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Türkiye Çocuk Hastalıkları Dergisi

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Ankara Bilkent Şehir Hastanesi, Çocuk Hastanesi Yayını

ANKARA BİLKENT ŞEHİR HASTANESİ
ÇOCUK HASTANESİ

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ÇOCUK HASTANESİ

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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.

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

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

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

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

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

Dergimiz asitsiz kâğıda basılmaktadır.

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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.

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

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

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

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

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STARD	Diagnostic accuracy
PRISMA	Systematic reviews and meta-analysis
ARRIVE	Experimental animal studies
TREND	Non-randomized public behavior

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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:

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Original Articles:

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

Title: maximum of 20 words

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

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

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

References: up to 40

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

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

Review Articles:

Word count: up to 5000

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

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

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

References: up to 80

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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.

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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.

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(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;

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

If the reference is a book;

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

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

If the reference is a book chapter;

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

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

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

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

If the reference is an online journal:

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

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

If the reference is a website:

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

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

If the reference is a thesis:

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

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

REVISIONS

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

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

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

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YAZARLAR İÇİN BİLGİ

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

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

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

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

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

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

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

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

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

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

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

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

3. Yayınlanacak kopyanın son onayı.

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

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

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

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

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

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

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

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

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

YAZININ HAZIRLANMASI

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

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

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

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

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

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

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

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

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

Kapak sayfasının hazırlanması:

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

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

Önemli Uyarı: Kapak sayfası ayrı bir belge olarak yüklenmelidir.

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

Yazı türleri:

Orijinal araştırma makalesi

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

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

Başlık: En çok 20 kelime

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

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

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

Referanslar: En çok 40.

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

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

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

Derleme:

Kelime sayısı: En fazla 5000

Özet: En fazla 500 kelime

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

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

Referanslar: 80'e kadar

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

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

Olgu Sunumu:

Kelime Sayısı: En fazla 2000 kelime

Özet: En fazla 200 kelime

Anahtar Kelime: En az üç en fazla altı kelime

Tablo ve Şekil: Toplamda en fazla beş ile sınırlandırılmıştır.

Referans: En fazla 15

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

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

Editöre mektup:

Kelime sayısı: En fazla 1500 kelime

Şekil ve tablolar: En fazla 3

References: En fazla 15

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

KAYNAKLAR

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cümlelerin sonunda metinde kullanıldıkları sıra ile numaralandırılmalıdır. Dergi adları "Index

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

Kaynak dergi ise;

Yazar(lar)ın soyadı adının başharf(ler)i (6 ve daha az sayıda yazar için yazarların tümü, 6'nın üzerinde yazarı bulunan makaleler için ilk 6 yazar belirtilmeli, Türkçe kaynaklar için "ve ark.", yabancı kaynaklar için "et al." ibaresi) kullanılmalıdır. Makalenin başlığı. Derginin Index Medicus'a uygun kısaltılmış ismi

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

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

Kaynak dergi eki ise;

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

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

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

Kaynak kitap ise;

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

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

Kaynak kitaptan bölüm ise;

Bölüm yazar(lar)ının soyadı adının başharf(ler)i. Bölüm başlığı. In: Editör(ler)in soyadı, adının başharf(ler)i (ed) veya (eds). Kitabın adı. Kaçıncı baskı olduğu. Basım yeri: Yayınevi,

Baskı yılı:Bölümün ilk ve son sayfa numarası.

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

Kaynak toplantıda sunulan bildiri ise;

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Editör(ler)in soyadı adının başharf(ler)i (ed) veya (eds). Kitabın adı. Toplantının adı; Tarihi; Toplantının yapıldığı şehrin adı, Toplantının yapıldığı ülkenin adı. Yayınevi; Yıl. Sayfa numaraları.

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.

Kaynak elektronik dergi ise;

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

Kaynak web sitesi ise:

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

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

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

Kaynak tez ise:

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

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

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Yazı gönderildikten sonra yazar listesinin/sırasının değiştirilmesi (yazar adlarının silinmesi veya yeni yazar adı eklenmesi gibi) talepleri yayın kurulunun onayına tabidir. Bu talep yazar değişiklik formunun doldurulup dergiye yüklenmesi ile talep edilebilir. Bu form aşağıdakileri içerecek şekilde doldurulmalıdır: Talebin gerekçesi, yani yazar listesi, tüm yazarlar tarafından (yeni ve eski) imzalanan yeni bir telif hakkı transfer formu, yeni yazar tarafından imzalanmış çıkar çatışması formu.

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Türkiye Çocuk Hastalıkları Dergisi yüksek kaliteli yazılar yayınlamayı ve yayın etiğini korumayı taahhüt etmektedir. Yazarlardan, yayın etiğinde ve yazıların kalitesinde tavsiye edilen kurallara uymaları beklenmektedir.

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

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Gastrointestinal and Sleep Problems in Children with Autism Spectrum Disorder: Their Relationship with Problematic Behavior

Otizm Spektrum Bozukluğu Olan Çocuklarda Gastrointestinal Sistem ve Uyku Sorunları: Bunların Problemli Davranışlarla İlişkisi

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ABSTRACT

Objective: The purpose of this research is to investigate sleep and gastrointestinal problems in children with autism spectrum disorder (ASD) and their relationship with each other, autism severity and problematic behavior.

Material and Methods: The children who were admitted to outpatient clinics of child psychiatry at our hospital in a 3-months period and had diagnosis of ASD according to DSM-5 were included. The parents filled Aberrant Behavior Checklist (AbBC), Rome-3 Diagnostic Questionnaire for Pediatric Functional Gastrointestinal Disorders Parent Report Form (QPGS-RIII), Children's Sleep Habits Questionnaire (CSHQ), Autism Behavior Checklist (ABC) and sociodemographic data form. The clinician applied Childhood Autism Rating Scale (CARS).

Results: Ninety-seven children with ASD were included. According to QPGS-RIII, 38.1% of the cases had probable functional gastrointestinal problems. Those were 26.8% (n=26) functional constipation, 8.2% (n=8) nonretentive fecal incontinence, 2.1% (n=2) aerofaji, 3.1% (n=3) rumination syndrome, 4.1% (n=4) irritable bowel syndrome, 1% (n=1) functional abdominal pain syndrome, 1% (n=1) functional dyspepsia, 3.1% (n=3) functional abdominal pain, 1% cyclic vomiting and 1% (n=1) abdominal migraine. According to CSHQ 58.8% of the cases had sleep problems. ASD patients with functional gastrointestinal problems, had higher total scores of CSHQ, ABC and AbBC, compared to children with no functional gastrointestinal problems.

Conclusion: Our findings revealed that frequency of gastrointestinal and sleep problems were high in children with ASD. It is appropriate to evaluate patients with ASD in terms of gastrointestinal and sleep problems especially if behavioral problems accompanies. And treating gastrointestinal and sleep problems might decrease challenging behaviors that seen in ASD.

Key Words: Autism, Gastrointestinal diseases, Sleep, Problem behavior

ÖZ

Amaç: Bu araştırmanın amacı, otizm spektrum bozukluğu (OSB) olan çocuklarda uyku ve gastrointestinal sorunları ve bunların birbirleriyle, otizm şiddeti ve problemli davranışlarla olan ilişkisini incelemektir.

Gereç ve Yöntemler: Hastanemizde 3 aylık bir sure içinde çocuk psikiyatrisi polikliniklerine başvuran ve DSM-5'e göre OSB tanısı alan çocuklar çalışmaya alındı. Ebeveynler tarafından Sorun Davranış Kontrol Listesi (SDKL), Pediatrik

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Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. Our study was approved by Ankara Children Hematology and Oncology Hospital Clinical Research Ethics Committee (2018-186 protocol number).

Contribution of the Authors / Yazarların katkısı*: *AKBAL BAĞCI K: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in 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. ***PARLAK GÖZÜKARA Ö:*** 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. ***ÇÖP E:*** 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. ***GÖKER Z:*** Taking responsibility in logical interpretation and conclusion of the results, Reviewing the article before submission scientifically besides spelling and grammar.

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Additional information / *Ek bilgi*: The preliminary findings of the study were presented as an oral presentation at the 29th national congress of child and adolescent mental health and diseases held in Istanbul Elite World Asia Hotel on May 2, 2019.

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Gastrointestinal Semptomlar Ölçeği- Ebeveyn Rapor Formu, Çocuk Uyku Alışkanlıkları Anketi (ÇUAA), Otizm Davranış Kontrol Listesi (ODKL) ve sosyodemografik veri formu dolduruldu. Klinisyen tarafından Çocukluk Otizm Derecelendirme Ölçeği (ÇODÖ) uygulandı.

Bulgular: Çalışmaya 97 OSB hastası dahil edildi. Pediatrik Gastrointestinal Semptomlar Ölçeği- Ebeveyn Rapor Formuna göre vakaların %38.1'inde olası fonksiyonel gastrointestinal problem saptandı. Bunlardan %26.8'i (n=26) fonksiyonel konstipasyon, %8.2'si (n=8) retansif olmayan fekal inkontinans, %2.1'i (n=2) aerofaji, %3.1'i (n=3) ruminasyon sendromu, %4.1'i (n=4) irritabl bağırsak sendromu, %1'i (n=1) fonksiyonel karın ağrısı sendromu, %1'i (n=1) fonksiyonel dispepsi, %3.1'i (n=3) fonksiyonel karın ağrısı, %1'i siklik kusma ve %1'i (n=1) abdominal migrendi. ÇUAA'ya göre vakaların %58.8'inde uyku problemi vardı. Fonksiyonel gastrointestinal problemi olan OSB hastalarının, fonksiyonel gastrointestinal problemi olmayan hastalara göre ÇUAA, ODKL ve SDKL toplam puanları daha yüksek saptandı.

Sonuç: Bulgularımız OSB'li çocuklara gastrointestinal ve uyku sorunlarının sıkça eşlik ettiğini göstermiştir. Özellikle davranış sorunları eşlik eden OSB'li hastaların, altta yatan gastrointestinal ve uyku sorunları açısından değerlendirilmesi önemli görünmektedir. Gastrointestinal hastalıkları ve uyku problemlerini tedavi etmek, OSB'ye sık eşlik eden davranış sorunlarını azaltabilir.

Anahtar Sözcükler: Otizm, Gastrointestinal Hastalıklar, Uyku, Sorunlu Davranış

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication, stereotypical repetitive behaviors and restricted interests (1). Recent studies estimated that 1 in 54 children has been identified with ASD and prevalence is increasing (2).

ASD develops from interaction of genetic, environmental and neurobiological factors (3). Although the pathophysiology of ASD is not fully known, gut and brain interaction has taken attention in recent years. In addition to neurological symptoms, ASD subjects frequently suffer from gastrointestinal (GIS) symptoms including constipation, encopresis, diarrhea, flatulence, gastroesophageal reflux and abdominal pain (4-6). Frequency of GIS symptoms in ASD children is 9 to 91% (5). Increased problematic behavior has been demonstrated in individuals with ASD and GIS symptoms. It has been observed that GIS symptoms trigger self-harm, aggression and anxiety behavior in children with autism (6).

Also, it has been indicated that sleep problems are highly common in ASD, with rates ranging from 40% to 80% (7). It was observed that impaired sleep leads to irritability and tendency to violence and causes emotional disregulation in ASD (8).

The purpose of this research is to investigate sleep and gastrointestinal problems in children with autism spectrum disorder (ASD) and their relationship with autism severity, problematic behavior and each other. We also aimed to drew attention to possible gastrointestinal and sleep problems that may be the underlying reasons for behavioral problems in ASDs. Unlike other studies we investigate all these factors in a single study.

MATERIALS and METHODS

Ninety-seven ASD patients aged 3-12 years who applied to the child and adolescent psychiatry outpatient clinics of Ankara Children Hematology and Oncology Hospital, in a 3 months period, were included in the study. Patients who had history of organic gastrointestinal disorder were excluded.

Clinical interview based on DSM-5 was conducted and Childhood Autism Rating Scale (CARS) was performed by the clinicians. Autism Behavior Checklist (ABC), Children's Sleep Habits Questionnaire (CSHQ), Aberrant Behavior Checklist (AbBC), Diagnostic Questionnaire For Pediatric Functional Gastrointestinal Disorders Parent Report Form (QPGS-RIII) and sociodemographic data form were filled by the parents and checked by the clinician. Clinician also questioned clinical features such as medical condition, drug use, family history of chronic diseases.

Our study was approved by Ankara Children Hematology and Oncology Hospital Clinical Research Ethics Committee (2018-186 protocol number). The research was conducted according to the Helsinki Declaration rules of good clinical practice and ethics.

Written and verbal informed consent was obtained from the parents.

CARS: The scale has 15 items. It was developed to diagnose ASD and to distinguish children with developmental delays from children with autism spectrum disorders. It categorizes autism severity from mild to moderate to severe.

ABC: The scale has 57 items and 5 subscales. Those are; sensory, relating, body and object use, language, and social and self-help. It evaluates autistic children's symptoms and behaviors.

AbBC: It has 58 items and five subscales. Those are irritability, lethargy/social withdrawal, stereotypic behavior, hyperactivity/noncompliance and inappropriate speech.

