childhood (2 – 5 year)	192 (26.7)
Middle Childhood (6– 11 year)	207 (28.8)
Early adolescence (12- 18 year)	96 (13.4)
Gender*	
Female	332 (46.2)
Male	387 (53.8)
Nationality*	
Turkish	655 (91.1)
Refugee†	58 (8.1)
Unknown	6 (0.8)
Province*	
Kahramanmaraş	216 (30)
Hatay	197 (27.4)
Gaziantep	84 (11.7)
Malatya	81 (11.3)
Adıyaman	71 (9.9)
Şanlıurfa	27 (3.8)
Adana	22 (3.1)
Diyarbakır	14 (1.9)
Osmaniye	4 (0.6)
Elazığ	2 (0.3)
Mardin	1 (0.1)

:** *n(%),* **†:Patients from Syria, Iraq, Afghanistan*

DISCUSSION

It has been shown that children's basic and/or medical needs increase after sudden and unexpected natural disasters. Although patient management is well defined in publications related to earthquake survivors; data on children who are not trapped under the rubble are limited and planning for patient management and organization is insufficient (8). To the best of our knowledge this is the first study of 'earthquake victims' children who are not trapped under rubble.

While applications due to accidents that occurred during and after the earthquake were highest in the first five days, the frequency of applications for this reason gradually decreased in the following days. In the second five days after the earthquake, the number of patient admissions increased and infectious diseases came to the fore.

In addition to acute medical complications after disasters, an emergency disaster plan should also be prepared for health effects due to post-disaster displacement (9). Health care services may be inadequate for many reasons, such as physical damage to hospitals after an earthquake, personnel providing health care services are also earthquake victims and multiple individuals needing simultaneous medical care (10). Lack of

Table II: Diagnosis of the patients according to the application day

Diagnosis, n (%)	Total (n=719)	First 5 Days (n=111)	Second 5 Days (n=436)	Third 5 Days (n=172)
Upper Respiratory Tract Infection	244 (33.9)	27 (24.3)	162 (37.1)	55 (31.9)
Acute Gastroenteritis	104 (14.4)	13 (11.7)	63 (14.4)	28 (16.2)
Urinary Tract Infection	26 (3.6)	2 (1.8)	13 (2.9)	11 (6.3)
Otitis Media	81 (11.2)	7 (6.3)	59 (13.5)	15 (8.7)
Conjunctivitis	15 (2.0)	0 (0)	9 (2.0)	6 (3.4)
Lower Respiratory Tract Infection	59 (8.2)	7 (6.3)	35 (8.0)	17 (9.8)
Routine Health Checkup	42 (5.8)	15 (13.5)	19 (4.3)	8 (4.6)
Chronic Disease	20 (2.7)	3 (2.7)	11 (2.5)	6 (3.4)
Other*	65 (9.0)	13 (11.7)	33 (7.5)	19 (11)
Scabies	9 (1.2)	0 (0)	8 (1.8)	1 (0.5)
Soft Tissue Injury **	35 (4.8)	19 (17.1)	12 (2.7)	4 (2.3)
Social Reason Referral ***	19 (2.6)	5 (4.5)	12 (2.7)	2 (1.1)

***Constipation, arthritis, urticaria, carbon monoxide intoxication, psychological problems, foreign body aspiration, acute appendicitis, drug intoxication, preseptal cellulitis, lymphadenitis, dental abscess, inguinal hernia, animal bite, anal fissure, myalgia, dysmenorrhea, **Burns, domestic accidents, injury while escaping during an earthquake, ***Patients who were referred from another hospital in the disaster area because they did not have a parent.*

transportation and logistics are other important problems for medical needs (11). Although our hospital is a tertiary center that accepts intensive referral from the earthquake zone, it is quite far from the earthquake zone. Therefore, the first patient who applied to our hospital as a victim of earthquake could reach our hospital 19 hours later.

Secondary accidents during and after the earthquake in the first days constituted the more critical patient group. Unexpected home accidents, displacement, crowdedness and poor living conditions after an earthquake can lead to secondary emergencies such as environmental emergencies. In our study, burns developed in 2 children as a result of a house accident due to the earthquake. After the earthquake, 3 brothers who were exposed to the smoke of the stove they burned in order to warm up in their shelter, applied to our hospital with symptoms of carbon monoxide intoxication and received hyperbaric oxygen therapy. Secondary accidents and environmental emergencies that may occur after a disaster should be kept in mind; organizations should be made to plan healthy and safe shelter areas (12).

The data revealed that the majority of applications occurred between the 6th and 10th days, with the primary reason being infections. After a certain natural disaster, infectious diseases may occur after 4 days to 4 weeks of action, and an increase in respiratory tract infections, gastrointestinal, vector-borne diseases and skin infections is expected (13). Both emerging diseases and diseases that are already endemic in the affected area can spread and turn into epidemics. In addition, AGE, dehydration and related complications are likely to occur due to contamination of water resources (fecal contamination), contamination of water during transportation and storage, use of water and food containers together, insufficient soap and contamination of foods (14). In our study, 512 (71.3%) patients applied due to an infectious disease; 54 (10.5%) of these patients applied within the first five days, and 458 (89.5%) after five days. There were 104 cases of AGE developing in the first 14 days. Only 9 patients (1.2%) were diagnosed with scabies. This situation can be explained by the fact that we are a hospital far from the earthquake area and that these cases may have applied to the local health units there.

Household mechanical ventilators, oxygen concentrators and aspiration devices work with electricity. An unexpected increase may occur in the applications of technology-dependent children to the emergency service due to power cuts or inaccessibility to medical equipment after an earthquake (15). Addressing such complex medical needs is not included in emergency plans (16). However, health care providers should also pay attention to children with special health care needs and disabilities (17). These children with access and mobility difficulties, chronic illnesses or mental and developmental disabilities often depend on medications, medical equipments (for example, ventilators, suction devices, and infusion pumps), complex care plans and often electrical sources for support (18). Twenty patients who applied for complaints related to their chronic disease and 3 (0.4%) patients who required special technology-dependent care were referred to our hospital from the earthquake zone only for their care needs.

After the earthquake, children are not only affected physically, but also face many problems such as leaving the place they live, losing family members, communication, transportation and security (19). Children are the responsibility of the state; in addition to their health and rehabilitation, their protection is also important. In our study, 18 (2.5%) newborns were referred from another hospital in the disaster area for social reasons such as

loss of parents. Six patients had no identification information. All patients were consulted to the social services unit, since the parental information of the other patients who applied with a companion was ambiguous. Before discharge, necessary measures were taken in line with the functioning of the Ministry of Family and Social Policies in our country. In this way, it was aimed to reunite the victimized children with the surviving family members. Clinicians should be aware of security vulnerabilities and risks of child abduction in case of simultaneous intensive emergency patient applications such as natural disasters, and this should be taken into account in all child emergency department disaster planning (20).

Limitations

Our study is a retrospective, single-center study and has some limitations due to its nature. In this study, we evaluated the applications of a pediatric emergency service, which is quite far from the earthquake zone. However, many affected children may have received primary health care in the earthquake area, or children in serious need of treatment may not have reached remote areas or have no access to care at all.

CONCLUSION

After the earthquake, which was called the 'Disaster of the Century', which affected 11 provinces in our country on February 06, 2023 we presented the reflection of the grievances of children who were not trapped under the rubble in a pediatric emergency clinic 700 km away from the region. In the first days, while secondary accidents were at the forefront of the earthquake, in the following days, infections followed. Children are the most vulnerable group in disasters. For this reason, good planning should be done to deal with secondary accidents, infectious diseases and special medical conditions that may occur during the 'healing' period after disasters. In order to prevent the abduction of unidentified children and to reunite them with their families, patients must be urgently registered by the social services unit.

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Neonatal Outcomes in Different Maternal Diabetes Types: Experience from a Tertiary Care Unit

Farklı Maternal Diyabet Tiplerinde Yenidoğan Sonuçları: Üçüncü Basamak Yoğun Bakım Ünitesi Deneyimi

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ABSTRACT

Objective: Infants of mothers with diabetes (IMD) may require hospitalization in neonatal intensive care units (NICU) for various reasons. In our study, our objective was to compare clinical and laboratory findings, as well as malformations and morbidities among IMD based on the types of maternal diabetes.

Material and Methods: The diabetic status of mothers of 4713 infants admitted to tertiary neonatal intensive care unit (NICU) at Ankara Bilkent City Hospital between January 1, 2020, and January 1, 2022, was examined. We retrospectively analyzed demographic data, clinical and laboratory characteristics, and morbidities for 616 infants born to mothers with impaired glucose tolerance (IGT), gestational diabetes mellitus (GDM), or pre-existing gestational diabetes mellitus (Pre-GDM).

Results: Of the 616 cases, 167 (27.1%) were infants of mothers with IGT, 394 (64%) with GDM and 55 (8.9%) with Pre-GDM. The prevalence of macrosomia was significantly higher in Pre-GDM (30.9%) than in the IGT (15%) and GDM (19.3%) groups (p=0.033). The most common malformations in the cases were related to the cardiovascular system (CVS) (77.4%). The frequency of septal hypertrophy was significantly higher in the Pre-GDM group compared to the IGT and GDM groups, and in the GDM group compared to the IGT group (p<0.001). The rates of septal hypertrophy, CVS malformation, LGA/macrosomia, and hypocalcemia were found to be significantly higher in infants of mothers with insulin requirement and high HbA1c levels, particularly in Pre-GDM group (p<0.001). According to the ROC analysis for the optimum maternal HbA1c value predicting septal hypertrophy, the threshold value was found to be 6% (AUC=0.693) with 62% sensitivity and 66% specificity. In logistic regression analysis, macrosomia and maternal HbA1c ≥6% were determined as independent risk factors for the presence of septal hypertrophy.

Conclusion: Despite variations in the type of maternal diabetes, IMD experience significant clinical challenges when hospitalized and monitored in the NICU. Infants born to mothers with IGT may also be subjected to maternal hyperglycemia. The likelihood of certain complications rises in infants born to pregnant women with inadequate glycemic control, particularly those with elevated HbA1c levels. By ensuring maternal glycemic control and closely monitoring these infants, it is possible to reduce both mortality and morbidity.

Key Words: Congenital abnormalities, Gestational diabetes, Septal hypertrophy, Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus

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ÖZ

Amaç: Diyabetik anne bebekleri (DAB) farklı nedenlerle yenidoğan yoğun bakım ünitelerine (YYBÜ) yatırılarak izlenebilir. Çalışmamızda DAB'lerinde perinatal ve postnatal dönemde ortaya çıkan malformasyonların, izlemde eşlik eden morbiditelerin, klinik ve laboratuvar bulguların maternal diyabet tiplerine göre karşılaştırılması amaçlandı.

Gereç ve Yöntemler: Ankara Bilkent Şehir Hastanesi'nde 3. Düzey YYBÜ'de 01.01.2020 ile 01.01.2022 tarihleri arasında yatırılarak izlenen 4713 yenidoğanın annelerinin diyabet durumu incelendi. Annelerinde bozulmuş glukoz toleransı (BGT), gestasyonel diyabetes mellitus (GDM) veya Pre-GDM olan 616 yenidoğan retrospektif olarak incelendi.

Bulgular: Altıyüzonaltı vakanın 167'si (%27.1) BGT'li, 394'ü (%64) GDM'li, 55'i (%8.9) Pre-GDM'li anne bebeğiydi. Makrozomi sıklığı Pre-GDM'de (%30.9), BGT (%15) ve GDM (%19.3) gruplarına göre anlamlı derecede yüksekti (p=0.033). Vakalarda en sık görülen malformasyonlar kardiyovasküler sistem (KVS) (%77.4) ile ilgiliydi. Septal hipertrofi sıklığı Pre-GDM'de BGT, GDM gruplarından, GDM grubunda da BGT grubundan anlamlı (p<0.001) olarak daha yüksekti. İnsülin ihtiyacı olan ve HbA1c düzeyi yüksek olan özellikle Pre-GDM'li anne bebeklerinde septal hipertrofi, KVS malformasyonu, LGA/makrozomi, hipokalsemi görülme oranları anlamlı olarak yüksek saptandı (p<0.001). Septal hipertrofiyi öngören optimum maternal HbA1c değeri için yapılan ROC analizi sonucuna göre %62 duyarlık ve %66 özgüllük ile eşik değer %6 (AUC: 0.693) olarak bulundu. Lojistik regresyon analizinde yenidoğanda makrozomi ve HbA1c ≥ %6 olması septal hipertrofi varlığı için bağımsız risk faktörü olarak belirlendi.