QPGS-RIII: The scale has 71items. It evaluates GIS symptoms, categorize functional GIS disorders (FGIDs) due to Rome-III criteria.

CSHQ: It has 33 items and investigates children's sleep habits and sleep-related problems. The cut off point off the scale is 41.

Statistical analysis, Continuous variables were expressed as arithmetic mean, standard deviation, median, minimum-

maximum values, and categorical variables were expressed as frequency (n) and percentage (%). Conformity of continuous variables to normal distribution was evaluated with Kolmogorov-Smirnov test. Age; Problematic Behavior Checklist (PBCL)'s sub-scores of latergy-social withdrawal, stereotypical behaviors, hyperactivity and speech; and all sub-scores of the Childhood Autism Rating Scale (CARS) did not show normal distribution. On the other hand, parental age, Problematic Behavior Checklist (PBCL)'s other scores, Childhood Autism Rating Scale (CARS) total score, Autism Behavior Checklist (ABC) total score and all sub-scores, Child Sleeping Habits questionnaire-total score distribution was found as normal. Mann-Whitney U test was used to compare the measurement variables that did not show normal distribution. Pearson Chi-square and Fisher's exact test were used in the analysis of categorical variables. Spearman correlation test was used in the correlation analysis of the variables. $p<0.050$ was accepted as the significance level.

RESULT

Ninety-seven ASD patients were included the study. 84.5% of the cases were male (n=82). The median age of the patients were 6.0 years (min-max: 3-12 years). 19.6% (n=19) of the cases had at least one physical diseases. 52.6% (n=51) of the cases

Table I: Demographic and clinical characteristics of patients with ASD

Variables	
Age (year)*	6 (3-12)
Gender†	
Boys	82 (84.5)
Girls	15 (15.5)
Sibling†	
Yes	78 (80.4)
Birth order†	
First	41 (42.3)
Second	38 (39.2)
Third	12 (12.4)
Fourth	5 (5.2)
Fifth	1 (1.0)
Medical disease†	
Yes	19 (19.6)
Epilepsia	9 (9.3)
Cerebralpalsy	3 (3.2)
Asthma	2 (2.1)
Cardiomyopathy	1 (1.0)
Nephroticsyndrome	1 (1.0)
Brain tumor	1 (1.0)
Nistagmus	1 (1.0)
Fragil X syndrome	1 (1.0)
At least one psychiatric disorder†	
Yes	51 (52.6)
Attention deficit hyperactivity disorder	40 (41.2)
Intellectual disability	22 (22.7)
Generalised anxiety disorder	1 (1.0)
Psychotropic medication use†	
No	54 (55.7)
Yes	43 (44.3)
Mother'sage (years)*	37 (29-55)
Father'sage (years)*	32 (24-50)
Mothers' education†	
Primary	36 (37.1)
Secondary	24 (24.7)
College	27 (27.8)
University	10 (10.3)
Fathers' education†	
Primary	28 (28.9)
Secondary	15 (15.5)
College	33 (34.0)
University	21 (21.6)
History of miscarriage†	11 (11.3)
Smoking during pregnancy†	14 (14.4)
History of prematurity†	24 (24.7)
History of regression†	41 (42.3)

***:** *Median (minimum-maximum),* **†:** *n(%)*

Table II: The score distributions of the scales

AbBC – Total Score*	56 (1-163)
Irritability	14 (0-40)
Lethargy/social withdrawal	15 (0-42)
Stereotypic behavior	7 (0-21)
Hyperactivity/noncompliance	21 (1-48)
Inappropriate speech	3 (0-12)
CARS – Total Score	34 (19-48)
Nonautistic (CARS – TS = 15-29.5)†	24 (24.7)
Mild-Moderate (CARS – TS = 30-36.5)†	40 (41.2)
Severe (CARS – TS = 37-60) †	32 (33.0)
ABC – Total Score*	62 (3-120)
Sensory stimuli	8 (0-23)
Relating	16 (0-32)
Body and Object Use	14 (0-36)
Language	12 (0-34)
Social and Self-Help skills	12 (0-25)
ABC – Total skor ≤39†	27 (27.8)
ABC – Total skor >39 †	70 (72.2)

:** *Median (Min-max),* **†:** *n (%),* ***AbBC: *Aberrant Behavior Checklist,* ***CARS:*** *Childhood Autism Rating Scale,* ***ABC:*** *Autism Behavior Checklist*

Table III: Children's Sleep Habits Questionnaire (CSHQ) Results

CSHQ-Total Score*	47 (34-68)
Presence of clinically significant sleep problems†	57 (58.8)
Amount of sleep (hours) (night+day)*	9.3 (5-12)
Time spent awake at night (minutes)*	10 (1-240)
Child's bedtime*	22.15 (20:00-02-30)

***:** *median (min-max),* **†n (%):** *CSHQ –total score>41*

Table IV: The relationship between functional GIS disease and autism symptom severity, problematic behavior and sleep problems

	Functional GIS Disease Yes (n = 37)	Functional GIS Disease No (n = 60)	Statistics zorχ²	p
Age (years)*	7 (3-12)	6 (3-12)	-1.88	0.060
Gender†				
Boys	36 (97.3)	46 (76.7)	7.45	0.008
Girls	1 (2.7)	14 (23.3)		
MR†	11 (29.7)	11 (18.3)	1.69	0.190
ABC scores*				
Total Score	79 (16-110)	51 (3-109)	-2.60	0.009
Sensory behavior	11 (3-22)	7 (0-19)	-2.69	0.007
Relating	18 (0-31)	14.5 (0-30)	-1.82	0.070
Body and Object Use	15 (0-34)	13 (0-29)	-1.35	0.180
Language	14 (0-34)	11 (0-27)	-1.45	0.150
Social and Self-Help skills	14 (4-21)	9 (0-25)	-3.00	0.003
AbBC scores*				
Total Score	75 (2-122)	46 (1-123)	-2.10	0.040
Irritability	17 (0-31)	10 (0-40)	-2.73	0.006
Lethargy/social withdrawal	16 (0-32)	14 (0-27)	-1.22	0.220
Stereotypies	7 (0-21)	4 (0-20)	-1.88	0.060
Hyperactivity	23 (2-46)	15.5 (0-40)	-1.70	0.090
Inappropriate speech	3 (0-10)	2.5 (0-12)	-0.71	0.480
CARS Total Score*	37.5 (19-45.5)	33 (19-44.5)	-1.30	0.200
CSHQ Total Score*	47 (35-68)	43 (32-68)	-1.88	0.060
Sleep problems (CSHQ scores)†				
No‡	7 (20.6)	26 (46.4)	6.08	0.010
Yes§	27 (79.4)	30 (53.6)		

:Median(minimum-maximum), †: n (%), ‡:No (CSHQ score ≤41), §:Yes (CSHQ score>41), **AbBC: Aberrant Behavior Checklist, **CARS:** Childhood Autism Rating Scale, **ABC:** Autism Behavior Checklist, **CSHQ:** Children's Sleep Habits Questionnaire*

Table V: Correlation between sleep problems, autism symptom severity and behavioral problems

	CARS	ABC	AbBC
CSHQ–Total			
Rho	.227*	.273**	.479**
p	.032	.010	.000

CSHQ:** Children's Sleep Habits Questionnaire, **CARS:** Childhood Autism Rating Scale, **ABC:** Autism Behavior Checklist, **AbBC:** Aberrant Behavior Checklist*, **:** p= .010, ***:** p = .050*

had at least one psychiatric comorbidities. The most common psychiatric comorbidities were attention deficit hyperactivity disorder (ADHD) (41.2%, n=40) and intellectual disability (ID) (22.7%, n=22). 33% (n=32) of the cases had severe (CARS total score= 37-60), 41.2% (n=40) had mild-moderate (CARS total score= 30-36.5) autistic symptoms according to CARS score. 72.2% (n=70) of the cases had a score above 39 according to the ABC (Tables I and II).

The median total score of CSHQ was 47 points (34-68). 58.8% of the subjects had clinically significant sleep problems (CSHQ total score >41). The median amount of the daily sleep of was 9.3 hours (min-max=5-12 hours). The median duration of waking up at night was 10 minutes (min-max: 1- 240 minutes) (Table III).

According to the QPGS-RIII, 38.1% of the cases had probable functional gastrointestinal disease: 26.8% (n=26) functional constipation, 2.1% (n=2) aerophagia, 8.2% (n=8) nonretensive fecal-incontinence (NFI), 4.1% (n=4) irritable bowel syndrome (IBS), 3.1% (n=3) adolescent rumination syndrome, 1% (n=1) functional abdominal pain syndrome and 1% abdominal migraine.

ASD group was divided into two subgroups according to having GIS disease: ASD +functional GIS disease and ASD without any GIS disease. And it was found that ABC total, sensory behavior, social and adaptive skills subscales and AbBC total and irritability subscale scores were statistically significantly higher in those with GIS disease comorbidity. In addition, it was demonstrated that children with functional GIS disease had a statistically significant higher clinical level of sleep problems than those without (Table IV).

A statistically significant positive correlation was found between the total CSHQ and the total scores of ABC, CARS and AbBC. No significant correlation was found between the children's night time awakening duration (minutes) and total daily sleep duration (hours) variables to the total scores of CARS, ABC and AbBC (p>0.050 for all) (Table V).

DISCUSSION

In our study, the frequency of functional gastrointestinal disorders and sleep problems and their relationship with each others, ASD severity and problematic behaviors were evaluated. ASD patients frequently have problematic behaviors. Oftenly clinicians overlook GIS and sleep problems that may be the underlying reasons for behavioral problems. Furthermore GIS symptoms might cause sleep disturbance and both aggravate problematic behaviors. It was thought that GIS dysfunction and sleep disturbance might increased ASD symptoms. And treating GIS and sleep problems might decrease ASD symptoms and challenging behaviors.

Among the many medical comorbidities associated with ASD, GIS symptoms drew considerable attention due to its prevalence and association with symptom severity (9). Studies has shown that GIS symptoms such as abdominal pain, constipation, diarrhea and flatulence are very common in children with ASD (6). Gorrindo et al. (10) identified constipation as the most common symptom (85%) in children with ASD. ASD children, who suffer from abdominal pain, gaseousness, diarrhea, constipation or pain on stooling have higher scores at AbBC subscales such as Irritability, Social Withdrawal, Stereotypy and Hyperactivity compared with children who don't have frequent GIS symptoms (11).

We demonstrated that functional gastrointestinal disorders are common in ASD patients and there is a positive correlation between autism severity and GIS problems. Most frequent GIS symptom was functional constipation according to our findings. GIS disorders might emerge as non-gastrointestinal symptoms especially with nonverbal patients such as sleep problems or challenging behavior. GIS symptoms might induce pain and inconvenience and lead to aggression and self harm behavior and sleep problems (12,13). According to our findings problematic behaviors such as irritability and sleep problems found more common in ASD patients who have GIS problems. Sometimes clinicians might consider problematic behaviors and sleep problems are occur due to autism itself. Yet, treating GIS disorder may decrease irritability, aggressive behavior and sleep problems. In our study increased/decreased sensory sensitivity was found higher in ASD with GIS disorder. Mazurek et al. (14) research the relationship between sensory hypersensitivity and GIS symptoms at ASD patients. They demonstrated that, autistic children who have chronic GIS problems had higher levels of sensory hypersensitivity. Sensory hypersensitivity might cause food selectivity which is a common problem in ASD. And food selectivity may give rise to constipation.

Sleep problems frequently accompanies ASD and increase the severity of behavioral and social skills problems and stereotypes (15,16). In a study conducted with a group of children, has shown that chronic sleep problems increase hyperactivity and impulsivity during school periods and predict poor performance in learning and neurodevelopmental tests (17). A positive correlation was found between autism severity and sleep problems in our study. Our findings revealed that, those who has sleep problems were more likely to demonstrated problematic behaviors than who hasn't. Therefore, treating sleep problems may reduce autistic symptoms, learning difficulties and problematic behaviours.

Limitations;

1. The mean age of the participants was young and some of them didn't developed language yet and they couldn't able to describe their symptoms well enough.
2. Some of the ASD patients were using medicine that was a confounding factor for the results.
3. Diet might affect GIS symptoms and we didn't use dietary dairy.

CONLUSION

In our study, it was shown that sleep problems and GI symptoms frequently accompany children with ASD, in line with the literature. It is appropriate to routinely evaluate patients with ASD in terms of gastrointestinal and sleep problems especially if behavioral problems accompanies. And treating GIS and sleep problems might decrease challenging behaviors that seen in ASD.

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Prenatal Substance Abuse: a 1-Year Single-Center Experience at a Tertiary Neonatal Intensive Care Unit

Prenatal Madde Maruziyeti: Tek Merkezli Bir Üçüncü Düzey Yenidoğan Yoğun Bakım Ünitesinde Bir Yıllık Deneyim

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ABSTRACT

Objective: Eight newborns diagnosed with prenatal substance abuse were evaluated for the clinical course of neonatal abstinence syndrome depending on the type of substances used by their mothers during pregnancy.

Material and Methods: A retrospective study of neonates with prenatal substance abuse admitted to our tertiary care university hospital's Neonatal Intensive Care Unit (NICU) was conducted between February 2022 and March 2023. Demographic data, withdrawal symptoms, need for pharmacological treatment, and duration of hospitalization were collected. Newborns exposed to substances were divided into two groups: opioid and non-opioid (methamphetamine, Bonsai, marijuana).

Results: Eight infants were included in the study. Four cases (50%) were in the group exposed to opioids. Pregnant users of opioids were older (28±6.73) than non-opioid substance users (21±4.83). The mean birth weight of newborns exposed to opioids (2541 g) was lower than that of the non-opioid group (3020 g). The average length of hospital stay was longer in the opioid group (34 days) compared to the non-opioid group (10 days). All newborns exposed to substances were born preterm (<37 gestational weeks). Withdrawal symptoms were observed in all cases in the opioid group and three cases in the non-opioid group to varying degrees. Medical treatment was required in three out of the seven cases with withdrawal symptoms. All patients requiring treatment were in the opioid group. All infants were discharged in good health.

Conclusion: Substance exposure during the prenatal period is a significant cause of preterm birth in neonates. Many of these substances can cause varying degrees of withdrawal syndrome in newborns. Replacement therapies used during pregnancy containing heroin and naloxone can lead to a more severe, prolonged, and treatment-requiring neonatal withdrawal syndrome than other substances. In cases where morphine and methadone are unavailable, the symptoms of withdrawal syndrome can be managed with phenobarbital. It is crucial to monitor all newborns with prenatal exposure to substances early because it allows for appropriate intervention and treatment.

Key Words: Abstinence, Newborn, Phenobarbital, Pregnancy, Substance use

ÖZ

Amaç: Doğum öncesi yasadışı uyuşturucu maruziyeti olan sekiz yenidoğan, gebelik sırasında kullanılan maddelerin türüne bağlı olarak gelişen neonatal yoksunluk sendromunun klinik seyri açısından değerlendirilmiştir.

Gereç ve Yöntemler: Hastanemizin üçüncü basamak Yenidoğan Yoğun Bakım Ünitesine (YYBÜ) Şubat 2022 ile Mart 2023 tarihleri arasında, doğum öncesi yasadışı madde maruziyeti nedeniyle yatırılan yenidoğanlarda retrospektif

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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. Health Sciences University, Bakirkoy Dr. Sadi Konuk Training, and Research Hospital Ethics Committee approved the study (Approval number 2022-20-05, 17/10/2022).

Contribution of the Authors / Yazarların katkısı*: *DOĞAN NN: Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***SALİHOĞLU Ö:*** Constructing the hypothesis or idea of research and/or article, Organizing, supervising the course of progress and taking the responsibility of the research/study, Reviewing the article before submission scientifically besides spelling and grammar.

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bir çalışma yürütüldü. Demografik veriler, yoksunluk belirtileri, farmakolojik tedavi ihtiyacı ve hastenede kalış süreleri kaydedildi. Madde maruziyeti olan yenidoğanlar opioid ve opioid-dışı (metamfetamin, Bonsai, esrar) olarak 2 gruba ayrıldı.

Bulgular: Çalışmaya toplam sekiz yenidoğan dahil edildi. Vakaların 4'ü (50%) opioide maruz kalan gruptaydı. Opioid kullanan gebeler (28±6.73), non-opioid madde kullanan gebelerden daha yaşlıydı (21±4.83). Opioide maruz kalan yenidoğanlarda ortalama doğum tartısı (2541 gr), non-opioid gruptan (3020 gr) daha düşüktü. Ortalama hastane yatış günü opioid grupta (34 gün), non-opioid gruptan daha uzundu (10 gün). Madde maruziyeti olan tüm yenidoğanlar preterm (<37 gestasyon haftası) doğmuştu. Opioid grubundaki tüm vakalar ile non-opiod grubundaki üç vakada çeşitli derecelerde çekilme semptomları gözlendi. Çekilme semptomları gözlenen vakaların 3'ünde medikal tedavi gerekti. Tedavi gerektiren hastaların tamamı opioid grubundaydı. Tüm yenidoğanlar sağlıklı olarak taburcu edildi.

Sonuç: Prenatal dönemde yasadışı madde maruziyeti yenidoğanlarda preterm doğumun önemli nedenlerindendir. Bu maddelerin birçoğu yenidoğanlarda çeşitli derecelerde yoksunluk sendromuna neden olmaktadırlar. Gebelikte kullanılan eroin ve nalokson içeren ikame tedavileri, diğer maddelere göre daha şiddetli, uzun seyirli ve tedavi gerektiren neonatal yoksunluk sendromuna neden olabilir. Morfin ve metadonun temin edilemediği durumlarda, yoksunluk sendromu bulguları fenobarbital ile kontrol altına alınabilir, Prenatal dönemde madde maruziyeti olan tüm yenidoğanların doğum sonrası erken izleme alınması, uygun müdahale ve tedaviye olanak sağladığından çok önemlidir.

Anahtar Sözcükler: Yoksunluk, Yenidoğan, Fenobarbital, Gebelik, Madde kullanımı

INTRODUCTION

Substance use remains an ever-growing global public health concern in all societies. Even though no studies have been conducted in our country, in the United States of America, the prevalence of using one or more substances during pregnancy was reported as 5.9% (1). The use of substances during pregnancy carries significant medical and social consequences for both the mother and the newborn (2). Many frequently used illegal substances, such as heroin, marijuana/hashish, synthetic cannabinoids (Bonsai), and stimulants like cocaine and methamphetamines, can cross the placenta and have various effects on the developing fetus (3). These effects include neonatal abstinence syndrome (NAS), cognitive deficit, sudden infant death syndrome, congenital defects, and behavioral problems (4). NAS has been reported to occur in 50 and 90% of neonates with intrauterine substance exposure. However, a considerable variation exists in NAS, the need for pharmacological treatment, hospitalization duration, and other associated morbidities (5, 6). In this article, we aim to evaluate withdrawal symptoms and clinical courses of neonates born to women with a history of substance use during pregnancy.

MATERIALS and METHODS

We evaluated neonates born at the University of Medical Science, Bakirkoy Dr. Sadi Konuk Training & Research Hospital between February 2022 and March 2023 and exposed to illicit substances in the prenatal period in this retrospective study. Health Sciences University, Bakirkoy Dr. Sadi Konuk Training, and Research Hospital Ethics Committee approved the study (Approval number 2022-20-05, 17/10/2022). The cases included in this study were selected based on the maternal history of substance use during pregnancy. We gathered demographic data of both the mothers and infants and other factors such as the necessity and duration of pharmacological treatment and the length of hospitalization. The demographic information collected encompassed gender, birth weight, gestational age at birth, mode of delivery, maternal age, and APGAR scores at 1 and 5 minutes. Eventually, eight infants were born to mothers meeting this criterion. In addition, we conducted interviews with the women to inquire about the specific types of substances they had used. Based on their responses, we categorized the substances into two groups: opioid and non-opioid. Similarly, the infants included in the study were also evaluated and classified into two groups: heroin and non-heroin (metamphetamine, Bonsai, hashish, marijuana). All newborns with a history of prenatal substance abuse were admitted to our neonatal intensive care unit for a post-delivery follow-up. The primary objective of their admission was to recognize any withdrawal symptoms and provide appropriate interventions promptly. Upon admission to the unit, routine hematological examinations (complete blood count, blood glucose, serum calcium, CRP, blood gas, serum vitamin D levels, blood group, and blood culture) were conducted and sent to the laboratory. In cases of respiratory distress, chest imaging was performed. Comprehensive cardiological evaluations and cranial-abdominal ultrasound examinations were conducted for all neonates. However, it was impossible to detect the substances in urine samples for all newborns due to collection difficulties and the unavailability of these tests in our laboratory during the study period. Withdrawal symptoms were assessed using a modified Finnegan scoring system every three hours for all newborns. Newborns with a birth weight below the 10% percentile (SGA) score according to the gestational week were recorded. Pharmacologic treatment was initiated for those with a score of ≥8. Furthermore, a consultation with a pediatric neurologist was sought for all cases.

RESULT

Eight newborns were born to pregnant women with a history of illicit substance abuse between February 2022 and March 2023. Therefore, our study included these newborns with substance exposure in utero. Five (62.5%) newborns were boys, while three (37.5%) were girls. All the neonates were inborn and were admitted to the NICU of our hospital on the first day of life. SGA was observed in one patient, accounting

Table I: Demographic Characteristics of Mothers With a History of Illicit Substance Use During Pregnancy

Variable	Mother 1	Mother 2	Mother 3	Mother 4	Mother 5	Mother 6	Mother 7	Mother 8
Age	32	30	17	28	18	19	20	32
Gestational Age (week)	38	34	37	35	35	35	36	36
Gravide	multiparae	multiparae	multiparae	multiparae	primiparae	multiparae	primiparae	multiparae
Education	Primary School	Primary School	-	Primary School	Primary School	-	High school	Primary school
Delivery Mode	c/s	Vaginal	Vaginal	c/s	c/s	c/s	Vaginal	c/s
Hepatitis B	-	-	-	-	-	-	-	-
Hepatitis C	+	+	-	-	-	-	-	-
HIV	-	-	-	-	-	-	-	-
Alcohol	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Cigarette (per/day)	15	10-15	15-20	10-15	40-60	20-25	10-15	20-25
Pre-pregnancy İllicit Use	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Marital Status	Yes	Single	Single	Single	Single	Single	Single	Single
Prenatal Visits	İrregular	No	No	No	No	No	İrregular	No
Illicit Drug Choice	Heroin Buprenorphin/ Naloxone	Heroin	Metamphetamine, Bonzai, Hashish	Metamphetamine, Cannabinoid	Heroin	Methamphetamine/ Bonzai	Metamphetamine	Heroin
Employement Status	-	-	-	-	-	-	-	-
Paternal/Partner Substance Use	Intermittant	Unknown	Unknown	Unknown	Unknown	Unknown	Yes	Unknown

Table II: Demographic Features and Clinical Properties of the Newborn Cases

Case No	1	2	3	4	5	6	7	8
Gender	male	female	female	male	male	male	male	female
Age on admission (days)	1	1	1	1	1	1	1	1
Gestational age (weeks)	38	34	37	35	35	35	36	36
Birth weight (g)	2320	2625	3275	2990	2620	2915	2900	2600
APGAR 1-minute	7	7	8	4	8	4	7	6
APGAR 5-minute	8	9	9	6	9	6	8	8
Minimum-Maximum Finnegan scores	12-16	11	1-6	0-2	2-6	1-5	0	4-11
NAS* (signs&symptoms)	+	+	+	+	+	+	-	+
fever	-	-	-	-	-	-	-	-
tremor/myoclonic jerks	+	+	-	-	-	-	-	+
tachypnea/retractions	+	-	-	-	+	+	-	+
ıncreased moro/sucking reflex	+	-	-	-	-	-	-	+
high pitched cry	+	+	+	+	-	+	-	+
watery stools	-	-	+	-	-	-	-	-
feeding difficulty	+	+	-	-	+	-	-	-
NAS onset (day of life)	1	3	4	2	2	2	-	1
Treatment	Phenobarbital Clonazepam Midazolam	Phenobarbital	-	-	-	-	-	Phenobarbital
Hospital stay (days)	62	17	10	12	34	12	6	21
Need of social service	+	+	+	+	+	+	+	+

NAS: *Neonatal Abstinence Syndrome*

Table III: Key features of Opioid and non-Opioid Groups

Substance	Mother Age	Gest. Age (week)	Birth Weight (g)	APGAR-1	APGAR-5	Onset of NAS (days)	Hospital stay (days)	Vit-D Levels
Opioid Group								
Heroin Buprenorphine /Naloxone	32	39	2320	7	8	1	62	5
Heroin	30	34	2625	7	9	3	17	9
Heroin	18	35	2620	8	9	2	34	7.2
Heroin	32	36	2600	6	8	1	21	3
Non-Opioid Group								
Meth†/bonz‡	17	37	3275	8	9	4	10	19
Meth/hashish	28	35	2990	4	6	2	12	6.7
Meth/bonz	19	35	2915	4	6	2	12	8.9
Meth	20	36	2900	7	8	0	6	7.8

†: Methamphetamine, ‡: Bonzai

for 12.5% of the cases, born to mothers with a history of heroin abuse. The demographic characteristics of mothers with a history of illicit substance use during pregnancy are presented in Table I, while Table II provides an overview of the characteristics of the newborns. The exact duration and amount of substance use could not be ascertained. Table III depicts the key features of opioid and non-opioid groups. Analysis of maternal serological status revealed two positive cases of Hepatitis C (25%), with neither being HIV positive. NAS occurred in seven newborns (87.5%), with three (37.5%) requiring medical treatment. Our treatment approach involved a combination of non-pharmacological and pharmacological management. Because morphine and methadone preparations were unavailable in our unit, our primary treatment option was phenobarbital. Newborns with a Finnegan score of 8 and higher received phenobarbital treatment. In one case where the signs of neonatal abstinence syndrome (NAS) were challenging to control, clonazepam and midazolam were added to the phenobarbital treatment, following a recommendation from pediatric neurology. After discharge, all infants were referred to a government social service because of parental incapacity and an unsuitable home environment.