Sonuç: Maternal diyabet tipindeki farklılığa rağmen YYBÜ'ye yatırılarak izlenen diyabetik anne bebeklerinde ciddi klinik sorunlar yaşanmaktadır. BGT'li annelerin bebekleri de maternal hiperglisemiye maruz kalabilir. Glisemik kontrolü bozuk olan özellikle de HbA1c değeri yüksek gebelerden doğan bebeklerde potansiyel olarak bazı sorunların görülme sıklığı artmaktadır. Maternal glisemik kontrol sağlanarak ve bu bebekler yakın takip edilerek mortalite ve morbidite azaltılabilir.

Anahtar Sözcükler: Konjenital anomali, Gestasyonel Diyabet, Septal hipertrofi, Tip 1 Diyabetes Mellitus, Tip 2 Diyabetes Mellitus

INTRODUCTION

Diabetes Mellitus (DM) refers to a group of metabolic diseases that progress with increased blood sugar (1). If the diagnosis of DM is detected for the first time during pregnancy, it is called gestational diabetes mellitus (GDM), and if it is present before pregnancy, it is called pre-existing gestational diabetes mellitus (Pre-GDM) (2). It is one of the common complications of pregnancy and its frequency is increasing. Women diagnosed with pre-GDM or GDM are at increased risk for pregnancy complications compared to other pregnant women (3). Maternal hyperglycemia is thought to be the most important teratogen. Controlling diabetes before pregnancy and monitoring it throughout pregnancy is important to reduce the effects of diabetes on the fetus and newborn (4). Potential complications should be aware of the management of infants of diabetic mothers (IMD), and common problems that cause these infants to be admitted to the neonatal intensive care unit should be anticipated. In our study, we aimed to evaluate the IMD who were followed up in 3rd level neonatal intensive care unit (NICU) and to compare their accompanying morbidities and clinical and laboratory findings according to the types of maternal diabetes.

MATERIALS and METHODS

The diabetic status of mothers whose infants were admitted and monitored in the tertiary NICU at Ankara Bilkent City Hospital from January 1, 2020, to January 1, 2022, was examined. Our NICU is located at a hospital where approximately 16,000 births take place annually. It is a specialized tertiary-level NICU affiliated with a perinatal center. It is designed to handle the most complex and critical neonatal cases. It has the capability to perform neonatal surgeries and provides post-operative care for newborns with congenital anomalies. It is a center with approximately 2000 admissions annually. Demographic data, follow-up morbidities, and clinical and laboratory characteristics of IMD and their mothers were retrospectively evaluated. The exclusion criteria comprised infants with incomplete data, those born to mothers without diabetes, and those who did not undergo GDM screening during prenatal care follow-up.

Throughout the study period, a total of 4713 patients were hospitalized in the NICU. However, 226 patients who were referred to our hospital were excluded from the study due to the unavailability of their data. In our analysis, the oral glucose tolerance test (OGTT) and hemoglobin A1c (HbA1c) results of the mothers from 4487 cases with accessible data were evaluated. The results of both two-stage and one-stage screening for gestational diabetes mellitus (GDM) were analyzed retrospectively.

Mothers exhibiting impaired plasma glucose levels identified through a 50 g oral glucose solution test, yet registering a sole elevated value in the 100 g oral glucose tolerance test (OGTT), were assigned to the 'impaired glucose tolerance group' (IGT). In the two-stage approach, mothers were classified into the gestational diabetes mellitus (GDM) group if their 1st hour plasma glucose (PG) exceeded 180 mg/dl with 50 g glucose or if PG ranged between 140-179 mg/dl with 50 g, along with two elevated values in the 100g OGTT. Additionally, in the one-stage approach, mothers with a single elevated value in the 75 g OGTT were also considered part of the GDM group. Mothers with a documented diagnosis of Type 1 or Type 2 diabetes mellitus before pregnancy were categorized into the Pre-GDM group. Those who displayed impaired plasma glucose levels detected by the 50 g oral glucose solution but declined to undergo the 100g OGTT, as well as those who exhibited elevated HbA1c levels but refused any form of OGTT, were also included in the IGT group.

A total of 616 newborns, born to mothers with IGT, GDM, or Pre-GDM, were enrolled in the study. Detailed examination of the infants' demographic characteristics, clinical issues, and laboratory data was conducted utilizing the electronic patient information system, and the findings were documented in the study form. The study also recorded maternal diabetes types, diabetes control status, and demographic characteristics. Comprehensive data analyses were performed both collectively and by making comparisons between different groups.

The study was approved by the Ankara Bilkent City Hospital clinical research ethics committee no. 2 (23.08.2023/E2-23-4767).

Statistical analysis

Mean, standard deviation, median, minimum, maximum, frequency and percentages were used in descriptive statistics of the data. Distribution of variables was measured with the Kolmogorov-Simirnov test. Kruskal-Wallis and Mann-Whitney u test were used in the analysis of quantitative independent data. Chi-square test was used in the analysis of qualitative independent data, and Fischer test was employed when chi-square test conditions were not met. IBM Statistical Package for the Social Sciences, version 27.0 (SPSS Inc., Armonk, NY, IBM Corp., USA) software was used in the analyses. The results were considered statistically significant for p <0.050 in the analyses conducted in this study.

RESULTS

Out of 4713 infants hospitalized during the study period, maternal data of 4487 infants were obtained; 167 (3.7%) had IGT, 394 (8.7%) had GDM, 38 (0.84%) had Type 2 DM, 17 (0.37%) had Type 1 DM and 3871 were healthy. Demographic characteristics of mothers and infants were analyzed according to maternal diabetes type (Table I). Maternal preeclampsia rate was significantly higher in the Pre-GDM (18.2%) group compared to the IGT (4.8%) and GDM (6.1%) groups (p=0.002).

Clinical problems and laboratory findings that may be observed in cases according to the type of maternal diabetes were analyzed (Table II). The frequency of macrosomia was found to be significantly higher in the Pre-GDM group (30.9%) compared to the IGT (15%) and GDM (19.3%) groups (p=0.033).

When the infants were grouped according to the diabetes control status of their mothers, the incidence of macrosomia, hypomagnesemia and hypocalcemia was found to be significantly higher in the insulin-requiring group compared to those who were regulated with diet alone (p<0.001). In infants with macrosomia and hypomagnesemia, the HbA1c values of their mothers were significantly higher (p<0.001).

There was no difference in terms of gastrointestinal system (GIS), central nervous system (CNS) and cardiovascular system (CVS) malformations in the study groups. There were a total of 83 (13%) cases with genitourinary system (GUS) malformations. In the GDM group, GUS anomalies were significantly higher than in the IGT group (p=0.048). Hydronephrosis (10%) was the most common type of GUS anomaly.

The incidence of CVS malformations was similar between the study groups (90.7% in Pre-GDM, 79% in GDM, 75.3% in IGT) (Table III).

TableI: Demographic characteristics of mothers and infants according to maternal diabetes type

	IGT (n=167)	GDM (n=394)	Pre-GDM (n=55)	p
Maternal age*	30 (26- 35)	32 (26-36)	33 (28-39)	0.026
Gravida*	2 (1-3)	2 (1-4)	3 (2-4)	0.126
Preeclampsia†	8 (4.8)	24 (6.1)	10 (18.2)	0.002
Hypertension†	8 (4.8)	36 (9.1)	8 (14.5)	0.056
Hypothyroidism†	15 (9)	46 (11.7)	11 (20)	0.088
Maternal HbA1c‡	5.9 (4.5-7)	5.7 (4.3-9.5)	7.15 (5.3-11.5)	<0.001
Maternal Diabetes Control				
Diet†	167 (100)	277 (70.3)	7 (12.7)	<0.001
Diet and Insulin†	0 (0)	117 (29.7)	48 (87.3)	<0.001
C/S†	135 (80.8)	330 (83.8)	49 (89.1)	0.347
Gestational age*	35 (33-38)	35 (33-37)	35 (32-36)	0.219
Male Gender†	91 (54.5)	247 (62.7)	31 (56.4)	0.165
Multiple Pregnancy†	26 (15.6)	59 (15)	2 (3.6)	0.064
Birth weight*	2590 (1860-3260)	2660 (1818-3190)	2690 (1920-3390)	0.761
LGA†	25 (15)	76 (19.3)	17 (30.9)	0.033
SGA†	19 (11.4)	55 (14)	5 (9.1)	0.484

:** *median (IQR),* **†:** *n(%),* **‡:** *median (min-max),* ***IGT: *Impaired Glucose Tolerance,* ***GDM:*** *Gestational Diabetes Mellitus,* ***Pre-GDM:*** *Pregestational Diabetes Mellitus,* ***IQR:*** *Interquartile range,* ***HbA1c:*** *Glycosylated hemoglobin A1c,* ***C/S:*** *Caesarean section,* ***LGA:*** *Large for gestational age,* ***SGA:*** *Small for gestational age*

Table II: Clinical and laboratory findings in infants according to maternal diabetes type

	IGT* (n=167)	GDM* (n=394)	Pre-GDM* (n=55)	p
Macrosomia	25 (15)	76 (19.3)	17 (30.9)	0.033
Fetal Growth Restriction	20 (12)	56 (14.2)	5 (9.1)	0.500
Preterm birth	104 (62.3)	263 (66.8)	42 (76.4)	0.154
Respiratory Distress	128 (76.6)	316 (80.4)	50 (90.9)	0.070
TTN	56 (33.5)	157 (40.2)	21 (38.2)	0.337
RDS	30 (18.1)	96 (24.6)	10 (18.2)	0.177
Pneumonia	16 (9.8)	34 (8.8)	6 (11.1)	0.839
PHT	11 (6.7)	20 (5.2)	3 (5.7)	0.790
Pneumothorax	4 (2.4)	13 (3.4)	4 (7.4)	0.557
EOS	82 (50)	189 (48.8)	34 (61.8)	0.196
LOS	34 (20.7)	85 (22.1)	14 (25.9)	0.727
Birth injury	0 (0)	3 (0.8)	0 (0)	0.558
Asphyxia	11 (6.7)	15 (3.9)	5 (9.3)	0.147
Portal Vein Thrombosis	2 (1.2)	5 (1.3)	2 (3.7)	0.936
Syndromic Infant	3 (1.8)	11 (2.8)	0 (0)	0.743
Feeding Intolerance	10 (6.1)	41 (10.6)	2 (3.7)	0.086
NEC	3 (1.8)	9 (2.3)	1 (1.9)	0.706
Hydrops fetalis	3 (1.8)	1 (0.3)	0 (0)	0.892
Hypoglycemia	27 (16.4)	53 (13.7)	12 (21.8)	0.251
Polycythemia	27 (16.3)	71 (18.3)	10 (18.2)	0.850
Thrombocytopenia	16 (9.6)	45 (11.6)	7 (12.7)	0.745
Anemia	7 (4.2)	23 (5.9)	3 (5.5)	0.721
Hyperbilirubinemia	123 (75.5)	290 (75.3)	47 (87)	0.156
Hypocalcemia	87 (53)	199 (51.7)	39 (72.2)	0.017
Hypomagnesemia	10 (6.1)	33 (8.6)	9 (16.7)	0.058

***:** *n(%),* ***IGT:** *Impaired Glucose Tolerance,* ***GDM:** *Gestational Diabetes Mellitus,* ***Pre-GDM:** *Pregestational Diabetes Mellitus,* ***TTN:** *Transient Tachypnea of the Newborn,* ***RDS:** *Respiratory Distress Syndrome,* ***EOS:** *Early Onset Sepsis,* ***LOS:** *Late Onset Sepsis,* ***PHT:** *Pulmonary Hypertension,* ***NEC:** *Necrotizing enterocolitis*

Table III: CVS malformations according to maternal diabetes type

	IGT* (n=167)	GDM* (n=394)	Pre-GDM* (n=55)	p
Septal Hypertrophy	5 (3)	53 (13.8)	14 (25.9)	<0.001
PDA	58 (35.2)	127 (33)	23 (42.6)	0.370
PFO	85 (51.5)	225 (58.4)	36 (66.7)	0.111
ASD	55 (33.3)	102 (26.5)	17 (31.7)	0.242
VSD	11 (6.7)	26 (6.8)	2 (3.7)	0.689
TGA	0 (0)	1 (0.3)	0 (0)	0.892
AoC	1 (0.6)	2 (0.3)	0 (0)	0.988
LVH	1 (0.6)	4 (1)	0 (0)	0.979
TOF	1(0.6)	3 (0.8)	0 (0)	0.986
Aortic Stenosis	0 (0)	1 (0.3)	0 (0)	0.899