DISCUSSION

Many studies worldwide suggest that substance use among pregnant women varies widely and reflects differences in drug availability, age, socioeconomic status, and screening modes. Substance abuse, including alcohol, nicotine, cocaine, cannabis, methamphetamine, and opioids during pregnancy, has been associated with preterm birth (1). According to previous research, tobacco is the most frequently used substance during pregnancy, followed by alcohol, cannabis, and cocaine (7). In our study, approximately 75% of the cases were classified as preterm (gestational age below 37 weeks). Notably, all mothers who delivered before term had a smoking history and 75% had a positive history of alcohol consumption. Even though opioid abuse during pregnancy has rapidly increased in the United States, studies also report increased methamphetamine abuse in women of childbearing age worldwide (8-10). Mothers who use methamphetamines during pregnancy exhibit characteristics such as being younger, having lower levels of education, having lower socioeconomic status, having a higher likelihood of drinking and smoking during pregnancy, and receiving less prenatal care before childbirth (11, 12). In the pregnant women who participated in our study, the prevalence of methamphetamine and heroin use was similar. Additionally, the mean age of mothers using methamphetamine was lower than that of mothers using heroin, aligning with existing literature on the subject.

Substance use during pregnancy has critical implications because it impacts the mother and negatively affects the developing fetus. One of these effects is Neonatal Abstinence Syndrome (NAS). NAS is a withdrawal syndrome that occurs when the placental transfer of substances, particularly opioids, is abruptly halted following chronic use by the mother. This phenomenon can disrupt postnatal adaptation to varying degrees. The opioid replacement therapy administered to the mother throughout pregnancy may also cause the development of NAS (13). The most characteristic symptoms of NAS include feeding problems, sleeping disorder, fever, jitteriness, myoclonic jerk, episodic activity, irritability, diarrhea, and high-pitched crying. The modified Finnegan scoring system is utilized to assess the severity of these symptoms and guide treatment, which assigns scores to each symptom based on their intensity. A score of eight or higher (≥ 8 points) indicates the need for close monitoring and treatment (14). The treatment of NAS can sometimes extend over several weeks. Currently, no standardized treatment protocol for NAS exists. Treatment approaches involve both pharmacological and non-pharmacological methods. Non-pharmacological interventions primarily focus on providing the baby with a calm and less stimulated environment. These measures include gentle and minimal touching, maintaining a quiet and dimly lit environment, swaddling, skin-to-skin care, offering a pacifier, and promoting breastfeeding (15).

Even though non-pharmacological interventions are effective, pharmacological treatment is recommended for newborns

with substantial abstinence symptoms (Finnegan score ≥ 8). Commonly recommended medications include oral morphine, diluted tincture of opium, methadone, clonidine, phenobarbital, and buprenorphine (16). In our study, three cases exposed to opioids and opioid replacement therapy in utero had a Finnegan score of 8 or higher, warranting pharmacological treatment. Managing the symptoms in the neonate of the first pregnant woman (Mother 1), who used heroin and Suboxone®, proved challenging as the onset of withdrawal symptoms occurred earlier compared to other cases. The presence of naloxone in the Suboxone® used by the mother contributed to a longer stay in the neonatal intensive care unit (NICU).

The most common treatment for managing substance addiction during pregnancy is replacement therapy with methadone. It is associated with improved obstetric care and is considered the gold standard for pregnant women with opioid addiction (17). However, in many centers, replacement therapy using buprenorphine during pregnancy has been reported to result in a milder abstinence syndrome (18, 19). A study involving ten pregnant women receiving buprenorphine/naloxone replacement therapy for opioid addiction during pregnancy reported no significant adverse effects for both the mother and the newborn. Nevertheless, the daily buprenorphine/naloxone dose used in that study did not exceed 16/4 (20). The FDA does not recommend the use of combined buprenorphine/naloxone treatment during pregnancy. However, if the prospective mother has already received this treatment before becoming pregnant and has achieved clinical stability, no further concerns were reported about continuing the same replacement therapy during pregnancy (21). In our study, the first mother received a buprenorphine/naloxone dose ranging from 24/6 to 32/8, higher than the doses reported in the literature. Additionally, the replacement therapy with the combined preparation containing naloxone was initiated during the 14th week of gestation, while the mother actively used heroin until the second trimester of her pregnancy. This finding was the reason for the severe abstinence syndrome observed. In our country, it is usually not possible to provide methadone treatment in daily clinical practice. Therefore, the combination of buprenorphine/naloxone remains the only replacement therapy option for pregnant women with opioid addiction.

Withdrawal symptoms in newborns typically become apparent within the first 24–72 hours after birth, but it is also possible for the symptoms to manifest later (>5 days) (22). In our study, withdrawal syndrome symptoms were observed in all newborns within the first five days of life. Because the onset of withdrawal symptoms may be delayed up to postnatal day five, it is safer to monitor newborns with in utero substance exposure in NICU for at least 5–7 days (22). Mild NAS was observed in newborns born to two pregnant women using synthetic cannabinoids, commonly known as Bonsai, in our country. Bonsai is a synthetic cannabinoid with similar effects and psychoactive properties to natural cannabis. Limited literature is available regarding synthetic cannabinoids during pregnancy, mainly in case presentations (23). In our study, pharmacological treatment was not required as the NAS symptoms were transient and resolved independently in both cases born to these pregnant women.

It is well-established that mothers with addiction issues are often young, unemployed, have low socioeconomic status, and have limited education. They may have extramarital pregnancies and lead irregular lifestyles. Their utilization of prenatal care services is typically minimal (12, 24). In our study, all the mothers were unemployed, the majority had low levels of education, and only one woman was married.

Most mothers in our study did not have prenatal visits. In addition to the medical importance, the participation of expectant mothers in prenatal visits is crucial for micronutrient supplementation, maternal preparation, and emotional bonding with the baby. Unfortunately, the rate of prenatal visits was only 22.5% in our study, and they were irregular.

In our study, newborns' serum vitamin D levels in both the opioid and non-opioid groups participating were found to be deficient (< 20 ng/ml) (25). This finding was attributed to inadequate nutrition and lack of vitamin D supplementation due to poor prenatal care, preterm birth, and low socioeconomic status associated with unemployment.

Women who engage in substance use during pregnancy are at a higher risk of acquiring HIV, hepatitis B, hepatitis C infections, and syphilis. Routine screening for HIV, HBV, and syphilis in pregnant women enables early detection and intervention (12, 26). Even though no routine screening test is conducted for HCV in pregnant women, the ever-increasing substance addiction rates during pregnancy also increase HCV infections (27). In our study, two cases tested positive for HCV, supporting this observation. Including HCV screening as part of the routine tests for pregnant women with substance use is critical for identifying vertical virus transmission and determining the infant's seroconversion after discharge.

It is encouraging to note that many women with substance abuse issues are motivated to quit or reduce their substance use when they become pregnant due to concerns about the potential harm to their babies (19). This motivation was also observed in our cases, with all women striving to quit the substances they were using. Pregnancy poses a unique opportunity for healthcare providers to support and assist pregnant women in discontinuing substance use. By providing appropriate medical care, counseling and support, physicians can help pregnant women achieve substance-free pregnancies.

CONCLUSION

In our study, we observed that illicit substance, especially opioid use during pregnancy, seems to cause NAS, with a severe course in the neonatal period, usually requiring pharmacological treatment. The preference for combined preparations containing

naloxone in replacement therapy used for treating substance abuse in pregnant women has been associated with increased severity and duration of the abstinence syndrome in newborns. However, the likelihood of illegal substances other than opioids causing severe withdrawal syndrome requiring pharmacological treatment seems low. All clinicians responsible for neonatal care should be alert about this issue.

It is important to note that the onset of abstinence symptoms may be delayed, necessitating close observation of newborns with a history of prenatal substance exposure for at least one week.

Phenobarbital is an effective adjuvant treatment option for controlling withdrawal symptoms in cases where morphine and methadone drugs are unavailable. Regular prenatal care, like all pregnant women, can contribute to achieving more reasonable vitamin D levels for pregnant women with addiction issues. Even cases with the most severe prognosis of abstinence syndrome can be successfully managed with early monitoring, intervention, and treatment. By ensuring timely and appropriate care, healthcare professionals can positively impact the outcomes of newborns affected by prenatal substance exposure.

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A Retrospective Study on the Availability of Arterial Lactate Levels as a Biomarker of Mortality in Critically Ill Children

Kritik Hasta Çocuklarda Arteriyel Laktat Düzeylerinin Mortalite Biyobelirteci Olarak Kullanılabilirliğine İlişkin Retrospektif Bir Çalışma

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ABSTRACT

Objective: We aimed to determine the threshold value of lactate levels, and to analyze its avaliability as mortality biomarker by correlating it with scoring systems in pediatric intensive care unit (PICU).

Material and Methods: Observational retrospective cohort study. Our study was conducted among patients admitted to the 24-bed tertiary PICU of our hospital in 2015. All children between the ages of 1 month and 18 years were evaluated. Among 433 patients whose arterial blood gases were obtained during hospitalization, a total of 382 were included in the study. Patients with congenital metabolic disease with lactic acidosis were excluded.

The arterial blood lactate levels on admission, PIM-2, PRISM-III and PELOD scores and survival status of the patients were evaluated. Correlation between lactate levels and mortality scores, threshold values of lactate levels and the factors affecting mortality risk were the main variable of interest.

Results: There was a significant correlation between lactate levels and scores in patients who died ($p<0.001$). Receiver operating characteristic (ROC) curve analysis showed that blood lactate level was an effective parameter on mortality (area under the curve=AUC: 0.861; $p<0.001$) with a cut-off value of 2.55 mmol/L. The mortality risk was 1.38 fold higher in patients with higher levels of lactate.

Conclusion: In our series, the levels of lactate were higher in critically ill children who died. Again, lactate levels and mortality scores of these children were correlated. In our series, the levels of lactate were higher in critically ill children who died. Again, lactate levels and mortality scores of these children were correlated. We were able to establish a cut-off point with high specificity for predicting evolution. These findings should be validated in prospective and multicenter studies for their incorporation into scoring systems.

Key Words: Lactate, Mortality, Pediatric intensive care, PELOD, PIM-2, PRISM-III

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ÖZ

Amaç: Çocuk yoğun bakım ünitesinde (ÇYBÜ) laktat düzeylerinin eşik değerini belirlemeyi ve bunun mortalite biyobelirteci olarak kullanımının skorlama sistemleriyle korelasyonunu analiz etmeyi amaçladık.

Gereç ve Yöntemler: Gözlemsel retrospektif bir kohort çalışmasıdır. Çalışmamız 2015 yılında hastanemizin 24 yataklı üçüncü basamak ÇYBÜ'sine başvuran hastalar arasında yapılmıştır. 1 ay-18 yaş arasındaki tüm çocuklar değerlendirildi. Yatış sürecinde takipte arteriyel kan gazı alınan 433 hastanın 382'si çalışmaya alındı. Laktik asidozlu konjenital metabolik hastalığı olan hastalar çalışma dışı bırakıldı.

Hastaların başvuru anında alınan arteriyel kan laktat düzeyleri, PIM-2, PRISM-III, PELOD skorları ve hastaların sağkalım durumları değerlendirildi. Laktat seviyeleri ile mortalite skorları arasındaki korelasyon, laktat seviyelerinin eşik değerleri ve mortalite riskini etkileyen faktörler ana değişkenlerdi.

Bulgular: Ölen hastaların laktat düzeyleri ile mortalite skorları arasında anlamlı bir ilişki vardı ($p<0.001$). ROC eğrisi analizinde kan laktat düzeylerinin mortalite üzerinde etkili bir parametre olduğu (eğri altındaki alan=AUC: 0.861; $p<0.001$) ve eşik değeri 2.55 mmol/L olarak bulundu. Laktat düzeyi yüksek olan hastalarda ölüm riski 1.38 kat daha fazlaydı.

Sonuç: Mortalite olan kritik çocuklar hastalarda laktat düzeyleri daha yüksekti. Aynı çocukların laktat seviyeleri ve mortalite skorları korele edildi. Tanımladığımız eşik değerlerin üzerinde mortalitenin arttığı görüldü. Bu bulguların skorlama sistemlerine dahil edilebilmesi için prospektif ve çok merkezli daha fazla çalışma ile doğrulanması gerekmektedir.

Anahtar Sözcükler: Laktat, Mortalite, Pediatrik yoğun bakım, PELOD, PIM-2, PRISM-III

INTRODUCTION

The aim of intensive care is to combat life-threating diseases involving multiple organs and systems. This requires the provision of life support, the implementation of possible treatment options, and accurate patient care and monitoring. Disease rating and risk assessment provide early detection of treatment requirements and necessary measures. Thus, the chance of survival of patients in intensive care, whose morbidity and mortality rates are considerably higher than other patients, can be increased (1).

The comparison of patients hospitalized in one unit or in different units in terms of morbidity is quite challenging since the clinical conditions of patients admitted to intensive care units (ICU) may vary significantly. Scoring systems are used to facilitate this comparison (1). The most commonly used mortality scoring systems are 'Pediatric Risk of Mortality' (PRISM) and 'Pediatric Mortality Index' (PIM) (2,3). In addition, the best known scoring system to assess organ failure is the 'Pediatric Logistic Organ Dysfunction' (PELOD) system (4).