***:** *n(%),* ***IGT:** *Impaired Glucose Tolerance,* ***GDM:** *Gestational Diabetes Mellitus,* ***Pre-GDM:** *Pregestational Diabetes Mellitus,* ***PDA:** *Patent Ductus Arteriosus,* ***PFO:** *Patent Foramen Ovale,* ***ASD:** *Atrial Septal Defect,* ***VSD:** *Ventricular Septal Defect,* ***TGA:** *Transposition of great arteries,* ***AoC:** *Aortic coarctation,* ***LVH:** *Left ventricular hypoplasia,* ***TOF:** *Tetralogy of Fallot*

Table IV: Independent risk factors for the development of septal hypertrophy

	OR	95% CI	p
LGA	4.5	2.3-8.7	<0.001
HbA1c≥ 6	2.26	1.15-4.46	0.018

CI: *confidence interval*

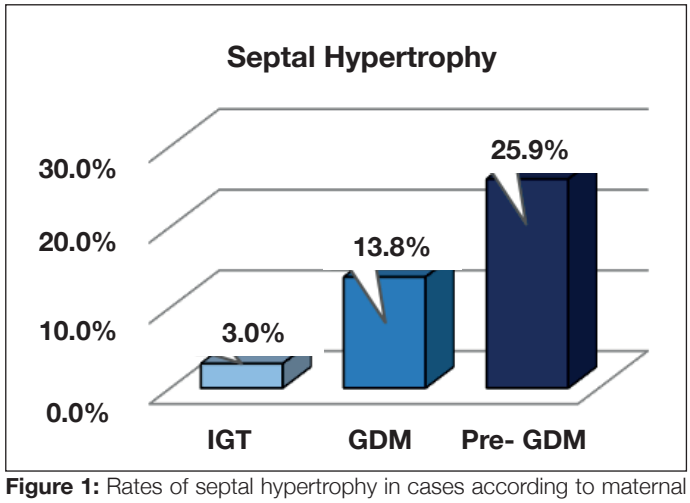

Figure 1: Rates of septal hypertrophy in cases according to maternal diabetes type.

IGT: Impaired Glucose Tolerance, **GDM:** Gestational Diabetes Mellitus, **Pre-GDM:** Pregestational Diabetes Mellitus

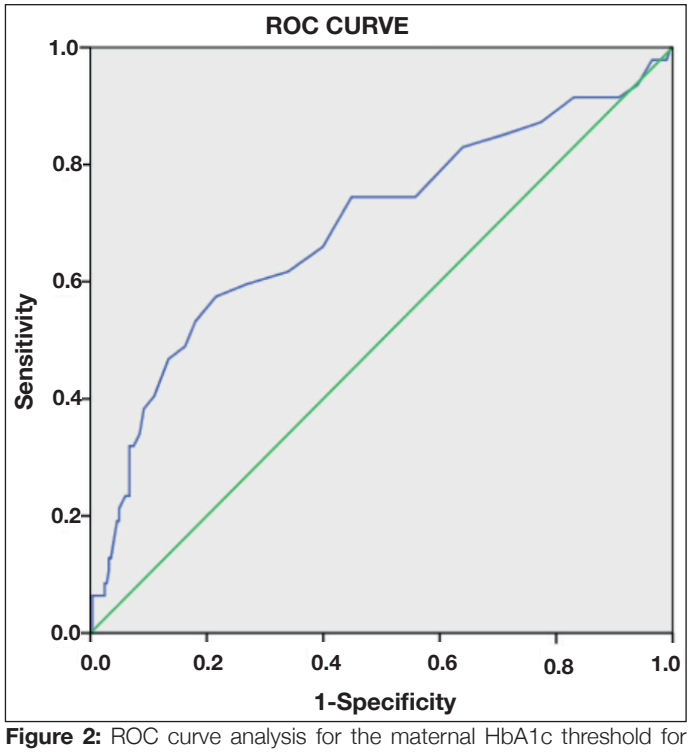

Figure 2: ROC curve analysis for the maternal HbA1c threshold for predicting septal hypertrophy.

In our study, the rate of septal hypertrophy in the Pre-GDM group was found to be significantly higher than the other groups (Figure 1). When all cases were compared based on the diabetes management approach in mothers, the incidence of CVS malformation, septal hypertrophy and PFO was significantly higher in the insulin-regulated group compared to the diet-regulated group (p<0.001). At the same time, HbA1c values of mothers were significantly higher in infants with septal hypertrophy and CVS malformations (p<0.001 and 0.007, respectively).

According to the ROC analysis for the optimum maternal HbA1c value predicting septal hypertrophy, the threshold value was found to be 6% (AUC=0.693) with a sensitivity of 62% and specificity of 66% (Figure 2).

In multivariate logistic regression analysis, macrosomia and maternal HbA1c ≥ 6% were determined as independent risk factors for the presence of septal hypertrophy (Table IV).

DISCUSSION

In our study, we observed that IMD who were hospitalized in the NICU frequently encountered similar clinical issues, regardless of the specific type of maternal diabetes. Higher rates of septal hypertrophy, CVS malformation, large for gestational age (LGA)/ macrosomia, and hypocalcemia were noted in infants born to mothers with elevated HbA1c levels and insulin requirements, particularly within the pre-GDM group.

A significant association was found between a HbA1c value of 6% and the occurrence of septal hypertrophy. Furthermore, it was demonstrated that having an HbA1c level of 6% or higher approximately doubled the risk of septal hypertrophy.

Congenital anomalies observed in infants of mothers with gestational DM and Type 2 DM have been reported to affect the same organ systems as those previously identified in pregnancies with Type 1 diabetes. High levels of hyperglycemia in mothers have been shown to lead to an increased risk of abnormalities in general (5,6). When the congenital malformations seen in IMD were examined in our study, it was determined that the same organ systems were affected in the IGT, GDM and Pre-GDM groups. This also suggests that the IGT group may be undiagnosed GDM patients.

In a study conducted in Canada between 2002 and 2010, involving approximately 2.3 million infants, a strong association was demonstrated between Type 1 or Type 2 DM and the risk of congenital heart disease (7). In our study, the rate of CVS malformation, septal hypertrophy, and PFO was found to be significantly higher in the group that needed insulin for diabetes control compared to the group that was regulated only by diet. When the literature is examined, it has been shown that the risk of septal hypertrophy is higher in infants of mothers with Pre-GDM than in infants of mothers with GDM (8). Septal hypertrophy is associated with fetal hyperinsulinism. High blood sugar levels in the mother cause fetal hyperglycemia, which in turn leads to fetal hyperinsulinemia. The anabolic effects of insulin can cause fetal macrosomia by increasing the amount of total body protein, glycogen and fat, as well as cellular

hypertrophy and hyperplasia in internal organs such as the heart and interventricular septum (9,10). In a retrospective study in which newborns diagnosed with congenital heart disease during hospitalization and follow-up between 2013 and 2017 were evaluated, septal hypertrophy was reported in 20.6% of IMD (11). In our study, the frequency of septal hypertrophy was 11.7% in all groups, but it was found to be 25.9% in Pre-GDM, 13.8% in GDM, and 3% in IGT. Septal hypertrophy rate was found to be significantly higher in the Pre-GDM group than in the IGT and GDM groups, and in the GDM group than in the IGT group. It is usually a benign and transient pathology in IMD. This condition usually has no clinical manifestations and is often detected incidentally during routine echocardiographic examination.

Due to standardization challenges and uncertainty regarding diagnostic thresholds, HbA1c has not been recommended as a diagnostic tool for diabetes for many years. Individuals with IGT or HbA1c levels ranging from 5.7% to 6.4% are noted to have prediabetes. The HbA1c cut-off point determined for the diagnosis of diabetes in the guidelines is accepted as 6.5% (12). In the presence of hemoglobinopathy or in situations that accelerate the erythrocyte life cycle (recent bleeding or blood transfusion, pregnancy, hemodialysis, erythropoietin treatment, etc.), HbA1c test is not preferred as a reliable diagnostic tool for the diagnosis of diabetes. We also found it to be high in infants of mothers with Pre-GDM in our study. In our study, we determined the optimal maternal HbA1c value predicting the presence of septal hypertrophy in infants born to mothers with Pre-GDM as 6%. We also identified that HbA1c ≥ 6% was an independent risk factor for the presence of septal hypertrophy.

When GDM mothers and their infants were retrospectively examined by Bai et al. (13), it was demonstrated that as the severity of OGTT abnormalities increased, the risk of fetal macrosomia also increased. In a study conducted by Persson et al.(14), it was shown that being an infant of a mother with Type 1 diabetes mellitus increased the risk of macrosomia. In a multicenter study conducted between 2000 and 2006, involving 23.316 pregnant women to examine the outcomes of maternal hyperglycemia, a strong relationship between hyperglycemia and increased birth weight was demonstrated. In infants of mothers with DM, the incidence of fetal macrosomia or LGA varies between 15-45% compared to 5-15% observed in the general population (15, 16). In a study investigating the effect of maternal hyperglycemia on macrosomia, a positive relationship was reported between increased maternal HbA1c and risk of macrosomia (17). In our study, consistent with the literature, the incidence of LGA was 19.2% in all groups, but the rate of macrosomia or LGA in the Pre-GDM group was found to be significantly higher than in the IGT and GDM groups. In our study, the significantly higher maternal HbA1c value in the Pre-GDM group suggests that infants are exposed to hyperglycemia for a longer period of time, which increases the incidence of macrosomia.

Our study's retrospective design and the single-center nature were identified as limitations. Infants of non-diabetic mothers could not be included in our study. Our data should also be evaluated considering the large number of mothers who did not undergo GDM screening during pregnancy follow-up processes.

In conclusion, the presence of comparable clinical issues and congenital malformations across both groups suggests that infants born to mothers with IGT are similarly exposed to maternal hyperglycemia. Vigilant monitoring during the postnatal period is essential for infants of mothers with IGT. Given that close perinatal and postnatal follow-up is believed to potentially reduce mortality and morbidity, it becomes crucial to educate mothers about potential conditions. The incidence of certain complications rises in pregnant women with inadequate glycemic control, particularly with elevated HbA1c levels, and affects infants born from such pregnancies. Further research supporting the significance of oral glucose tolerance tests should be undertaken.

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Characteristics of Drug Hypersensitivity Reactions in Children: A Retrospective Analysis in an Allergy Outpatient Clinic

Çocuklardaki İlaç Aşırı Duyarlılık Reaksiyonlarının Özellikleri: Alerji Polikliniğinde Retrospektif Analiz

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ABSTRACT

Objective: Confirmation of drug hypersensitivity reactions (DHRs) is crucial—as various nonallergic reactions, such as viral infections, in children can mimic such reactions. This study aimed to evaluate the characteristics of children with suspected DHRs applying to an allergy outpatient clinic.

Material and Methods: This study involved children who visited our hospital's pediatric allergy outpatient clinic between April 1 and December 31, 2023, with suspected DHRs . The data of patients analyzed retrospectively. Patient demographics, reaction characteristics, culprit drugs, diagnostic procedures (including skin and/or provocation tests), and final diagnoses were recorded.

Results: The study included 163 reactions of 140 patients with 176 suspected drugs. The median age was 7.7 years (interquartile range [IQR]; 5.1–12 years), with an equal gender distribution. Notably, 27.1% of the patients presented with concurrent atopic diseases. The median age at the onset of reaction was 72 months (IQR; 34.5–108 months), with 16% of reactions occurring within hospital settings and the remainder at home. Oral administration accounted for 84.7% of the reactions, with antibiotics being the most common culprit drug group (75.5%). Immediate reactions constituted 41.1% (n = 67) of reactions, while delayed reactions accounted for 58.9% (n = 96). Skin symptoms were predominant (97.5%). DHRs were excluded in 75.5% (n = 123) of reactions but confirmed by diagnostic drug allergy tests in 4.9% (n = 8).

Conclusion: A through evaluation of suspected DHRs in children is essential. Despite high suspicion rates, confirmation via diagnostic tests was low, emphasizing the need for referral to specialized clinics and appropriate diagnostics for accurate management.

Key Words: Antibiotic allergy, Drug allergy, Drug hypersensitivity reactions

ÖZ

Amaç: Çocuklardaki viral enfeksiyonlar gibi alerjik olmayan çeşitli reaksiyonlar ilaç hipersensitivite reaksiyonları (İHR)'yi taklit edebildiğinden, ilaca aşırı duyarlılık reaksiyonlarının (İADR) doğrulanması çok önemlidir. Bu çalışma, alerji polikliniğine İADR şüphesi ile başvuran çocukların özelliklerini değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntemler: Çalışmaya 1 Nisan 2023-31 Aralık 2023 tarihleri arasında hastanemiz çocuk alerji kliniği'ne İADR şüphesi ile başvuran çocuk hastalar dahil edildi. Hasta verileri retrospektif olarak analiz edildi. Hastanın demografik verileri, reaksiyon özellikleri, şüpheli ilaçlar, uygulanan tanısal testler (deri ve/veya provokasyon testleri) ve reaksiyonların nihai tanıları kaydedildi.

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

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Bulgular: Çalışmaya 140 hastanın 176 süpheli ilaç ile olan 163 reaksiyonu dahil edildi. Ortanca yaşları 7.7 yaş (Çeyrekler Arası Aralık [ÇAA]; 5.1-12) ve cinsiyet dağılımı eşitti. Hastaların %27.1'inde eşlik eden diğer atopik hastalık mevcuttu. Reaksiyon ortaya çıkış yaş ortancası 72 ay (ÇAA; 34.5-108 ay)'dı. Reaksiyonların %16'sı hastanede, %84'ü hastane dışında gelişirken; ilaçların % 84.7'si oral yolla alınmıştı. En sık sorumlu ajanlar antibiyotiklerdi (%75.5).Reaksiyonların %41.1'i (n=67) erken, %58.9'u (n= 96) ise geç tip reaksiyondu. En sık cilt semptomu (%97.5) görüldü. Reaksiyonların %75.5'inde (n=123) İHR ekarte edildi; %4.9'unda (n=8) ilaç alerjisi tanısal testler ile doğrulandı.

Sonuç: Çocuklarda şüpheli İADR'nin ayrıntılı bir şekilde değerlendirilmesi önemlidir. Yüksek şüphe oranlarına rağmen tanı testleri ile doğrulama oranı düşüktü; bu da doğru yönetim için uzman kliniklere yönlendirmenin ve doğrulanmış tanıların gerekliliğini vurgulamaktadır.

Anahtar Sözcükler: Antibiyotik alerjisi, İlaç alerjisi, İlaç aşırı duyarlılık reaksiyonları

INTRODUCTION

Adverse drug reactions (ADRs) are unpredictable and dose-independent reactions caused by drugs (1). ADRs are divided into two main groups: allergic (IgE and non-IgE) and nonallergic. Allergic reactions include reactions that occur strictly through immunological pathogenesis, with prevalence varying by age and country (1). The prevalence of pediatric drug hypersensitivity reactions (DHRs) in the literature is approximately 10%, and a small proportion of these reactions have been found to be associated with confirmed drug allergies (2). According to recent studies, DHRs can be confirmed in only 4.4%–6.9% of patients with suspected drug allergies (3–5). The most common culprit drugs for drug allergies in the pediatric population are beta-lactam antibiotics, followed by nonsteroidal anti-inflammatory drugs (NSAIDs) and non-beta-lactam antibiotics (3,5).

DHRs can occur in a wide clinical spectrum from a mild rash to severe anaphylaxis or life-threatening drug reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis (6). However, not every clinical finding is related to DHRs; some nonallergic reactions, such as viral infections, can mimic DHRs (7-9). Therefore, for admissions due to DHRs, it is crucial to exclude other possible causes and confirm such reactions. For DHR diagnosis, a detailed history, physical examination, and appropriate allergological tests (skin tests, specific IgE measurement, and/or drug provocation tests [DPTs]) are necessary (6,7).

Incorrect labeling of a child with a DHR may lead to less-effective, more harmful, and more expensive alternative drug treatments. Conversely, DHR underdiagnosis may cause the same or a more severe reaction when the same drug is taken (10). Hence, identifying and confirming DHRs is important for improving public health, clinical practices, and socioeconomic load. To confirm DHRs, patients with suspected DHRs should be referred to pediatric allergy clinics, and diagnostic allergological drug tests should be performed. This study aimed to retrospectively analyze the evaluation of children with suspected DHRs in an allergy outpatient clinic and contribute valuable insights to the literature.

MATERIALS and METHODS

Study Population

A total of 140 children (<18 years old) who admitted to Ankara Training and Research Hospital Pediatric Immunology and Allergic Diseases Clinic with suspicion of DHRs between April 1and December 31, 2023, were included in the study, retrospectively.

Sociodemographic characteristics of the patients, accompanying allergic disease/atopy status, family history of allergic disease and drug allergy, characteristics of the suspected allergic reaction, symptoms occurring at the time of the reaction, and information about the suspected drug (drug use duration and last dose at the time of the reaction, as well as route of administration) were recorded retrospectively in the data record form.

The diagnostic tests performed (skin and/or provocation tests), the final diagnoses of the reactions and the recommendations given to the patients were retrieved from the electronic records and also recorded in the data record form.

The study was approved by the Ankara Training and Research Hospital Ethics Committee (decision number: E-24-40).

Classification of reactions

Reactions were classified mainly based on the time of onset. Reactions occurring within 1 hour after drug intake were considered immediate reactions, and reactions occurring >1 hour later were considered delayed reactions (11). Reactions that occur with NSAIDs are exceptionally classified as immediate reactions, even if they occur within the first 6 hours, depending on the reaction character (7). Anaphylaxis and its severity were defined according to the European Academy of Allergy and Clinical Immunology (EAACI) anaphylaxis criteria (10).

Identification of the culprit drugs

Suspected drugs were defined as those taken in less than 1 hour before reaction onset for patients with immediate reaction findings (1–6 hours for NSAID reactions), after 1 hour, and within the last ≥1 day for patients with maculopapular exanthema.

Diagnostic Work-up

Diagnostic tests were performed based on national and international guidelines (2,4). Diagnostic tests were performed 4–6 weeks after nonsevere drug reactions. For patients with

chronic diseases, testing was performed within the first year after they became clinically stable and eligible for diagnostic testing. Diagnostic tests were not performed on patients who developed anaphylaxis, those who do not need to take the responsible drug in the near future, and those for whom consent could not be obtained. Patients with immediate reactions other than anaphylaxis were tested using skin prick and intradermal testing with the suspected drug(s). Provocation tests were performed only if these tests were negative. Direct provocation tests were applied to patients with delayed reactions.

Skin Tests

Skin tests were performed as skin prick and intradermal tests using the doses recommended in the national guide and EAACI guidelines (12,13). Antihistamines and other medications that may affect the results of skin tests were discontinued at least 1 week before testing (7,12,13).

Drug provocation tests

National and EAACI-ENDA guidelines were used to determine indications, contraindications, and application of DPT (12,14). If any reaction (urticaria, angioedema, respiratory symptoms, vomiting, or hypotension) occurred during the DPT, the test was immediately terminated, managed appropriately, and considered positive, confirming DHR diagnosis.

Final recommendations given to patients

We advised patients whose diagnostic drug test results were negative or who used the suspicious drugs later without any reaction that they could reuse such drugs. For patients with positive diagnostic drug test results, we advised they could no longer use the implicated drugs. We advised patients whose tests had not been completed or who had not been tested that they should not use the suspect drugs until their diagnostic tests are completed.

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences version 22.0 (IBM Corp., Armonk, NY). Categorical values were presented as frequency and percentages. Continuous numerical values were not normally distributed and were presented as the median and interquartile range (IQR;25th–75th percentiles). A p-value <0.050 was considered significant.

RESULTS

Characteristics of patients

This study comprised 163 reactions to 176 drugs from 140 patients, with 50% being male. The median age was 7.7 years (IQR: 5.1–12 years). Table I shows the characteristics of the patients.

Characteristics of reactions

Of the 140 patients, 121 experienced a single reaction, while 15 patients reacted to different drugs at different times, resulting in a total of 163 distinct reactions. Of these 163 reactions, 152 involved a single suspected drug, 9 involved 2 different types of culprit drugs, and 2 involved 3 different suspected drugs. Therefore, this study identified a total of 176 suspected drugs.

The median age at the reaction was 72 months (IQR; 34.5–108 months). Eighty-four percent (n = 137) of the reactions

Table I:Demografic characteristics of patients (n:140)

Age (Month)-median (IQR*)	7.7 (5.1-12)
Gender (male)†	70 (50)
Other Atopic Diseases†	38 (27.1)
Asthma	19 (13.6)
Allergic Rhinitis	22 (15.7)
Atopic Dermatitis	1 (0.7)
Previous DHR history†	13 (9.3)
DHR history of family†	3 (2.1)
Atopic Diseases of family†	13 (9.3)

***IQR:** Inter Quartile Range, **†:** n(%), **DHR:** Drug Hypersensitivity Reaction*

Table II: Characteristics of reactions, n:163

Age at reaction (month)*	72 (34.5-108)
Type of reactions†	
Delayed type	96 (58.9)
Immediate type	67 (41.1)
Anaphylaxis	18 (11)
Symptoms during reactions†	
Dermatologic	159 (97.5)
Respiratory	14 (8.6)
Gastro-intestinal	6
Neurological	6
Cardio vascular	1
Time interval between reaction and admission, month*	5 (0.5-24)
Places which reaction occured†	
Home	137 (84)
Hospital	26 (16)
Administration Routes of Drugs†	
Oral	138 (84.7)
Intravenous	16 (9.8)
Intramuscular	6 (3.7)
Subcutaneous	3 (1.8)
Dosage of drugs at the reactions*	1 (1-6)
Types of culprit drugs (Total number of drug used in 163 reactions = 176)†	
ANTİBİOTİCS	
Betalactam	123 (69.8)
Penicillin	109 (61.9)
Aminopenicillin	8 (4.5) (
Amoxicillin clavulanic acid	83 (47.1)
Ampicillin	79 (44.8)
Sulbactam ampicillin	2 (1.1)

Table II: Characteristics of reactions, n:163	
Cephalosporins	2 (1.1)
Ceftriaxone	16 (9)
Cefixime	6 (3.4)
Cefuroxime axetil	5 (2.8)
Cefazolin	2 (1.1)
Cefdinir	2 (1.1)
Meropenem	1 (0.6)
Trimethoprim Sulfamethoxazole	1 (0.6)
Non-Betalactam	14 (7.9)
Macrolides	9 (5.1)
Clarithromycin	7 (3.9)
Azithromycin	2 (1.1)
Other	5 (2.8)
Vancomycin	1 (0.6)
Gentamycin	1 (0.6)
Amikacin	1 (0.6)
Ciprofloxacin	1 (0.6)
Unknown	1 (0.6)
NSAID	36 (20.4)
Paracetamol	15 (8.5)
Ibuprofen	17 (9.6)
Other	4 (2.3)
Dexketoprofen	2 (1.1)
Metamizole	1 (0.6)
Diclofenac sodium	1 (0.6)
Others	17 (9.6)
Local Anesthetics	5 (2.8)
General Anesthetics	1 (0.6)
Myorelaxan	1 (0.6)
Vitamin D	2 (1.1)
Iron Supplements	3 (1.7)
PPI	2 (1.1)
Prednisolone	1 (0.6)
Antipsychotics	1 (0.6)
Methylphenidate	1 (0.6)

***:** *Median (IQR),* **†:** *n(%),* ***IQR:** Inter Quartile Range,* ***NSAID:** Non-steroid anti-inflammatory drug,* ***PPI:** Proton Pump Inhibitor, Selective serotonin reuptake inhibitors*

occurred at home, and 16% (n = 26) occurred at the hospital. While 84.7% of the drugs were given via the oral route, 9.8% were given intravenously. The most common symptom was dermatological symptoms (96.9%). While 41.1% (n = 67) of the reactions were immediate, 58.9% (n = 96) were delayed. Anaphylaxis was detected in 18 (11%) of those with early reactions. Reaction characteristics are given in Table II.

Culprit drugs

The most common suspected drug group was antibiotics (n = 118, 72.4%), followed by NSAIDs (n = 31, 23%). Figure 1 presents the distribution of drugs.