Although the general approach to critically ill patients has changed over the last few years, there is still no definitive indicator for predicting mortality. With the inclusion of additional parameters such as the level of lactate, which is the most important determinant of tissue perfusion and oxygenation, in the scoring systems used to determine mortality in adult patients, some previous studies have attracted attention due to their significant results (5,6).

Lactate has been used as an indicator of tissue hypoperfusion and cellular hypoxia and its relation with mortality and prognostic importance have been shown in various studies (7,8). The results of both serial lactate measurements and studies predicting mortality with a single lactate measurement taken during hospitalization are limited and controversial. Furthermore, a cut-off limit of lactate for predicting the risk of death in critically ill children has not been established (9,10).

In this study, we aimed to measure arterial blood gas lactate levels during the onset of critical illness in children and analyze its avaliability as a mortality-biomarker by correlating it with validated PIM-2, PRISM-III and PELOD scoring systems. We also aim to show that measuring the level of lactate within 24 hours after the onset of critical illness may contribute to the capabilities of existing predictive scoring systems.

MATERIALS and METHODS

The study was approved by the Izmir Behçet Uz Training and Research Hospital Clinical Research Ethics Committee on February 16, 2017 (decision number: 2017/02-05). Informed consent from the parents of the patients were obtained.

The data of patients hospitalized in our pediatric intensive care unit (PICU) between January and December 2015 were obtained using the electronic database of our hospital. Patients who were hospitalized in the PICU during the study period, whose data could be accessed, and whose arterial blood gases and lactate levels were measured at the time of hospitalization were included in the study.

Patients with congenital metabolic disease with lactic acidosis and organic acidosis, patients in the neonatal period of 0-30 days, patients followed-up postoperatively, and patients who were referred to another hospital were excluded from the study. Although arterial sampling is preferred for blood gas analysis in the PICU, this is not possible in all patients. Since arterial blood samples are required to evaluate blood gas lactate levels, venous samples were not included in the study. Patients referred to the PICU from other centers were excluded from the study because it was thought that previous interventions performed on these patients may have been partially documented and these interventions may have affected the arterial blood gas lactate measurements. Since the data of our study were obtained retrospectively from the file records, cases in which the necessary data could not be accessed were also excluded.

Patients were classified according to age, gender, duration of PICU stay, etiology, C-reactive protein (CRP) and procalcitonin (PCT) levels in patients with sepsis, presence of chronic disease, duration of stay in mechanical ventilation (MV)/non-invasive mechanical ventilation (NIMV)/high-flow nasal cannula (HFNC), survival status, arterial blood gas lactate level, PIM-2, PRISM-III and PELOD scores.

The lactate levels of the patients were obtained from the first arterial blood gas samples collected during the first interventions at the time of admission to the pediatric intensive care unit. The survival rate of the patients was determined according to their mortality in the first 28 days after hospitalization.

In our clinic, the diagnosis of organ dysfunction is made according to the criteria reported by Pediatric Sepsis International pediatric sepsis consensus conference in 2005 (11). According to these diagnostic criteria, arterial blood lactate levels of hemodynamically unstable patients with cardiovascular dysfunction were also evaluated.

Mortality calculations of scoring systems were performed logarithmically in a digital environment (12,13).

According to the definitions of the National Center for Health Statistics (NCHS) and the World Health Organization (WHO), we considered a disease as chronic if it lasts longer than 3 months, progresses slowly, cannot be completely cured, and prevents the person from maintaining daily life and activities (14, 15). In accordance with this definition, cerebral palsy, severe congenital cardopathy, metabolic diseases, bronchiolitis obliterans, bronchopulmonary dysplasia, malignancy, renal failure and multiple congenital anomalies are considered as chronic diseases.

Blood lactate levels were measured in our hospital laboratory using ABL90 series blood gas device (Radiometer Medical ApS, Åkadej 21, DK-2700brønshøj, Denmark). Blood samples were transported in cold chain with heparinized syringes. Normal lactate level, hyperlactatemia, and lactic acidosis were defined as 0.5-2.50 mmol/L, 2.5-50 mmol/L, and >5 mmol/L, respectively (16-18).

For descriptive statistical evaluation, percentage (%) and frequency values were used for categorical variables; median (minimum (min) and maximum (max); and interquartile range (IQR) or mean and standard deviation (SD) values were used for numerical variables. Chi-square or Fisher's exact test was used for categorical variables and Mann-Whitney U test was used for numerical variables that were not normally distributed to compare the deceased and surviving patient groups. Pearson correlation analysis was performed between lactate levels and mortality scores of deceased patients.

Receiver operating characteristics (ROC) curve analysis was used to determine a lactate threshold value to predict mortality and calculate predictive power. The parameter was assumed to be discriminative if the area under the curve (AUC) was above 0.50. After constructing the ROC curve, the AUC value was used to show that lactate is a predictor of mortality risk. Then, the coordinates of the ROC curve and the sensitivity and specificity values for each coordinate were determined. The coordinate with the highest sensitivity and specificity was selected as the cut-off value and then positive and negative predictive values were calculated by cross-tabulation by using this cut-off value. Furthermore, Youden's index was calculated to determine whether the cut-off values were suitable for diagnostic use and values above 50% were considered significant.

One-way analysis of variance (ANOVA) was performed to determine whether there was a difference in lactate levels between etiologic groups and if there was a difference, to determine where the difference originated from.

Logistic regression analysis was performed to determine the factors affecting mortality risk and to create a model.

Statistical analyses were performed using SPSS 22.0 Microsoft for Windows. P value less than 0.050 was considered significant.

RESULTS

A total of 433 patients were evaluated. Among the 382 patients included in the study, 170 (44.50%) were female and 212 (55.50%) were male. The mean age was 18 months (min:2, max:300; IQR 54). The mean follow-up period was 5 days (min: 1, max: 372; IQR 10). Forty-nine (12.80%) patients died (Table I).

The most common etiology for hospitalization was respiratory diseases (n=140, 36.60%). In 201 patients (52.60%), an underlying chronic disease was identified. Respiratory support was needed in 147 (38.50%) cases and invasive mechanical ventilation was applied in 85 (57.90%) patients. The median duration of respiratory support was 5 days (min: 1, max: 230; IQR: 18). The median arterial blood gas lactate level of all patients was 1.8 mmol/L (min: 5, max: 18; IQR: 1.6) and hyperlactatemia and lactic acidosis were detected in 29.8% (n=114) of these patients. The median values of PRISM 3, PIM 2 and PELOD scores were 5, 0.90 and 1, respectively (Table I).

It was determined that there was a significant difference in the level of lactate between all etiologic groups and this difference was due to the sepsis group ($p<0.001$ post hoc test: Bonferroni). The mean lactate value was higher in the sepsis group compared to the other groups [5.10 ± 4.14 mmol/L (min: 0.70, max: 18)].

Sepsis (n=19, 38.80%) was the most common diagnosis among 49 patients who died. When sepsis cases were evaluated in terms of CRP and PCT values, there was no difference in PCT values between survivors and non-survivors, while CRP values were higher in non-survivors ($p = 0.245$; $p = 0.024$, respectively).

The prevalence of chronic disease (81.60%) and respiratory support therapy (95.90%) was higher in patients who died

Table I: Comparison of patients who died and were alive.

	Patients who died	Patients who were alive	Total	p
Number and percentage of patients	49/12.8	333/87.2	382	-
Etiology*				
Respiratory tract diseases	14/28.6	126/37.8	140/36.6	
Neurologic disorders	4/8.2	61/18.3	65/17	
Intoxication and trauma	1/2	50/15	51/13.4	
Sepsis	19/38.8	18/5.4	37/9.7	0.032
Cardiovascular diseases	7/14.3	24/7.3	31/8.1	
Dehydration	1/2	19/5.7	20/5.2	
Renal diseases	2/4.1	14/4.2	16/4.2	
Diabetic ketoacidosis	-	12/3.6	12/3.2	
Others	1/2	9/2.7	10/2.6	
CRP value in patient with sepsis (mg/dl)†	11.7; 2.42-49.04; 9,66	5.8; 2.05-24.2; 6.83	7.6; 2.05-49.04; 9.03	0.024
Procalcitonin value in patient with sepsis (ng/ml)†	2.1; 0.14-7.16; 4.4	1.2; 0.02-9.6; 3.03	1.44; 0.02-9.6; 3.64	0.245
Presence of chronic disease*	40/81.6	161/48.3	201/52.6	<0.001
Lactate values in patients with cardiovascular dysfunction (mmol/L)†	5.35; 0.8-18; 9.7	2.3; 0.7-16; 2.4	3.1; 0.7-18; 3.6	<0.001
Need for respiratory support*	47/95.9	100/30	147/38.5	
Invasive mechanical ventilation	46/97.8	39/39	85/57.9	<0.001
Non-invasive mechanical ventilation	0/0	9/9	9/6.1	<0.001
High flow nasal cannula	1/ 2.2	52/52	53/36	
Duration of respiratory support (days)†	7, 1-180, 24	5, 1-230, 13	5, 1-230, 18	0.413
Blood lactate level (mmol/L) †	5.1, 0.8-18, 9.4	1.7, 0.5-16, 1.3	1.8, 0.5-18, 1.6	
Hyperlactatemia*	15/30.6	66/19.8	81/21.2	<0.001
Lactic acidosis*	25/51	8/2.4	33/8.6	<0.001
Normal level*	9/18.4	259/77.8	268/70.2	
PRISM III score†	21; 2-45; 18	3; 2-35; 5	5; 2-45; 7	<0.001
PIM 2 score†	52.9; 24-99; 51.6	0.8; 0.5-80; 2	0.9; 0.6-99; 8.7	<0.001
PELOD score†	23; 12-52; 20	1; 0-32; 10	1; 0-52; 11	<0.001
PELOD mortality‡	26; 13-100; 83.4	0.1; 0-87.7; 1	0.1; 0-100; 1	<0.001

:** *n(%),* **†:** *median, min-max, IQR,* **‡:** *median,* ***PRISM III: *Pediatric risk of mortality score III,* ***PIM 2:*** *Pediatric index of mortality – 2,* ***IQR:*** *interquartile range,* ***PELOD:*** *Pediatric logistic organ dysfunction*

Table II: Results of correlation analysis between lactate levels and scoring systems.

Pearson correlation analysis	PRISM-III score		PIM-2 score		PELOD score	
	r	p	r	p	r	p
Lactate level	0.658	<0.001	0.693	<0.001	0.557	<0.001

r: *correlation coefficient,* ***PRISM III:*** *pediatric risk of mortality score III,* ***PIM 2:*** *pediatric index of mortality – 2,* ***PELOD:*** *pediatric logistic organ dysfunction*

compared to those who were alive (p<0.001, p<0.001, respectively). Invasive mechanical ventilation was the most commonly used respiratory support therapy in patients who died (97.80%). The need for respiratory support therapy was higher in patients who died compared to those who were alive (p<0.001). While there was no difference in the duration of respiratory support therapy between the two groups, arterial blood level of lactate (median: 5.10; min:0.8, max:18; IQR:9.40) was higher in patients who died compared to those who were alive (median: 1.70; min:0.50, max:16; IQR:1.30) (p<0.001) (Figure 1). As expected, the median PRISM3, PIM2 and PELOD scores were significantly higher in patients who died (p<0.001, p<0.001 and p<0.001, respectively) (Table I).

The most common organ dysfunction in our patient group was respiratory system dysfunction with a rate of 38.40% (147/382). Cardiovascular dysfunction was detected in 26.40% (101/382) of the patients. This group had a higher median arterial blood gas lactate (median 3.10mmol/L, min 0.70-max 18, IQR 1.30) than the group of patients without cardiovascular dysfunction (median 1.60mmol/L, min 0.50-max 13.70, IQR 1.30) (<0.001). Furthermore, mortality was observed in 37.60% (38/101) of patients with cardiovascular dysfunction compared to 3.90% (11/281) in the other group (p<0.001). Arterial blood gas lactate levels were higher in patients with cardiovascular dysfunction, who died, compared to patients with cardiovascular dysfunction who were alive (p<0.001) (Table I).

Table III: Receiver operating characteristic (ROC) analysis showing that arterial blood gas lactate values were effective on the mortality risk.

Lactate level (mmol/L)	
Cut-off value	2.55
Sensitivity*	81.6
Spesifity*	77.8
Positive predictive value*	35.1
Negative predictive value*	96.6

**(%)*

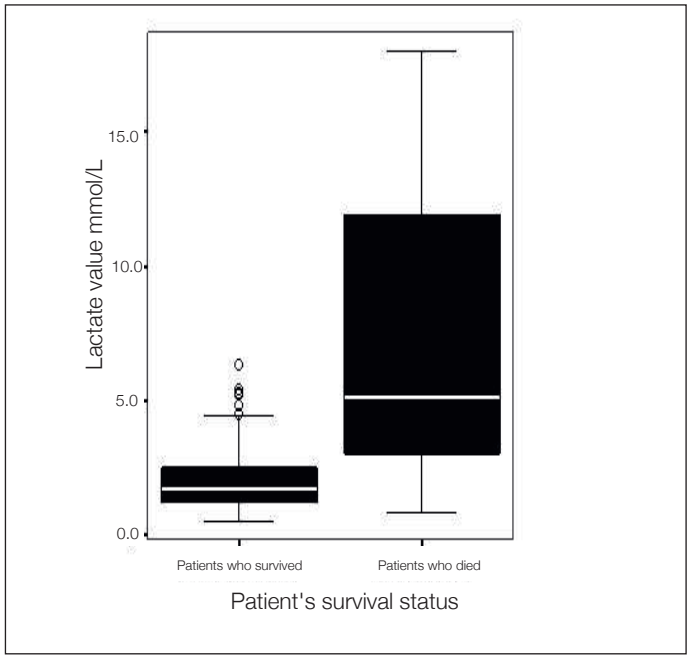

Figure 1: Box plot graph showing lactate levels of patients who died and were alive.