Diagnostic work-up

During the diagnostic process, 116 DPTs (113 of which were via the oral route) and 70 skin tests were performed. Consequently, DHRs were confirmed in 8 (5.7%) patients (5 with intradermal tests and 3 with DPTs), while drug reactions were excluded in 123 patients (Table IV). Diagnostic testing is ongoing for

Table III: Characteristic of the patient with confirmed drug allergy						
Patient	**Age***	**Gender**	**Culprit drug**	**İnitial reaction symptoms**	**İnitial reaction type**	**Diagnostic tests**	**Alternative drug**
1	5.5	M	Methylprednisolone	Acute Cyanosis (in a minutes)	Immediate	Prick: negative, intradermal: positive	Deltacortil (prick negative, intradermal negative, OPT negative)
2	8	M	Lidocaine	Angioedema	Immediate	Prick: negative, intradermal: positive	Prilocain (prick negative, intradermal negative, subcutan provocation test negative)
3	7.5	M	Articaine	Angioedema	Immediate	Prick: negative, intradermal: positive	Prilocain (prick negative, intradermal negative, subcutan provocation test negative)
4	6	M	Ibuprofen	Angioedema	Immediate (15 minutes)	OPT: positive (at 2,5 hour, angioedema at right eye)	Paracetamol (since he has already used paracetamol without experincing any reaction, testing was not conducted)
5	6.5	F	Paracetamol	Urticaria+angioedema	Immediate	Prick: negative, intradermal: positive	Ibuprofen opt pozitif Diagnostic tests are continue
6	10	M	Paracetamol	Angioedema (recurrent history)	Delayed (at 24 hour)	OPT: positive (at 2 hour angioedema + urticaria)	Ibuprofen OPT negative
7	2.5	M	CAM	MPE	Delayed (4 hour)	OPT: positive (urticaria at 2. Dosage of OPT)	Macrolid (since he has already used macrolides without experincing any reaction, testing was not conducted)
8	11	F	Ceftriaxone	Urticaria, itching of throat, dyspnea (anaphylaxis)	Immediate	Prick: negative, intradermal: positive	Penicilin V/G, amoksisilin sIgE negative CAM OPT negatif

***:** *Age at reaction,* ***CAM:** Amoxicillin clavulanic acid,* ***F:** Female,* ***M:** Male,* ***OPT:** Oral provocation test,* ***MPE:** maculopapular exanthema*

TableIV: Allergological test and their results n (% of 163 reactions)	
Allergological tests*	
Skin tests	70 (42.9)
Prick	36 (22)
Intradermal	34 (20.8)
Specific IgE	3 (1.8)
Provocation tests	116 (71.1)
Oral	113 (69.3)
Subcutaneous	3 (1.8)
Last status of DHR based on allergological tests*	
Confirmed (tests were positive)	8 (4.9)
Excluded (tests were negative)	123 (75.5)
Tests were ongoing	32 (19.6)
Patients with determinated Alternative drugs*	21 (12.9)
Advices for patients*	
Can use again, tests were completed	116 (70.6)
Can use again, allergological tests were unnecessary (because had been given same drug without any reaction)	7 (4.3)
Can't use again, because tests were positive	8 (4.9)
Shouldn't be used again until tests would be completed	32 (19.6)

:** *n(%),* ***DHR: *Drug Hypersensitivity Reaction*

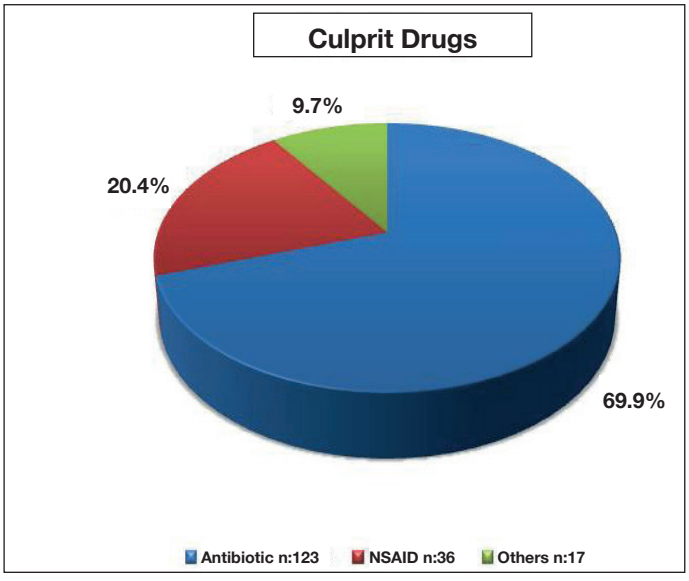

Figure 1: Distribution of culprit drugs.

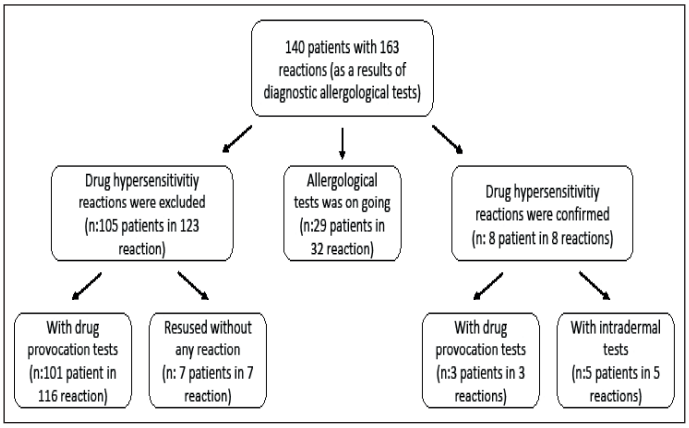

Figure 2: Last status of drug hypersensitivity reactions based on the allergological tests.

32 patients, and alternative treatment was determined for 21 patients with DPTs. The diagnostic approach is summarized in Figure 2, and the allergological work-up is depicted in Table III.

DISCUSSION

This study evaluated the diagnostic approach applied to children suspected with DHRs in the pediatric allergy outpatient clinic, and a DHR diagnosis was confirmed in only 4.9% of the reactions based on the results of diagnostic drug allergy tests.

The true prevalence of DHRs in children is not clearly known because the results of several studies in the literature were not confirmed by drug allergy tests, implying some of these results may include drug side effects (15). While approximately 10% of parents report that their children have DHRs, DHRs can be confirmed in only a very small number of them with drug allergy tests (2). In Capanoglu et al.'s (15) study , while 7% of parents stated that their children had DHRs, only 1.47% of them were suspected of having DHRs based on allergologists' evaluations, and drug allergy could be confirmed in 0.05% of them with the drug allergy tests. In another study, while the frequency of drug allergy was found to be 7.8% according to family declaration in secondary school students with an average age of 12.9 years, it was reported that this rate decreased to 1.16% after detailed anamnesis, and the frequency of drug allergy confirmed after diagnostic drug allergy tests was found to be 0.11% (5).

Milosevic et al. (16) reported that DHRs could be confirmed in 4.4% of patients presenting with suspicion of DHRs. Similarly, in our study, drug allergy could be confirmed in 4.9% of the reactions with drug allergy tests. The most important reason why the rates of confirmed DHRs in our study and Milosevic et al.'s (16) study are higher than those of other previous studies is because while the study population in both studies consisted of patients referred by another physician with suspicion of DHRs for applying to the allergy clinic, other studies adopted more of a population screening design. Moreover, the increase in the frequency of drug allergies over the years may be a secondary reason.

The low frequency of confirmed DHRs in studies conducted in patients presenting with suspected DHRs emphasizes the importance of diagnostic drug tests (15,16). Because many untested children with suspected DHRs may be incorrectly identified with drug allergy labels, which may lead to the unnecessary use of broad-spectrum, less-effective, and/or more expensive medications. This may increase the risk of antibiotic resistance and economic burden at both the individual and population levels (17,18) .

DHRs are most commonly reported with antibiotics and NSAIDs (15,19). In our study, antibiotics and NSAIDs were the most frequently reported suspicious drugs by families. In addition to the frequent use of these drugs in this age group (children), the fact that antibiotics can be used especially for viral infections

may be an important reason for the relevant situation. While viral infections themselves can often cause various rashes, less commonly, they can increase the allergenicity of some drugs through various immunological pathways (9). Therefore, it is recommended that drug allergy tests be performed to rule out these conditions. In Dibek Mısırlıoglu et al.'s (8) study, it was reported that rash developed in 16.6% of children who received antibiotics during Epstein-Barr virus infection, but when patients with rashes were evaluated with allergy tests, drug allergy was confirmed in only 3 (15%) patients. Therefore, drug testing in children is important to prevent over- or underdiagnosis because rashes caused by viral infections can lead to DHR overdiagnosis in children. On the other hand, real DHRs attributed to viral infections and not tested lead to DHR underdiagnosis.

Although the most common symptom in pediatric patients presenting with DHRs is dermatological findings, isolated other system findings or anaphylaxis can be seen. Milosevic et al. (16) reported that 96.2% of patients with suspected DHRs had skin findings, but and also extracutaneous findings had a statistically significant relationship with a positive allergy test. there weren't any skin findings in only 4 (2.4%) reactions, while and 18 (11%) reactions were anaphylaxis. It should be noted that DHRs may develop without skin findings so as to prevent more serious reactions and even mortality.

Based on drug allergy tests, patients are told that they can or cannot reuse the responsible drugs. Such patients should be informed about alternative drugs they can use when needed. Therefore, diagnostic testing may be sometimes required to determine alternative medications (15). In our study, alternative drugs were determined for 21 patients through DPTs. DHR drug identity were issued to the patients with confirmed DHRs.

CONCLUSION

The diagnostic approach for patients presenting to the pediatric allergy clinic with suspicion of DHRs indicates that DHR diagnosis is confirmed at a low rate based on drug allergy tests. Hence, referring pediatric patients with suspected DHRs to allergy clinics and performing diagnostic allergological examinations are crucial for preventing over-and underdiagnosis of DHRs in children. In addition, it is important to perform diagnostic tests to determine alternative drugs for cases diagnosed with confirmed DHRs

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Sodium Taurocolate Cotransporting Polypeptide Mutation Associated Transaminase Elevation

Sodyum Taurokolat Taşıyan Polipeptit Mutasyonuna Bağlı Transaminaz Yüksekliği

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ABSTRACT

Familial hypercholanemia-2 is a condition caused by mutations in the human solute carrier family 10 member 1 (SLC10A1) gene, which results in the inability to transport conjugated bile salts from plasma to hepatocytes. This is due to the sodium taurocholate cotransport polypeptide encoded by the gene being affected. Although the gene was first described in 1994, there is limited knowledge on the clinical features of the disease. In the few reported cases, both clinical and laboratory findings have varied. We reported a twelve-year-old girl was diagnosed with familial hypercholanemia-2 through a whole gene exome sequencing study. She was brought in with asymptomatic hypertransaminasemia, and after comprehensive studies on etiology failed to detect the cause, genetic testing was done. The patient had no clinically abnormal findings but had hypercholanemia (bile acid level 81.9 µmol/L) (fasting < 10 µmol/L, postprandial < 15 µmol/L) and hypertransaminasemia in laboratory examinations.

It is believed that the disease can present with a wide range of phenotypes, and laboratory findings may differ between patients depending on the underlying genetic mutation or mechanisms that have not yet been identified. Therefore, it is recommended to expand diagnostic genetic examinations in patients with hypertransaminasemia whose cause cannot be determined.

Key Words: Bile acids and salts, Cholestasis, Hypercholanemia, Sodium taurocholate cotransporting polypeptide

ÖZ

Ailesel hiperkolanemi-2, SLC10A1 genindeki mutasyonların neden olduğu, konjuge safra tuzlarının plazmadan hepatositlere taşınmasındaki bozukluk ile sonuçlanan bir durumdur. Bunun nedeni, etkilenen gen tarafından kodlanan sodyum taurokolat kotransport polipeptididir. Gen ilk olarak 1994 yılında tanımlanmış olmasına rağmen hastalığın klinik özelliklerine ilişkin bilgiler sınırlıdır. Bildirilen birkaç vakada da hem klinik hem de laboratuvar bulguları farklılık göstermiştir. Bu yazımızda; tüm ekzon dizi analizi çalışmasıyla; ailesel hiperkolanemi-2 tanısı alan on iki yaşında bir kız hastayı sunuyoruz. Asemptomatik hipertransaminazemi nedeniyle getirilen hastaya, etiyolojiye yönelik kapsamlı çalışmalar sonucunda nedenin belirlenememesi üzerine genetik temelli tanı testleri yapıldı. Klinik olarak asemptomatik olan hastanın, laboratuvar incelemelerinde hiperkolanemi (safra asidi düzeyi 81.9 µmol/L) (açlık < 10 µmol/L, tokluk < 15 µmol/L) ve hipertransaminazemi mevcuttu.

Hastalığın çok çeşitli fenotiplerle ortaya çıkabileceği ve altta yatan genetik mutasyon veya henüz tanımlanamayan mekanizmalara bağlı olarak laboratuvar bulgularının hastalar arasında farklılık gösterebileceği düşünülmektedir. Bu nedenle nedeni belirlenemeyen hipertransaminazemili hastalarda tanısal genetik incelemelerin yaygınlaştırılması önerilmektedir.