There was a good and significant correlation between the levels of lactate and mortality scoring systems in patients who died (Table II).

ROC analysis revealed that the arterial blood gas lactate level was an effective parameter on mortality risk (AUC: 0.861 (95% confidence interval (CI): 0.79-0.93; p<0.001)) and the cut off value was 2.55 mmol/L (sensitivity 81.6%, specificity 77.8%, positive predictive value: 35.10%, negative predictive value: 96,60%) (Table III). This cut-off value had a low value for predicting a high risk of mortality in patients with a lactate level >2.55 mmol/L (positive predictive value: 35.10%) and a high value for predicting a low risk of mortality in patients with a lactate level ≤2.55 mmol/L (negative predictive value: 96.60%) (Figure 2). After determining the coordinates of the curve obtained by ROC analysis, the lactate level with the highest sensitivity and specificity was selected as the cut-off level and the Youden index of this value was found to be 59.40, which was statistically significant (p<0.001).

The lactate value was >2.55 mmol/L in 40 (81.60%) of 49 patients who died, while it was below the limit value in 259

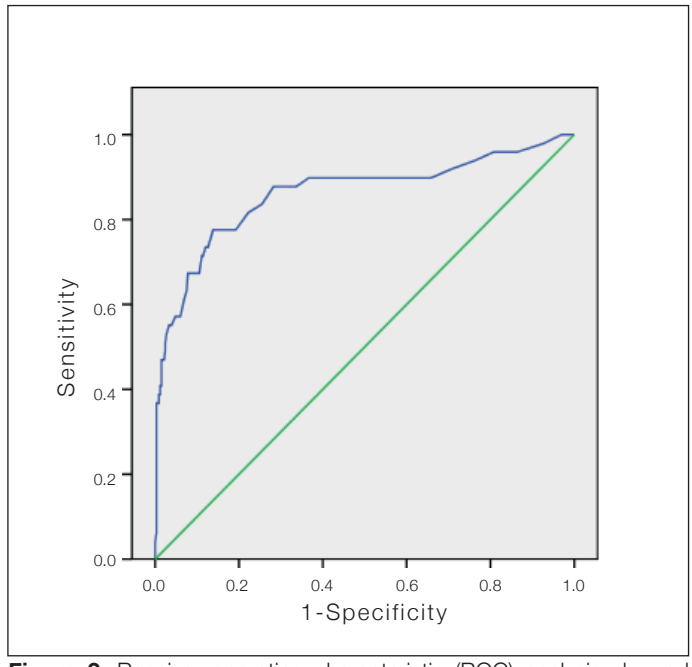

Figure 2: Receiver operating characteristic (ROC) analysis showed that the arterial blood gas lactate values were effective on mortality risk.

(77.80%) of 333 patients who survived (p<0.001). Furthermore, 11 of 13 patients (84.60%) with sepsis and lactate levels >2.5 mmol/L died, while only 8 of 24 patients (33.30%) with sepsis and lactate levels ≤2.50 mmol/L died (p=0.003).

Logistic regression analysis was performed to determine the factors affecting mortality risk. As a result, the mortality risk was 1.38-fold higher in patients with lactate levels above the threshold (Odds ratio: 1.38; p<0.001; 95% CI: 1.1-1.6).

DISCUSSION

Standard mortality scoring systems are systems used to identify risky patients in ICUs, to determine the treatment plan early, and to ensure quality control of ICUs. In order to improve these systems, they should be applied in different units and patient groups and their validity should be tested. The systems should be updated over time, taking into account changes in health care quality and treatment practices. Ideal scoring systems are those that have successfully passed reliability and validity tests (19, 20).

According to the consensus decision of the ethics committee of the intensive care association, it is not appropriate to use scoring systems as the sole source for making the decision to start and continue intensive care treatment (20). Therefore, in addition to scoring systems developed for early recognition of mortality, parameters that will give rapid and effective results should also be used.

Lactate has been used as an indicator of tissue hypoperfusion and cellular hypoxia and its relation with mortality has been shown in several studies (7,8). Lactate values can be obtained

quickly and easily in arterial blood gas which is used in the first step in diagnosis and treatment at ICUs. Hyperlactatemia is a predictive marker in determining the risk of death in adult patients admitted to ICUs. Hyperlactatemia has been proven to increase the ability of prognostic scoring systems in predicting mortality when included (5,6). In children, lactate levels are not included in standard scoring systems. In our study, we aimed to find a cut-off value for lactate obtained from blood arterial gas at hospitalization that predicts mortality, to determine the relationship between lactate and mortality and survival, and to prove its efficacy by correlation with the validated PIM-2, PRISM-III and PELOD scoring systems.

Lactate is a by-product of anaerobic cellular metabolism. Anaerobic metabolism becomes dominant to provide energy in the absence of tissue perfusion and in cases such as hemorrhagic shock or septic shock where tissues are provided with insufficient oxygen. This leads to increased lactate metabolism in the liver and kidneys and elevated lactate levels in the blood (9,21). In this study, the median lactate value in all patients was 1.8 mmol/L (min:0.5, max:18; IQR:1.6). In 29.80% of these patients, lactate levels were above 2.50 mmol/L. In a study conducted on 140 patients admitted to PICU, lactate levels in the first 24 hours after hospitalization were shown to have higher sensitivity and specificity in predicting mortality risk (22). El-Mekkawy et al. (9) reported that hyperlactatemia persisting 24 hours after hospitalization was associated with mortality. In a single-center study including a large number of patients, a significant correlation was found between serum lactate levels during hospitalization and mortality (21). In another study, patients with lactate levels > 2 mmol/L obtained within 48 hours of hospitalization had poor neurological outcomes as well as mortality (23). In another study in which serum lactate level was examined as an indicator of mortality, mortality rate was 24% in 79 patients and serum lactate levels were found to be 0.79-17.17 mmol/L in survivors and 1.14-24.50 mmol/L in those who died. The relationship between lactate levels in deceased and surviving patients was significant ($p<0.050$) (24). In our study, lactate levels during hospitalization were shown to be a significant indicator of mortality ($p<0.001$).

Several studies have shown that blood lactate levels can be considered as a useful indicator in determining the severity of diseases and mortality rates (21,25,26). On the other hand, there are also studies showing that the initial lactate level measured at the time of hospitalization is a poor predictor of mortality. Mortality studies with a single lactate value at the time of hospitalization as well as studies with serial lactate measurements are still controversial (10,22,27).

However, there is no acceptable lactate cut-off value for predicting mortality in critically ill children. In our study, we calculated the cut-off value of blood lactate level for predicting in-hospital mortality. ROC curve analysis revealed that the lactate cut-off value for predicting mortality was 2.55 mmol/L (sensitivity 81.60%, specificity 77.80%, positive predictive value: 35.10%, negative predictive value: 96.60%). The low positive predictive value but high negative predictive value of this cut-off suggested that the mortality rate would be lower in patients with lactate levels below 2.55 mmol/L. In a similar study, the lactate cut-off value for in-hospital mortality was 5.50 mmol/L. The sensitivity, specificity, positive and negative predictive values of this cutoff value were found to be 61%, 86%, 84% and 66%, respectively (21).

While the adjusted probability of death in patients with a lactate value between 2.50-4 mmol/L is 2.20 (1.10-4.20), there is a 7.10 (3.60-13.90) fold higher probability of death in patients with lactate≥4.0 mmol/L (28). In a study conducted by Anıl et al. on pediatric patients admitted to the emergency department, It was shown that high lactate levels during hospitalization could predict mortality ($p<0.001$) and the lactate cut-off value was calculated as 5.10 mmol/L (sensitivity 93.30%, specificity 80.60%, positive predictive value 70%, negative predictive value 96.20%) (29). In another study conducted in 1299 children with sepsis, it was emphasized that lactate levels above 36 mg/dL (=3.60 mmol/L) on admission were associated with 30-day mortality (odds ratio, 3.26; 95% CI: 1.16-9.16) (30).

Patients with high lactate levels are critically ill patients at risk of developing multiple organ failure. Lactate concentrations and mortality rates increase almost linearly. Patients with high lactate levels (>2 mmol/L) beyond the first 24 hours have a higher mortality rate (31). In our study, we found that the mortality rate increased significantly (81.60%) in patients with lactate levels above the cut-off value (>2.55 mmol/L) ($p<0.001$).

In our study, the median value of arterial blood gas lactate in patients who did not survive in the cardiovascular dysfunction group was found to be above the cut-off value (5.35 mmol/L) and below the cut-off value (2.30 mmol/L) in the surviving group.

In this study, it was found that lactate levels were higher in patients with sepsis compared to other etiologies and mortality was higher in patients with sepsis. Andre et al. found that the initial lactate value measured in the emergency service was associated with mortality in patients (32). In our study, lactate levels were >2.55 mmol/L in 84.6% of patients who died due to sepsis. We emphasize the necessity of early initiation of targeted treatment in such patients.

Many studies on human lactate levels have shown that an increase in lactate level from 2.10 to 8 mmol/L decreased survival from 90% to 10% (33). In our study, arterial blood gas lactate level was found to be higher in patients who died. There was a significant correlation between blood lactate levels and mortality scores of the dead patients. Patients with lactate levels above the lactate cut-off value of 2.50 mmol/L had a 1.38-fold increased risk of mortality. Bai et al. reported that a 1 mmol/L increase in lactate levels resulted in a 1.38-fold increase in the risk of death (21).

In our study, we found a high correlation between lactate levels during hospitalization and PRISM-III, PIM-2 and PELOD scores of patients admitted to the PICU ($p<0.001$). In a previous study, the combined assessment of PRISM-III scores and lactate levels during hospitalization was shown to better in predicting mortality ($p=0.018$) (21). In another study, lactate level during hospitalization was shown to predict mortality independently of PIM-2 scores in patients admitted to the PICU (10). In their study in patients with sepsis, Scott et al. showed that the median lactate level obtained from venous catheters was 2.26 (IQR: 1.76-3.63) mmol/L in patients with a PELOD score ≥10 and 2.02 (IQR: 1.44-2.83) in patients with a PELOD score <10 (34).

As known, mortality scoring systems are calculated by using laboratory and clinical parameters predicting the risk of mortality and give a mortality rate predicted by logarithmic method in terms of the score obtained (20). We think that if arterial blood gas lactate level measurement, which is an important tissue perfusion marker and was shown to be effective in determining the mortality risk in our study, is added to the laboratory parameters in the currently used scoring systems, this may increase the predictive power of the scoring systems.

The most important limitation of our study is that it was retrospective. Reflecting the experience of a single center is another limitation of our study. Another limitation is the uncertainty of the duration of arterial blood gas analysis. We could not accurately measure the time between admission and arterial blood gas sampling. In addition, the lactate value used in the study is the baseline value, not the patient's worst lactate level. In our observational study, patient-specific clinical decisions may also have an impact on the prognosis of patients. However, the adequacy of the number of patients and the threshold value determined for lactate levels are positive aspects of our study. In addition, the results of future studies may contribute to the inclusion of lactate levels in pediatric intensive care mortality scoring systems, which will increase the value of our study.

In conclusion, we found that measuring lactate level in arterial blood gas analysis is useful in predicting mortality in patients admitted to PICUs. We also found a significant correlation between arterial blood gas lactate measurements and mortality scores. We showed that the risk of mortality is increased in patients with lactate levels above the determined cut-off value. In our study, we showed that lactate is a good indicator of mortality. Measurement of lactate levels in PICUs may be useful in early mortality risk classification.

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Behavior Problems in Preschoolers with Developmental Language Disorder

Gelişimsel Konuşma Bozukluğu Olan Okul Öncesi Çocukların Davranış Problemleri

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ABSTRACT

Objective: Children with developmental language disorder (DLD) are prone to numerous adverse outcomes throughout their lives. The aim of the study was to investigate risk factors and behavior problems in children aged 1.5 to 5 years with DLD in a low/middle-income country.

Material and Methods: This case-control study included 101 preschoolers (54 children with DLD and 47 children with typical development (TD)). A developmental pediatrician evaluated each child's development using the Ages and Stages Questionnaire. Children Behavior Checklist and Beck Depression Inventory were completed by mothers. Socio-demographic information and screen parameters were obtained using a researcher-developed form.

Results: Risk factors for DLD were identified as less frequent reading books with parents, consanguineous marriage, and having a family member with language disorders. Preschoolers with DLD had more behavior problems (except sleep and somatic problems) than preschoolers with TD ($p<0.050$). The risk factors for behavior problems of preschooler with DLD in the multivariable regression model included: ages of parents and children, paternal education, lack of having their own room, and maternal depressive symptoms.

Conclusion: Consistent with the findings of this study, consanguineous marriage, family history of language disorders, and infrequent reading of books with parents were associated with the development of DLD. Attention should be given to behavioral problems in preschool children with DLD. Maternal depressive symptoms, lower paternal education, younger father, and lack of having their own room can be highlighted factors for behavior problems of children with DLD. Parents play a crucial role in shaping behavior and language development during the preschool period.

Key Words: Behavior problems, Developmental language disorder, Preschool period

ÖZ

Amaç: Gelişimsel konuşma bozukluğu (GKB) tanısıyla izlenen çocuklar, yaşamları boyunca birçok olumsuz durumla karşılaşabilirler. Çalışmanın amacı, düşük/orta gelirli bir ülkede yaşayan 1.5-5 yaş arası GKB olan çocukların davranış problemlerini ve GKB risk faktörlerini araştırmaktır.

Gereç ve Yöntemler: Bu vaka-kontrol çalışmasına, okul öncesi yaş grubundaki 101 çocuk (GKB tanısı olan 54 çocuk ve tipik gelişim gösteren (TD) 47 çocuk) dahil edildi. Her çocuğun gelişimi Erken Gelişim Envanteri kullanılarak gelişimsel pediatri uzmanı tarafından değerlendirildi. 1.5- 5 Yaş Çocukları İçin Davranış Değerlendirme Ölçeği ve Beck Depresyon Envanteri anneler tarafından doldurduldu. Sosyo-demografik özellikler ve ekran parametreleri, araştırmacılar tarafından geliştirilen anketle kaydedildi.

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

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Bulgular: Ebeveynlerle birlikte az kitap okunması, akraba evliliği ve ailede konuşma bozukluğu olan bir bireyin olması GKB açısından muhtemel risk faktörleri olarak saptandı. GKB tanısıyla izlenen okul öncesi çocukların, tipik gelişim gösteren çocuklara nazaran daha fazla davranış problemlerine sahip oldukları görüldü (uyku ve somatik problemler dışında) ($p<0.05$). Çoklu regresyon modelinde, çocukların yaşları, ebeveynlerin yaşları, babanın eğitim durumu, çocukların kendi odalarının olması ve annenin depresif belirtileri GKB tanısıyla izlenen çocukların davranış problemleriyle ilişkili bulundu.

Sonuç: Çalışmanın bulguları doğrultusunda, akraba evliliği, ailede konuşma bozukluğu olan bireylerin olması ve ebeveynlerle daha az kitap okunması GKB gelişimiyle ilişkili bulunmuştur. GKB tanısıyla izlenen okul öncesi çocuklarda, davranış problemleri açısından dikkatli olunmalıdır. Anne depresyonu, baba eğitiminin düşük olması ve çocuğun kendine ait odasının olmaması GKB olan çocukların davranış problemlerinde öne çıkan risk faktörleri olabilir. Okul öncesi dönemde davranış şekillenmesinde ve dil gelişiminde ebeveynler önemli bir rol oynamaktadır.

Anahtar Sözcükler: Davranış problemleri, Gelişimsel konuşma bozukluğu, Okul öncesi dönem

INTRODUCTION

Developmental language disorder (DLD) is characterized by delays or difficulties in the development of receptive and/or expressive language skills, including learning, understanding, and using language, without cognitive delay and not accompanied by genetic, neurological, or other neurodevelopmental disorders (1). It is the most common neurodevelopmental disorder in childhood, with approximately 20% of children experiencing language delay in the early years of language acquisition (2). About 10% of preschool children have developmental language disorder (3).

Developmental language disorder, which is an important public health problem, is associated with low academic achievement (4), learning difficulties, and working in a low-skilled job in the future, and leading to economic burden (5). In addition, it has been shown that, children with DLD may also experience difficulties in social interaction and are at risk of psychosocial adjustment problems, behavior, and emotional social problems (6,7).

We are aware that DLD does not draw attention that it merits given its negative consequences according to other neurodevelopmental disorders like autism spectrum disorder, attention-deficit/hyperactivity disorder, and dyslexia, especially in low/middle-income countries (LMIC) (8,9). And, we know that culture, socioeconomic status, and linguistic difference can affect language development and risk factors of DLD(10). Therefore, studies from different cultural backgrounds are necessary to identify risk factors of DLD and to increase awareness of DLD. In our country, the risk factors and the adverse consequences of DLD were less studied (7). The aim of this article was to investigate risk factors and the relationship between DLD and behavior problems in preschool children in a LMIC.

MATERIALS and METHODS

Study Design and Participants

This case-control study was conducted at the Developmental Pediatrics Department of Mersin City and Training and Research Hospital between January and March 2023. The participants were included in the study after obtaining written consent from parents on a voluntarily basis. Inclusion criteria in the study group; (i) children who exhibited a delay in the communication domain according to the Ages and Stages Questionnaire-3 (ASQ-3), (ii) willingness to participate in the study, and (iii) aged between 1.5 to 5.5 years. The exclusion criteria were: (i) presence of neurological, genetic, hematological, endocrinological, or psychiatric diseases, (ii) presence of delays in more than one developmental domain based on developmental evaluation, (iii) lack of willingness to participate in the study, and (iv) sensory impairments such as hearing or vision problems. Following the inclusion criteria, 54 children were included in the study group. During study, all parents with a child diagnosed with DLD participated in the study. Parents of 61 children, who applied to general pediatric outpatient clinics, wanted to participate in the study and showed typical development in the developmental evaluation using the Age and Stages Questionnaire -3 (ASQ-3), were invited to the study. Ten parents declined participation due to time constraints, and four children were excluded due to chronic diseases. Consequently, a total of 47 children were included in the control group.

Evaluation Tools

A questionnaire was prepared by the researchers specifically for the study. It included sociodemographic data such as age, sex, parental age, working status of parents, parental education, birth order, reading book with parents weekly, family income, the number of siblings, history of language disorder in the family, screen parameter such as child's screen time, the types of screens they use (TV, tablet, computer, phone) and why the parent uses the screen. Family income was categorized into two groups: low family income (below or equal to the minimum wage) and high family income (above the minimum wage).

Maternal depressive symptoms were assessed with the Beck Depression Inventory (BDI). BDI was developed by Beck et al.(11). The validity and reliability study for Turkish was carried out by Hisli (12). Higher scores indicate more depressive symptoms.

The development of each child included in the study was evaluated using the Turkish version of the Ages and Stages Questionnaire-3 (ASQ-3) (13). ASQ-3 is a developmental screening tools for children aged 0-6y. ASQ-3 has 19 age-specific sub-questions that assess children's development

in terms of communication, gross motor skills, fine motor skills, problem-solving, and personal-social skills. Children who score below the threshold values in at least one area are screened with a developmental delay, while those who score above the threshold values in every area are considered typical development (TD) (14). Children whose communication scores were below the threshold values of communication and the scores of other developmental areas were in the normal range were defined as DLD.

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

In this study, the CBCL/1.5–5 was completed by mothers to evaluate the behavioral problems of the participants (15,16). CBCL/1.5-5' subscales are (i) emotionally reactive, (ii) anxious/depressed, (iii) somatic complaints, (iv) withdrawn, (v) sleep problems, (vi) attention problems, and (vii) aggressive problems. The amount of withdrawn, emotionally reactive, anxious/depressive, and somatic complaints carve out the score of internalizing problems. The sum of aggressive scores and attention problems creates the score for externalizing problems. The sum of the scores of internalizing, externalizing, sleeping problems, and other problems constitutes the total problems. Higher scores indicate more behavioral problems.

Treatment and follow-up of all children diagnosed with DLD were sustained by a developmental pediatrician.

Statistical Analysis

The normality of continuous variables was assessed using the Shapiro-Wilk test. For the comparison of two independent groups, the Mann-Whitney U test and Independent Samples t-test were used. Covariate Analysis was applied to compare variables affected by age and the weekly number of reading books. Spearman's Rho Correlation coefficients were calculated to examine the linear relationship between continuous variables. Multiple Linear Regression models were constructed with variables that could affect problem scores. Statistically significant models were obtained using backward elimination method. Data analysis was performed using TIBCO Statistica software.

RESULTS

As a result, the study included a total of 101 children, with 54 children in the DLD study group and 47 children in the TD control group. The mean age of the study and control groups were 2.76±1.01 years (mean±SD) and 3.32± 1.24 years (mean ±SD), respectively (p= 0.021). Among the study group, 66.7% (n=36) were male, while in the control group, 53.2% were male (p=0.167). In the study group, 11.1% (n=6) of mothers described premature birth; this rate was 10.6% (n=5) in the control group (p=0.939). Comparing the study group to the control group, it was found that the number of weekly reading books with parents was significantly lower in the study group (p=0.013).

Table I: Descriptive sociodemographic parameters and screen parameters

	Studied group	Control group	p
Maternal age, years*	30.93±6.89	30±4.33	0.946
Maternal education level, years†	12 (8-12)	12 (8-12)	0.811
Employed mother ‡	7 (13)	10 (21.3)	0.626
Paternal age, years*	35.35±7.43	32.98±5.64	0.133
Paternal education level years†	10 (7.75-12)	12 (8-14)	0.196
High family income ‡	20 (42.6)	18 (33.3)	0.634
Having a bedroom ‡	17 (31.5)	19 (40.4)	0.407
Consanguineous marriage ‡	18 (33.3)	7 (14.9)	0.032
Having a family member with language disorder ‡	25 (46.3)	6 (12.8)	<0.001
Number of siblings†	2 (1.75-2)	2 (1-2)	0.527
Order of Birth †	2 (1-2)	2 (1-2)	0.603
Viewing of TV, hrs, daily†	1 (0-3)	2 (0.5-2)	0.246
Viewing of phone, hrs, daily†	1 (0-3)	1 (0-2)	0.191
Viewing of tablet, hrs, daily†	0 (0-0)	0 (0-0)	0.636
Viewing of computer, hrs, daily†	0 (0-0)	0 (0-0)	0.921
Total screen time hrs, daily†	3.5 (1-6)	2.5 (2-4.5)	0.338
Number of reading book with parents weekly†	0 (0-2)	2 (0-7)	0.013

***p:** Mann Whitney U test, Independent Samples t test, ***:** mean±SD, **†:** median (IQR), **‡:** n (%)*

Table II: Compare behavior problems among children with Developmental Language Disorder (studied group) and children with typical developing (control group)

CBCL1.5/5 Subscales	Studied group	Control group	p
Emotionally reactive	5 (2-7)	2 (1-4)	0.002
Anxious/depressed	7 (4-8)	4 (2-6)	0.001
Somatic complaints	3 (2-5)	2 (1-4)	0.819
Withdrawn	4.5 (2.75-7)	2 (1-4)	<0.001
Sleep problems	5 (2.75-6)	3 (2-5)	0.438
Attention problems	4 (3-6)	3 (1-4)	0.001
Aggressive problems	17 (9-23.5)	9 (4-13)	<0.001
Internalizing problems	19.5 (14-24)	12 (7-16)	<0.001
Externalizing problems	21.5 (12-31)	11 (8-16)	<0.001
Total problem score	62.5 (44.75-76)	31 (21-43)	<0.001

*Median (IQR), **p:** Covariance Analysis (age and number of reading books)*

Consanguineous marriage and having family members with language disorder were more common in the study group (p=0.032, p<0.001, respectively). No statistically significant differences were observed in other sociodemographic data and screen parameters between the two groups (Table I).

The median daily screen time of children in the study group was: 3.5 hrs. (IQR:1-6), the median daily screen time of children

Table III: Correlation of behavior problems and sociodemographic factor, maternal depressive symptoms, screen time

CBCL1.5-5 y subscales	Maternal BDI	Total screen time	Maternal age	Maternal education level	Paternal age	Paternal education level
Studied group						
Internalizing problems	.200	-.006	-.196	-.124	-.236	-.273*
Externalizing problems	.444**	.141	-.223	-.288*	-.198	-.322*
Total problem score	.391**	.040	-.248	-.274*	-.253	-.389**
Control group						
Internalizing problems	.400**	-.024	-.159	-.086	-.170	-.123
Externalizing problems	.357*	-.006	-.066	-.282	-.050	-.160
Total problem score	.396**	-.039	-.142	-.166	-.132	-.116

p: *Spearman Rho Correlation* *******p<0.05,* ********p<0.01*

Table IV: Multiple Linear Regression of risk factor of behavior problems of preschoolers' with Developmental Language Disorder

	Standardized Coefficients	95.0% Confidence Interval for B		t	p
	Beta	Lower Bound	Upper Bound		
Total problems score					
R^2:0.479 F:7.199 p<0.001					
(Constant)		77.36	135.28	7.39	<0.001
Age	0.28	1.20	11.99	2.46	0.018
Number of Reading a book, weekly	-0.21	-4.34	0.06	-1.96	0.056
Having a bedroom	-0.19	-20.61	1.71	-1.70	0.095
Paternal age	-0.43	-2.11	-0.66	-3.87	<0.001
Paternal education level	-0.28	-2.96	-0.34	-2.53	0.015
BDI	0.30	0.16	1.03	2.77	0.008
Internalizing problems score					
R^2:0.294 F:6.925 p<0.001					
(Constant)		22.38	44.68	6.04	<0.001
Age	0.37	0.96	5.04	2.95	0.005
Paternal age	-0.39	-0.71	-0.16	-3.13	0.003
Paternal education level	-0.35	-1.19	-0.23	-2.96	0.005
Externalizing problems score					
R^2:0.427 F:5.841 p<0.001					
(Constant)		18.71	46.57	4.71	<0.001
Age	0.21	-0.32	4.83	1.76	0.084
Having a bedroom	-0.30	-12.54	-1.30	-2.48	0.017
Maternal age	0.41	0.00	1.29	2.03	0.048
Paternal age	-0.65	-1.54	-0.34	-3.17	0.003
Paternal education level	-0.28	-1.38	-0.12	-2.40	0.020
BDI	0.46	0.20	0.63	3.88	<0.001

p: *Multiple Linear Regression,* ***BDI:*** *Beck Depression Inventory*

in the control group was: 2.5 hrs. (IQR: 2-4.5) (p=0.338). In both groups, the majority of the families described that children watched the screen for leisure time (study group 61.1%, control group 66%).