Anahtar Kelimeler: Safra asitleri ve tuzları, Kolestaz, Hiperkolanemi, Sodyum taurokolat birlikte taşınan polipeptit

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INTRODUCTION

Familial hypercholanemia-2 (FHCA2) is a rare condition that affects the way bile salts are transported into the liver. It is caused by a mutation in the human SLC10A1 gene, which codes for the Sodium taurocholate cotransporting polypeptide (NTCP) protein (1). The disease has a genetic basis and is usually found in people with homozygous or compound heterozygous mutations in this gene. However, there is limited knowledge about the disease's symptoms and characteristics. The reported cases show different clinical presentations. In this article, we present and discuss a pediatric patient who was diagnosed with familial hypercholanemia type 2 after being examined for hypertransaminasemia.

CASE REPORT

A 12-year-old girl complained about abdominal pain and fatigue in May 2017 and was taken to the pediatrics outpatient clinic. During examination, it was discovered that her ALT (alanine transaminase) was 78 U/L (normal range: 10-60 U/L) and AST (aspartate transaminase) was 44 U/L (normal range: 10-55 U/L). A follow-up examination conducted one week later revealed that her ALT had increased to 192 U/L, while her AST had increased to 93 U/L. As a result, she was referred to the pediatric gastroenterology outpatient clinic for further examination. The patient had no history of liver disease or any other specific medical conditions, and there was no such condition in her family medical history. Her height was 158 cm (75-90 percentile) and her weight was 50 kg (75-90 percentile). There were no pathological findings during the abdominal and other system examinations. During laboratory examinations, the patient's hemoglobin level was measured at 13.2 g/dl (10.3-14.9 g/dl), white blood cell count level was 7900/mm^3, and platelet level was 380.000/mm^3. The patient's INR (international normalized ratio) was 1 (0.8-1.2). In routine biochemistry examinations, total bilirubin measured at 0.6 mg/dl (0.2-1.3 mg/dl), while direct bilirubin level was 0.13 mg/dl (0-0.2 mg/dl), and gamma glutamyl transferase level was 80 U/L (5-55 U/L). In the lipid profile, total cholesterol was 179 mg/dl (<170 mg/dl), low-density lipoprotein cholesterol was 121 mg/dl (<110 mg/dl), high-density lipoprotein cholesterol was 41 mg/dl (40-85 mg/dl), and triglycerides measured at 83 mg/dl (30-130 mg/dl). In examinations for the etiology of hypertransaminasemia, viral hepatitis markers were detected as follows: HBsAg (hepatitis B surface antigen) nonreactive, anti HIV (human immunodeficiency virus) nonreactive, anti HBs reactive (861.7 mIU/mL), and anti HCV (hepatitis C virus) nonreactive. Ceruloplasmin measured at 0.31 g/L (20-63 mg/dl), while 24-hour urine copper was 15 µg (<40 µg). No Kayser-Fleischer ring was detected in the eye examination. Anti-tissue transglutaminase IgA and IgG were negative. TSH (thyroid stimulating hormone) measured at 1.1 mIU/Ml, T4 measured at 0.91 ng/dl, IgG measured at 1227 mg/dl (579-1610), and IgA measured at 182 mg/dl (27-198). ANA (antinuclear antibody), anti-dsDNA (double-stranded DNA antibody), AMA (anti-mitochondrial antibody), ASMA (anti-smooth muscle antibody), LKM (liver kidney microsomal antibody) results were negative. Metabolic evaluation tests were within normal limits. AFP (Alpha fetoprotein) level was measured at 10ng/ml (0-14 ng/ml), and alpha-1 antitrypsin level was measured at 100 mg/dl (90-200 mg/dl). Bile acid level was detected as 81.9 µmol/L (0-10 µmol/L). The patient underwent a whole abdominal ultrasonographic examination in radiological examinations, which turned out to be normal. However, during follow-up in July 2019, the patient's AST and ALT levels increased to 117 and 229, respectively, after a liver biopsy. During the biopsy, few lymphocytes were observed scattered individually in the liver tissue, along with minimal reactive changes in hepatocytes. However, there was no evidence of portal inflammation, bile duct damage, or iron/bile/alpha 1 antitrypsin, which could have suggested a chronic hepatic process. As the liver biopsy did not provide any clear diagnostic findings, a whole exome sequencing was conducted. The genetic study identified a homozygous mutation in the SLC10A1 gene, which encodes the NTCP protein associated with FHCA-2. No other mutation was detected during the genetic examination.

DISCUSSION

Liver transaminases are enzymes that are present in low levels in the plasma. In children, elevated levels of these enzymes can be caused by various reasons. Bile salts play a crucial role in digesting fats in the small intestine. They are formed when cholesterol undergoes enzymatic steps in the liver. The transport of conjugated bile salts from the plasma into the hepatocyte is carried out by the main carrier protein known as sodium taurocholate cotransporting polypeptide. On the other hand, the non-sodium-dependent bile salt transporter is responsible for the transport of unconjugated bile salts to the hepatocyte. This protein belongs to the SLC10A1 solute carrier family and provides uptake from the basolateral membrane by cotransporting two Na+ molecules for every one bile salt from the basolateral membrane (2). This process is crucial for enterohepatic circulation. NTCP deficiency is a condition that needs to be identified early as it can cause damage to hepatocytes and bile ducts. The first case of NTCP deficiency was reported in 2015 by Vaz et al. (3). The patient had clinical hypotonia, growth retardation and motor delay with significant hypercholanemia. However, the patient had no clinical pruritus or jaundice, and their serum bilirubin and bile acid levels were normal, and their liver functions were unaffected. In another study by Tan et al. (4), two monozygotic female twin cases with transient neonatal cholestasis that resolved at seven months of age were presented. It was reported that NTCP deficiency may cause transient neonatal cholestasis in early infancy. Dong and

their team have presented clinical and histopathological data of 13 patients with NTCP deficiency (5). Eight patients experienced visible jaundice and twelve patients had hyperbilirubinemia. Mild chronic inflammation was observed in all eleven patients who underwent biopsy. The researchers concluded that diagnosing NTCP deficiency is crucial, as it can result in both hepatocellular and biliary histological involvement. In another study, Zou et al. (6) reported a patient with NTCP deficiency who experienced self-limiting conjugated bilirubin elevation. Additionally, Lin et al. (7) reported that they discovered NTCP deficiency in three patients with cholestatic liver disease as a result of citrine deficiency. Despite the cholestasis symptoms improving with appropriate treatment, their hypercholanemia persisted. It seems that our patient didn't exhibit any noticeable symptoms but was found to have high liver enzyme levels without high bilirubin levels. The patient did not exhibit the typical symptoms of hypotonia, growth retardation, motor delay, itching, jaundice or transient cholestasis in the neonatal period that have been reported in other cases. This highlights that NTCP deficiency in childhood can occur without any noticeable clinical symptoms. After examining the lab results, it was found that our patient did not have high bilirubin levels, which are often present in reported cases. It was also noted that plasma bile acid levels varied between patients. In our patient, bile acid levels were significantly elevated at 81.9 µmol/L (<10 µmol/L), which is over eight times higher than normal. The diagnosis was made based on the laboratory results which showed elevated levels of transaminases. It has been observed in the literature that there are no cases of asymptomatic hypertransaminasemia patients who have been examined and diagnosed. Therefore, the case we are presenting here is a valuable addition to the literature as a new presentation of NTCP deficiency (5). In our patient, the liver biopsy showed sparse lymphocytes scattered singly in the parenchyma and minimal reactive changes in hepatocytes. It has been reported in the literature that almost all NTCP patients have minimal chronic inflammation findings in liver biopsy. The biopsy findings in our case are partially similar to the results reported in the literature, thus supporting the knowledge that histopathologically mild changes are observed in the liver in NTCP deficiency. We examined all possible causes of hypertransaminasemia in our patient and ruled out other causes. The diagnosis was made by detecting a homozygous mutation in the SLC10A1 gene in the whole exome sequencing.

CONCLUSION

Our research shows that NTCP plays a crucial role in maintaining bile salt balance, and its deficiency can cause persistent hypercholanemia in children. The findings suggest that the disease can manifest in different ways and laboratory results may vary among patients. It is believed that these differences might be due to genetic mutations or other unidentified factors. More comprehensive research is needed to determine the long-term effects of this newly discovered genetic disease on bile acid transport. Additionally, genetic testing should be expanded to diagnose patients with hypertransaminasemia of unknown origin.

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Neurogenic Bladder: A Rare Autonomic Sign in a Patient with Preserved Speech Variant of the Rett Syndrome (Zappella Variant)

Nörojen Mesane: Konuşmanın Korunduğu Rett Sendromlu (Zappella Varyanti) Bir Hastada Nadir Bir Otonomik Belirti

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ABSTRACT

Rett syndrome is characterized by the loss of speech and purposeful hand movements, ambulation problems, and typical hand stereotypies. Preserved speech variant of the Rett syndrome (Zappella Variant) is a much less common form where speech is relatively preserved. We aimed to emphasize neurogenic bladder due to autonomic dysfunction in a patient with preserved speech variant of the Rett syndrome.

A 7-year-old female patient who had been diagnosed with severe neurogenic bladder when 11 months old was suspected of suffering from Rett syndrome after observing intense eye contact and the stereotypic movement of hand wringing. The patient could talk with phrases, can walk, and have purposeful hand movements. The presence of the c.961C>T (p.Arg321Trp) heterozygous mutation in the C terminal region of the methyl-CpG-binding protein 2 (*MECP2*) gene was demonstrated. The patient is currently 13 years old. She continues to be monitored for chronic renal disease.

The presence of hand stereotypies and intense eye pointing could indicate the Zappella variant Rett syndrome since the patient has developmental problems, even though the patient can talk and has purposeful hand skills. The development of intermittent urinary retention associated with neurogenic bladder caused by autonomic dysfunction should be considered in these patients.

Key Words: Autonomic dysfunction, Neurogenic bladder, Preserved speech variant, Rett syndrome, Zappella variant

ÖZ

Rett sendromu, konuşma ve anlamlı el hareketlerinin kaybı, yürüme sorunları ve tipik el stereotipleri ile karakterizedir. Konuşmanın korunduğu Rett sendromu varyantı (Zappella Variant), çok daha az yaygın bir formdur. Konuşmanın korunduğu varyant Rett sendromlu bir hastada otonomik disfonksiyona bağlı nörojenik mesaneyi vurgulamayı amaçladık.

Onbir aylıkken şiddetli nörojenik mesane tanısı konulan 7 yaşındaki kız hastada, yoğun göz teması ve basmakalıp el ovuşturma hareketi gözlemlendikten sonra Rett sendromundan şüphelenildi. Hasta cümlelerle konuşabiliyor, yürüyebiliyor ve amaçlı el hareketleri yapabiliyordu. *MECP2* geninin C terminal bölgesinde c.961C>T (p.Arg321Trp) heterozigot mutasyonunun varlığı gösterildi. Hasta şu anda 13 yaşında olup kronik böbrek hastalığı açısından takip edilmeye devam etmektedir.

Gelişimsel sorunları olan, el sterotipileri ve yoğun göz teması varlığı ile Rett sendromu tanısı almış hastalarda konuşma ve amaçlı el becerilerinin korunmuş olması Zappella varyantı Rett sendromuna işaret edebilir. Bu hastalarda aralıklı idrar retansiyonu gelişiminin otonomik tutuluma bağlı nörojenik mesane ile ilişkili olabileceği akılda tutulmalıdır.

Anahtar Kelimeler: Otonom fonksiyon bozukluğu, Nörojen mesane, Konuşmanın korunduğu variant, Rett sendromu, Zappella variant

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INTRODUCTION

Rett syndrome (MIM: 312750, ORPHA: 3095) is a neurodevelopmental disorder characterized by the loss of speech and purposeful hand movements, ambulation problems, and emerging typical hand stereotypies (1). It is one of the most common genetic reasons of intellectual and developmental delay in girls with an incidence rate of 1 in 10.000 (2). Girls with typical Rett syndrome present with a regression period characterized by the loss of speech and motor functions that result in intellectual disability and typical hand stereotypic movements, following a relatively normal neurodevelopmental period in the first 6 to 18 months of life (3). The preserved speech variant is a clinically milder form of Rett syndrome. Autistic behavior is common and this variant has frequently been associated with the p.Arg133Cys mutation or C terminal deletion (4, 5).

Loss of function mutations in the *MECP2* gene are known to play a role in more than 90% of typical Rett syndrome patients and up to 75% of the Zappella variant patients. The best known function of the *MECP2* gene is to regulate the transcription of multiple genes through repression or promotion after binding to methylated DNA (6). *MECP2* contributes to the normal development and function of the central nervous system by regulating neuronal development and synaptic and cellular plasticity (6).

Autonomic dysfunction is quite common in Rett syndrome patients, without regard to the location and type of the mutation (7,8). These patients suffer from a severe imbalance between sympathetic and parasympathetic activity due to a very immature vagal tonus and various resultant autonomic problems such as hyperventilation, apnea, breath holding, shallow respiration, prolonged QT intervals, reduced heart rate variability, dysphagia, constipation, abdominal bloating, neurogenic bladder, mood disorders, sleep disorders, and cold and blue extremities caused by peripheral circulatory disorders (9,10).

Although there are many studies on autonomic dysfunction involving various organ systems in Rett syndrome, there are only a few publications on neurogenic bladder and the related problems. This study focuses on a very rare combination of an early onset severe neurogenic bladder, vesicoureteral reflux, and secondary hydronephrosis in a patient with Zappella variant of Rett syndrome developing due to a missense mutation in the C terminal region of the *MECP2* gene.

CASE REPORT

A 7-year-old female patient presented to the pediatric neurology department for epileptic seizures. The patient borned via spontaneous vaginal birth following an uncomplicated delivery from non-consanguineous parents. Her mother reported that the patient had started to walk when she was 2 years old and had started to talk when 5 years old. She had undergone a vesicostomy procedure for neurogenic bladder plus fourth grade vesicoureteral reflux when she was 11 months old due to her inability to urinate. This had been followed by bladder augmentation and the initiation of clean intermittent catheterization. The seizures has first started in this period of illness and she was still on dual antiepileptic treatment. The head circumference was 50 cm (50th percentile) on neurological examination. Excessive activity, echolaly, hand wringing type stereotyped movements of the hand, and intense eye contact were noted. She could form sentences of two or three words, respond in a meaningful manner to questions, and count to five. She has been receiving special education for cognitive impairment. The brain magnetic resonance imaging (MRI) was normal except slightly thick corpus callosum. The spinal MRI, echocardiography, and electrocardiogram (ECG) results were normal. Urinary ultrasound sonography (USG) revealed that the kidney parenchyma on both sides had thinned to a point that could not even be measured in many places and all collecting systems were markedly dilated to include both extrarenal pelvises, calyxes, and ureters in a manner that was consistent with grade 5 hydroureteronephrosis.

Following the consent of the family, the patient's DNA was extracted from peripheral blood lymphocytes. All the exons and exon-intron boundaries of the *MECP2* gene were sequenced by the Sanger method on ABI PRISM 3130 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). A heterozygous missense c.961C>T (p.Arg321Trp) variant was detected in exon 3 of the *MECP2* (NM_001110792.2) gene. The variant was replaced in a mutational hotspot region of the gene (PM1). The variant was not found in healthy populations (PM2) whereas it was submitted as likely pathogenic to the Clinvar database before (PP5). So the variant is classified as likely pathogenic in the light of these criteria. Also her mother was tested for *MECP2* gene pathology but no pathogenic change was found.

The patient was 13 years 6 months old at the last visit and had not suffered from seizures during the last year. She could read and write in syllables but could not perform simple arithmetic calculations. She had problems due to her aggressive behaviors and she sometimes laughed inappropriately. The patient's serum creatinine level was 1.14 mg/dl and urea level was 39 mg/dL at her last visit. Her estimated GFR (glomerular filtration rate) was 71 ml/min/1.73 m^2 revealing grade 2 chronic renal disease. She was followed by the pediatric nephrology department for neurogenic bladder and chronic renal disease. She has been performing intermittent self-catheterization and has been receiving prophylactic antibiotics.

Written informed consent to publication of the case report was received from the family.

DISCUSSION

The patient presented to the pediatric neurology department with epileptic seizures. She could form sentences, had manual

skills, and could walk, in a more limited manner than her peers. She received a diagnosis of preserved speech variant of Rett syndrome with intense eye contact and stereotypies in the hands. The preserved speech variant is known to be less common (5.7%) than classic Rett syndrome (3). These patients have most of the features of classic Rett syndrome but developmental delay, head growth deceleration, and hyperventilation are either absent or less common (11). The clinical picture is milder than the classic Rett syndrome, making the diagnosis more difficult and delayed. Our patient had been followed up at the pediatric neurology department for epileptic seizures that had first started when she was 11 months old. However, she had only been reported with intense eye pointing and hand stereotypies when 7 years old. Hand stereotypies are seen at a rate of 68.1% and intense eye pointing at 87.6% in Rett syndrome patients (3). The presence of hand stereotypies and intense eye pointing may indicate a diagnosis of preserved speech variant of Rett syndrome in a female patient who can talk, has purposeful manual skills, and can walk despite having developmental problems. Similar to the findings of Renieri et al. (4), this patient has shown moderate developmental delay, hand stereotypies and milder reduction of hand skills. This variant has frequently been found to be associated with C terminal region changes, as in our case (Figure 1) (5).

The evaluations performed in this patient due to decreased urinary output and inability to pass urine when she was 11 months old, which had resulted in neurogenic bladder and vesicoureteral reflux detection. However, these evaluations were done before the Rett syndrome clinical picture had appeared. Neurogenic bladder is a condition characterized by detrusor overactivity, detrusor sphincter dyssynergia, or sphincter underactivity and affects both bladder capacity and urination function. The long-term presence of this clinical picture can result in inadequate bladder capacity, incontinence, high post-void residual volumes, and also future problems that can be life-threatening such as upper urinary tract dysfunction with chronic renal disease and hydronephrosis as in the case (12). Many conditions may result in neurogenic lower urinary tract dysfunction but other etiologies were ruled out in the current patient with the history, examination, and brain-spinal MRI.

The presence of autonomic symptoms related to the cardiac, respiratory, gastrointestinal, and other systems in Rett syndrome patients has been shown both in patients in the clinic and in Rett syndrome mouse models with *MECP2* mutations (13). However, only a limited number of cases with neurogenic lower urinary tract dysfunction have been reported. The Rett Syndrome Natural History Study including the clinical information of 1165 Rett syndrome patients reports urinary retention in 11, vesicoureteral reflux in 9 and neurogenic bladder in 3 patients (13). Urinary retention has been found to be 17 times more common in these patients than in the normal population (13, 14). Another study has reported urinary retention in four patients and urinary incontinence in one patient in adult Rett syndrome patients presented for urological evaluation (14). Neurogenic bladder was found in all these patients (14). Another

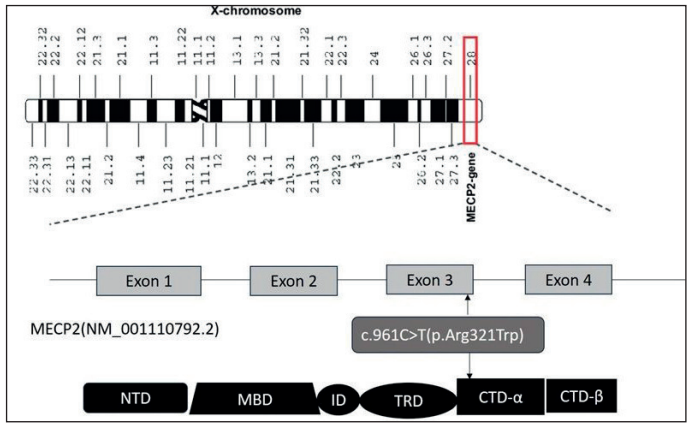

Figure 1: Visualization of *MECP2* gene exons and *MECP2* protein domains. The variant detected is replaced in exon 3 of the *MECP2* gene and CTD-α domain of Methyl-CpG-binding protein 2. (NTD: N-terminal domain, MBD: methylated DNA-binding domain, ID: interdomain, TRD: transcription repression domain, CTD-α and β: C-terminal domains)

case report concerns a Rett syndrome patient with intermittent urinary retention and overflow incontinence (15). These cases and our own case demonstrate that urological dysfunction is more common in Rett syndrome patients than in the general population, although still rare. Evaluating these results together with those from mouse models indicate that this disorder could cause significant morbidity, such as chronic renal disease and secondary renal failure, and mortality. However, the presence of only a few reports on neurogenic bladder and its complications in this group of patients could show that these clinical conditions are disregarded because of the developmental problems that are at the forefront.

The expression of the *MECP2* gene is regularly increased during the postnatal period where there is a marked cerebral synapse formation and maturation, and its lifelong normal function of the *MECP2* gene is required for the maintenance of neurons. *MECP2* dysfunction is not a monogenic disorder as it was previously thought. It is a very complex disorder that causes deregulation of the transcription of more than 1000 genes for which it is a repressor or an activator (16). The *BDNF* (Brain Derived Neurotrophic Factor) gene that plays role in Rett syndrome pathogenesis shows its main effect on the spinal cord in the central nervous system, and its transcription is severely affected in Rett syndrome (17). The expression of *BDNF* is low in the prenatal period and dramatically increases in the postnatal period, similar to *MECP2*. *BDNF* expression is not affected in the early presymptomatic period in *MECP2* knockout mice but the level decreases with the appearance of Rett-like symptoms (16). The lower urinary tract dysfunction and neurogenic bladder seen in these patients could be the result of *BDNF* deficiency in the spinal cord.

CONLUSION

The presence of hand stereotypies and intense eye pointing can indicate a diagnosis of preserved speech variant of Rett

syndrome in a female patient who can talk, has purposeful manual skills, and can walk despite having developmental problems. Autonomic lower urinary tract dysfunction can also be seen in Rett syndrome patients although it is less common than cardiac, respiratory, and gastrointestinal autonomic involvement. It should be remembered that clinical conditions such as intermittent urinary retention and vesicoureteral reflux could be related to neurogenic bladder due to autonomic involvement in these patients and one must be aware of the serious complications like chronic renal disease. Neurogenic lower urinary tract dysfunction can be overlooked in Rett syndrome, one of the most common causes of development delay in girls, due to the severe developmental problems at the forefront and this needs to be evaluated in studies with a large number of subjects.

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Language Delay in Children

Çocuklarda Gecikmiş Konuşma

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ABSTRACT

Concerns about language development are among the most common complaints that parents seek medical advice regarding their children's development. Developmental language disorder refers to a delay in children's receptive or expressive language development without an underlying medical condition. Risk factors such as prematurity, low socioeconomic status, screen exposure, maternal depression and family history can affect language development in children. In a child presenting with a complaint of delay in language development, a detailed anamnesis should be taken, including developmental history, home environment, family history and psychosocial risk factors.

The evaluation of a child should include not only language development but also all areas of development (language, cognitive, motor, relationship, social-emotional) using a standatdized developmental assessment tool. A detailed physical examination should be performed to check for accompanying genetic, neurological and other medical conditions (e.g. cleft palate). Regardless of the result of newborn hearing screening, all children should undergo hearing tests, and if necessary, hemogram and iron parameters should be evaluated. If there is a history of regression, delay in the relationship area, or signs of accompanying neurudevelopmental problems, further evaluation should be performed. It should not be fogotten that a delay in language development may be the initial sign of problems such as cognitive delay, autism spectrum disoeder, hearing loss, and speech pronounciation disorder.

Early intervention shoul be planned for children with delayed language development and should not be waited for. Monitoring and supporting each child's development with family-centered methods is the most effective method for the prevention, early diagnosis, and early intervention of all developmental difficulties, including delay in language development.

Key Words: Language delay, Speech, Early childhood development

ÖZ

Dil gelişimi ile ilgili kaygılar ailelerin çocuklarının gelişimleri ile ilgili hekim başvurusunda bulundukları en sık yakınmalardandır. Gelişimsel dil bozukluğu altta yatan tıbbi bir neden olmadan alıcı ya da ifade edici dil gelişimindeki gecikmeyi ifade eder. Prematürite, düşük sosyoekonomik düzey, ekran maruziyeti, anne depresyonu, aile öyküsü gibi risk etmenleri çocuklarda dil gelişimini etkileyebilmektedir. Dil gelişiminde gecikme yakınması ile başvuran bir çocukta, gelişimsel öykü, ev ortamı, aile öyküsü ve psikososyal risk etmenlerini içeren ayrıntılı bir anamnez alınmalıdır. Çocuğun sadece dil gelişimi değil, tüm gelişim alanları (dil, bilişsel, hareket, ilişki, sosyal duygusal) standart bir gelişimi değerlendirme aracı ile değerlendirilmelidir. Eşlik edebilecek genetik, nörolojik ve diğer tıbbi durumlar (örneğin yarık damak) açısından ayrıntılı fizik muayene yapılmalıdır. Yenidoğan işitme taraması sonucundan bağımsız olarak tüm çocuklarda işitme testi yapılmalı, gerekli durumlarda hemogram, demir parametreleri değerlendirilmelidir. Regresyon öyküsü, ilişki alanında gecikme ya da eşlik edebilecek nörogelişimsel sorun bulgularının olması durumunda ileri değerlendirme yapılmalıdır. Dil gelişimindeki gecikmenin bilişsel gecikme, otizm spektrum bozukluğu, işitme kaybı, konuşma sesletim bozukluğu gibi sorunların ilk bulgusu olabileceği unutulmamalıdır. Dil gelişiminde gecikmesi olan çocuklara erken girişim planlanmalı, beklenmemelidir.

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Her çocuğun sağlık izlemi içerisinde gelişiminin aile merkezli yöntemler ile izlenmesi ve desteklenmesi dil gelişiminde gecikme de dahil olmak üzere, tüm gelişimsel zorlukların önlenmesi, erken tanınması ve erken müdahalesi için en etkili yöntemdir.

Anahtar Kelimeler: Dil gelişiminde gecikme, Konuşma, Erken çocukluk dönemi gelişimi

INTRODUCTION

Concerns about language development are among the most common developmental issues that lead parents to seek medical advice. Communication skills, fundamental to language development, can affect an individual's ability to engage with others, convey their thoughts, ideas, and needs. While often used interchangeably, "language" and "speech" have distinct meanings. Expressive language refers to the ability to produce speech and create visual or symbolic language outputs, while receptive language refers to the ability to understand others' language outputs visually and auditorily. Speech, on the other hand, refers to the vocal output of the language system, necessary the proper functioning of oromotor mechanisms for vocal sound production and respiratory coordination.

Speech delay is defined as development of language skills for a given age slower than expected in the same developmental sequence. An evaluation using a standardized developmental assessment tool indicates that language development is considered delayed when it falls below -1 standard deviation (SD) (1). Speech disorders refer to difficulties in the production or perception of speech sounds including articulation, breath, oromotor movements, planning, speed, rhythm, and fluency (2).

Developmental Language Disorders (DLD), previously known as specific language impairment (SLI), refer to a persistent condition not associated with any other medical or causal conditions, where children have difficulties in understanding and using spoken language.

EPIDEMIOLOGY

Research in the United States has shown that approximately 10-15% of children at the age of 2 have language delay while between the ages of 2 and 5 language delay without an underlying cause can be observed in 5-12% of cases (3,4). Language delays are more commonly seen in boys compared to girls, and the frequency of other neurodevelopmental issues that can affect language development is also higher in boys than in girls (1, 5, 6).

Language and Speech Development

The language development of all children worldwide is similar in the first 6 months. In subsequent periods, babies learn to speak through social interaction with their parents and caregivers and exposure to language (7). Over time, children begin to distinguish sounds in the language to which they are exposed. Like all areas of development, language development is most rapid during early childhood when the central nervous system develops most rapidly and neuroplasticity is most intense. Language development progresses not only through biological development but also through the interaction of biological development with environmental factors. Therefore, both medical and environmental risk factors can contribute to language delay in children (8,9).

Risk Factors

- ***Prematurity:*** Babies born prematurely are at risk for language delay, as well as delays in all other areas of development such as cognition and motor skills. It has been shown that approximately one-third of babies born before 29 weeks of gestation experience language development issues (10). A meta-analysis evaluating the language development of preterm infants revealed that, irrespective of socioeconomic status and accompanying developmental difficulties, preterm infants have lower scores in complex language skills compared to full-term infants (11).
- ***Poverty and low socioeconomic status:*** Socioeconomic status significantly impacts children's cognitive and socio-emotional development, as well as language skills. Noble et al. (12), in their longitudinal studies, demonstrated that children from low socioeconomic backgrounds have language development scores 0.8 SD lower than those from higher socioeconomic backgrounds, with this effect observed as early as 21 months of age. Justice et al. (13) showed that poverty disrupts parent-child interaction, resulting in a 1SD decrease in language development in children by the age of 2. A study examining factors influencing child development in low to middle-income countries found a relationship between both maternal and paternal education levels and children's language scores (14). The number of words used in the home environment is crucial for children's language development, with children's vocabularies being nearly 98% parallel to their parents' vocabularies. It has been predicted that there is a 30-million-word gap in vocabulary by the age of 48 months between children from high socioeconomic backgrounds and those from low socioeconomic backgrounds (15).
- ***Screen time:*** The American Academy of Pediatrics recommends that children under 18-24 months of age should not be exposed to screens, and after 24 months, screen time should be limited to 1 hour per day with appropriate content, watched with parental guidance (16). A recent meta-analysis found that both excessive screen exposure and having a screen on in the background are associated with poorer language development scores in children. However, later exposure to screens, co-viewing with an adult, and watching educational programs are

associated with better language skills (17). Screen exposure at the age of one has been shown to be associated with delays in personal, social, and communication domains at ages 2 and 4 (18). Increased screen exposure has been shown to decrease the number of words used by adults and their interactions with children, with each additional minute of screen time correlating with adults using 6.6 fewer words, children vocalizing 4.9 times less, and 1.1 times fewer parent-child interactions (19). In addition to reduced interaction with parents, children with excessive screen exposure also have lower rates of engagement in book reading activities (20). A study evaluating patients presenting with speech delay in Turkiye found that 82% of children were exposed to screens for more than 4 hours per day, and approximately half of them did not have books (21).

- ***Maternal depression:*** Maternal depression can affect the parent-child relationship and early childhood development in all areas. Several studies have shown that children of mothers with depression experience impaired language development. These studies have found that postpartum depression affects the reciprocity between the mother and the baby, leading to reduced maternal vocalizations and speech directed towards the baby (22-24).
- ***Genetics:*** While there is no direct genetic etiology for language development disorders, a review found an association between language development disorders and sex chromosome aneuploidies, structural chromosomal abnormalities, and copy number variations and variants (25-28).
- ***Family history:*** Having a family history of language problems increases the frequency of developmental language disorders in children (29). Twin studies have shown that monozygotic twins have a higher rate of language development issues compared to dizygotic twins. Heritability estimates for language development have been found to be approximately 0.50 in various studies (30-32).

Bilingualism: It is acknowledged that bilingualism in early childhood does not cause language development delays in children; however, the acquisition rates of each language may vary depending on the child's exposure to the languages. Therefore, it is recommended to assess skills in both languages in developmental evaluations (33). The American Speech-Language-Hearing Association recommends early exposure to multilingualism and encourages parents to engage in frequent practice and support their children's speech. Initially, children may occasionally mix the grammar rules of the two languages, but this tends to improve over time (34). Speaking multiple languages at home has not been found to be associated with expressive language delays in children. A study involving a bilingual ethnic minority group from the UK birth cohort found no association between bilingualism and expressive language delay (35).

Assessment of language development

Families of children with language delay may not always present with this complaint. Behavioral problems such as tantrums, anger outbursts, and self-regulation issues may also be presenting complaints.

A detailed history should include prenatal, natal, and postnatal history, acquisition of developmental milestones, risk factors for hearing loss, as well as family history including any neurodevelopmental disorders and psychosocial risk factors such as poverty, depression, and inappropriate language stimuli. A comprehensive physical examination should be conducted, including anthropometric measurements, skin, neurological, and dysmorphic assessments

Since language delay can be the initial symptom of other developmental conditions, all children should undergo detailed developmental assessments in all developmental domains (language, cognition, motor, and social interaction) using a standardized assessment tool. For this purpose, the International Guide for Monitoring and Child Development (I-GMCD), a comprehensive tool for monitoring, supporting, and early intervention developed in our country, and endorsed by the World Health Organization can be utilized (36).

Various tools for assessing development are available in Turkey, such as the Bayley Scales of Infant and Toddler Development, International Guide for Monitoring Child Development, Early Development Inventory, Ankara Developmental Inventory, and Gazi Early Childhood Assessment Tool, which have been standardized (37-41).

Evaluation

All children suspected of language development delay should undergo hearing assessment, even if they have passed newborn hearing screening (42).

Laboratory tests can be planned according to history and physical examination findings. However, since iron deficiency can affect development, a complete blood count and, if necessary, iron parameters can be evaluated (43).

If there is regression in developmental milestones, suggestive signs of Autism Spectrum Disorder, the presence of features that are part of developmental disorders, and no progress despite implementing recommendations such as enrichment of language exposure and social interaction in the home environment, the child should be referred for further investigation and evaluation to developmental and behavioral pediatrics, child psychiatry and child neurology (44,45).

Differential diagnosis:

In a child presenting with delayed language development, a thorough assessment involving history, physical examination,

and developmental evaluation is conducted to determine whether the delay is isolated. It should be noted that delayed language development may be associated with inadequate nurturing caregiving in the home environment, as well as hearing loss, intellectual disability, autism spectrum disorder, or it may be the initial sign of a speech disorder.

To reach their full potential, children need the five inter-related and invisible components of care, which is describes as Nurturing Care. These components are good health, adequate nutrition, safety and security, responsive caregiving and opportunities for learning (46).

- ***Intellectual disability (ID):*** It is a neurodevelopmental condition that is seen with difficulty in cognitive and adaptive functions, occurring in approximately 1-2% of cases (5,45). A diagnosis is made when detailed developmental assessment shows difficulty in cognitive development with a score below 70, along with challenges in conceptual, social, and practical adaptive functions of the child. The term General Developmental Delay (GDD) is a temporary diagnosis used for children aged 0-5 years who are at risk for ID. GDD is defined as a delay of ≥2 SD in two or more areas of development, including gross/fine motor, speech/language, cognitive, social/personal, and daily living activities. (45). It is reported that approximately two-thirds of children diagnosed with GDD receive an ID diagnosis after the age of 5.
- ***Autism Spectrum Disorder:*** It is a biologically based neurodevelopmental disorder characterized by difficulties in social communication and interaction, restricted and repetitive behaviors, interests, and activities (45). A prevalence study covering the year 2020 in the United States found its frequency to be 1/36 (47). In addition to language delay, these children may also exhibit difficulties in social communication skills and limited and repetitive behaviors.
- ***Speech Sound Disorder:*** This term encompasses difficulties with perceiving, producing, or representing speech sounds and segments, either organically or functionally. Organic speech sound disorders result from underlying motor/neurological (e.g., apraxia, dysarthria), structural (e.g., cleft lip/palate), or sensory/perceptual (e.g., hearing impairment) causes. Functional speech sound disorders are idiopathic and known as articulation and phonological disorders (48,49).
- ***Hearing Impairment:*** Children with moderate to severe hearing loss may struggle to understand and produce certain sounds. As receptive language development may appear normal in cases of mild hearing loss, the normality of receptive language does not rule out hearing loss. Therefore, all children with expressive or receptive language delay should undergo objective hearing assessment (50).

Management

Early childhood is a critical period characterized by rapid brain development and intense neuroplasticity, making it crucial for language development, like all other developmental domains. Children learn language very quickly during this period. Therefore, when a delay in language development is identified, the most effective intervention can be achieved during early childhood. Therefore, the “watch and wait” approach is not recommended (51).

Initially, adjustments should be made in the home environment to enrich language and enhance the child’s language development and interaction. Screen exposure should be completely avoided during the first 24 months, and selected programs should be watched with parents between the ages of 2 and 5. After the age of five, the time children spend with screens should be limited to a reasonable duration (16). Reading aloud with the child in interactive sessions should be encouraged. Interactive book reading programs such as Reach Out and Read and Dolly Parton’s Imagination Library have been shown to have positive effects on children’s language development (52). A meta-analysis evaluating the effectiveness of Parent Education Programs in early interventions for Developmental Language Disorders showed a positive relationship between parents’ participation in these programs and children’s language development (7).

High-quality preschool education has been shown to have positive effects on children’s language and cognitive development in both the short and long term (53,54). Following detailed evaluations of children with Developmental Language Disorders, it may be recommended for children and families to begin appropriate preschool education together.

Children with Developmental Language Disorders should be recommended for speech-language therapy. According to a Cochrane review, speech-language therapy has been shown to have a positive effect, especially in children with limited vocabulary and phonological issues (55).

In conclusion, beyond all interventions, it is important to monitor the development of all children, especially during early childhood when brain development is rapid, to detect and intervene early in developmental delays in areas such as language, cognition, and motor skills.

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