After adjusting for age and the weekly number of books read as covariate variables, the subscales of CBCL 1.5-5 for the study group were found to be significantly higher than those of the control group, except for sleep problems and somatic complaints (Table II).

In the study group, the maternal Beck score was (mean±SD): 13.93±12.1, in the control group maternal BDI was (mean±SD): 9.28±7.13 (p= 0.06). It was found that the mothers' BDI was positively correlated with behavioral problems in both groups. Parental age, parental education, and the number of siblings were negatively associated with behavioral problems only in the study group (Table-III).

Through Backward regression analysis in the study group, the mother's BDI score was found to be related to the children's total problem score and externalizing score, and the father's age, and education level were found to be associated with internalizing, externalizing, and total problems. The child's age was also found to be associated with internalizing and total problems. Maternal age and having their own room were associated with externalizing problems (Table IV).

DISCUSSION

The current study successfully investigated the risk factors and behavior problems in children with DLD, compared to healthy control groups. Additionally, the study evaluated the probable risk factors of behavior problems in children with DLD in a low/middle-income country.

Both biological and environmental factors are related to development of DLD. Consanguineous marriage and having a family member with language disorder were found as biological risk factors in line with previous studies and our experience (17,18). The relationship between male sex and DLD remains a subject of debate, and this study did not find a significant difference in DLD prevalence between males and females (17, 19).

Environmental factors play important role for language development and they can be used as protective factors for DLD (17). Environmental factor such as maternal depressive symptoms, reading books with parents, and screen time have been shown to influence language development (20). The screen time and maternal Beck score in the studied group were higher than the control groups. But there was not found any statistical difference between the two groups likely due to the small sample size. However, the study did find a significant association with less frequent reading of books with parents and DLD. The meta-analysis made by Dowdall et al. showed that regardless of parental education, reading a book with parents had a positive effect on language development in line with the study (21). And they demonstrated that book-sharing intervention was effective in promoting language development (21).

Approximately 10% of preschoolers experience clinically significant mental health problems, including socio-emotional and behavior problems (22). This study revealed a higher prevalence of behavior problems among preschoolers with DLD compared to those with typical development, suggesting that DLD itself may be a risk factor for behavior problems during the preschool period. The link between language and behavior is well-established (6). We know that children who live in a LMIC and having DLD are at risk of not getting their developmental potential (23). Therefore, evaluating language development is particularly important for children in these contexts.

Previous studies have also highlighted parenting and parental characteristics as risk factors influencing the persistence of behavior problems into adulthood (20, 24, 25). The study made by Toseeb et al. (26) demonstrated that positive early language and communication environment were related to fewer externalizing behavior problems of children with DLD. Early language and communication environments contain positive home environment like numbers of toys, books and positive parent interaction. Valera-Pozo et al. (25) showed that family involvement was inversely related to internalizing behavior of children with DLD.

Maternal depressive symptoms, lower paternal education, and younger fathers were identified as potential risk factors for behavior problems in children with DLD, in our study. Maternal depressive symptoms were positively associated with externalizing and total problems, paternal age and education were inverse associated with externalizing and internalizing behavior problems in children with DLD. Several studies found a strong association between maternal mental health with child behavior development (27,28). Maternal depression is a communication environmental risk factor (20). According to the mother involvement, the effect of father involvement on children's developmental outcomes has been less studied. The family investment model posits that parents with higher education may invest more money, resources, and more quality time in their children than parents with lower education (29). A study by Jeong in low/middle-income countries found that parental education is associated with supporting child development and positively influences both parents' parenting practices (30). Another study made in LMIC shown that maternal and paternal education independently associated with childhood development and they found the most heterogeneity between paternal education and child development (31). And lower paternal education and younger parental age are inversely associated with socioeconomic status and parenting skills (32).

The surprising finding was having own room was a protective factor against externalizing problems. This finding may be attributed to socioeconomic level and overcrowding, as observed in previous experiences (33). Lower family income was associated with lower quality of home environment and higher parental stress; overcrowding was related to externalizing problems in line with the current study (33,34).

The study had limitations that need to be acknowledged. It was a case-control study with a small sample size, which limits the generalizability of the findings. Although each participant (studied and control group) were evaluated by a developmental pediatrician, the overall sample size was small. While the study identified infrequent reading books with parents as a risk factor for DLD, the duration of activities such as playing games with parents or co-viewing screen time was not investigated. Paternal age and paternal education were identified as potential risk factors for behavior problems; however, paternal mental health was not included in the study. The use of the Ages and Stages Questionnaires (ASQ-3) as a screening instrument limited the ability to make definitive assessments regarding the developmental status of the children. Despite these limitations, the study successfully draw attention to the risk factors of DLD and behavior problems of children with DLD in a LMIC. The study filled out the gap of topics; DLD and behavior problems of preschoolers in LMIC.

In conclusion, healthcare professionals should consider recommending reading books with parents as a protective factor against DLD. Father's age, maternal mental health, and education of father can be investigated for the intervention of behavior problems in children with DLD. Large-scale and longitudinal studies are necessary to gain a comprehensive

understanding of DLD and its negative consequences in low/middle-income countries.

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Impact of COVID-19 Pandemic on Delays in Diagnosis and Treatment: Outcomes in Pediatric Malignant Solid Tumors

COVİD-19 Pandemisinin Teşhis ve Tedavi Gecikmesine Etkisi: Çocukluk Çağı Maliyn Solid Tümör Sonuçları

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ABSTRACT

Objective: The restricted access to healthcare during the coronavirus disease 2019 (COVID-19) pandemic has been particularly problematic for cancer patients. Although childhood cancers are highly curable, disruptions in diagnosis and treatment obviously lead to poor results. In the present study, we investigate the effects of the delays in the diagnosis and the treatment of those with cancer during the pandemic, as well as the clinical course and outcomes of cancer patients diagnosed with COVID-19 during the pandemic.

Material and Methods: An 18-question survey was applied in the pediatric oncology clinic to garner data from newly diagnosed patients on the duration of complaints, delays due to hospital refusals and delays in diagnostic examinations. Patients under treatment, on the other hand, provided information on any interruptions in their chemotherapy treatments (whether caused by the patient or the clinician). The data of patients infected with COVID-19 during cancer treatment were collected from their medical files.

Results: The cancer diagnosis was delayed by a median of 60 (14-150) days in 13 patients due to late presentation to the hospital or the refusal of hospitals to accept patients due to overcrowding. Furthermore, the chemotherapy treatments of 9 patients were delayed by a median of 15 (10–60) days due to exposure to COVID-19 infection (in the patient or a family member). A total of 58 of the patients contracted COVID-19 at different stages of their anticancer treatment, and almost all recovered from COVID-19 with mild symptoms.

Conclusion: Restrictions during the pandemic led to delays in the diagnosis and treatment of pediatric solid tumors. In pediatric patients with cancer who contract COVID-19, their anticancer treatments should be continued based on an evaluation of their clinical status.

Key Words: Cancer, Children, COVID-19

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Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by both the Turkish Ministry of Health and the ethics committee of Ankara City Hospital, and was carried out in accordance with the Declaration of Helsinki principles and all applicable regulations (E1-20-1013).

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ÖZ

Amaç: Koronavirüs hastalığı 2019 (COVİD-19) salgını sırasında sağlık hizmetlerine erişimin kısıtlanması, kanserli hastalar için önemli bir sorundur. Çocukluk çağı kanserleri yüksek oranda tedavi edilebilse de tanı ve tedavi aksamalarının kötü sonuçlara yol açacağı aşikardır. Çalışmamızda yeni tanı konulan ve tedavi gören çocukların kısıtlamalardan etkilenip etkilenmediğini ve kanser tedavisi sırasında COVİD-19 tanısı alan hastaların klinik seyir ve sonuçlarını araştırdık.

Gereç ve Yöntemler: Hasta ebeveynlerine 18 sorudan oluşan bir anket uyguladık. Kanser tedavisi sırasında COVİD-19 tanısı alan hastaların dosyaları taranarak veriler kaydedildi.

Bulgular: Hastaların 35'i yeni tanı grubunda, 55'i ise tedavisi devam eden gruptaydı. Yeni tanı alan hastaların 13'ü (%38) hastaneye geç başvurduğu için kanser tanısı gecikti. Kemoterapi alan hastaların 9'unda (%16) tedavide gecikme yaşandı. Elli sekiz hasta, kanser tedavisinin farklı aşamalarında COVİD-19 enfeksiyonu geçirdi. Hastaların tamamına yakını hafif semptomlarla COVİD-19'dan iyileşti.

Sonuç: Salgını kontrol altına almak için sıkı önlemler alınması gerekirken, kanser gibi ağır kritik hastalığı olan hastalar dikkatle değerlendirilmeli ve hayati sonuçlar doğurabilecek tedavi gecikmelerinden kaçınılmalıdır. Koronavirüs hastalığı 2019 ile enfekte olan kanserli çocuk hastalarda, hastanın klinik durumu değerlendirilerek kanser tedavisine devam edilmesi düşünülmelidir.

Anahtar Sözcükler: Kanser, Çocuk, COVİD-19

INTRODUCTION

The new coronavirus disease (COVID-19), first reported in Wuhan in December 2019, spread rapidly around the world and developed into a global crisis (1). As of November 27, 2022, a total of 641.494.322 confirmed cases of COVID-19 and 6.63 million deaths had been reported to the World Health Organization (WHO) globally (2). The first case in Türkiye was identified in March 2020, and the country would soon be reporting some of the highest numbers in the world with 17,042,722 cases of COVID-19 and 101.492 deaths reported (3).

Strict social distancing measures were implemented around the globe to curtail the spread of the disease, leading to billions of people isolating themselves at home, while heavy restrictions were placed on travel between countries and cities, and educational and business premises were closed. In hospitals, as the highest-risk environments, stringent measures were put in place to protect the health both of the patients and the healthcare staff. These included strict restrictions on hospital visits by non-emergency patients and postponed elective surgeries, all of which were taken to reduce the density of patients in hospitals, to facilitate social distancing and to make more room for COVID-19 patients. The important issues that needed to be resolved at the height of the pandemic were the postponement of the treatments of cases with special needs/serious illnesses, and the difficulties encountered by non-COVID-19 patients in gaining access to healthcare services.

Childhood cancers are highly curable with early diagnosis and appropriate treatment, however, delays in diagnosis and in the timely provision of lifesaving treatments can lead to the disease progressing to an advanced stage, and missed chances of a cure. A small number of studies to date have investigated the clinical course and outcomes of COVID-19 in pediatric patients, including those with cancer, and the effect of unexpected disruptions and uncertainties in access to healthcare on the care of pediatric oncology patients (4-6). The present study investigates the effects of the COVID-19 pandemic on the diagnosis, treatment and outcomes of children with cancer.

MATERIALS and METHODS

Children with cancer receiving chemotherapy at the Pediatric Oncology Department of Ankara City Hospital of the Ministry of Health and those diagnosed with cancer after March 11, 2020 were included in the study. Patients who had completed their chemotherapy courses were excluded from the study. An 18-question survey was applied to the parents during outpatient clinic visits between March and September 2020, in full compliance with the restrictions applied during the lockdown period.

Survey Organization

The 18-question survey applied to the respondents (parents of patients) garnered data on any delays experienced in the diagnosis of COVID-19 or cancer. The parents of newly diagnosed patients were asked how many days after their first complaint they were admitted to the hospital, whether they delayed presenting to the hospital due to fears of contracting COVID-19, whether they had been turned away by the hospital, whether there were any delays in radiological examinations, whether the results had been reported late, and whether biopsy or pathology results were delayed. They were also asked whether they had applied to our clinic late, or whether the start of the first treatment (chemotherapy) was delayed. The response options were "yes" or "no", and if they answered "yes", the duration of the delay was inquired in days. Delays beyond the expected date in each stage were defined in days, such as for radiological imaging, the reporting of results, taking biopsy samples and obtaining pathology results, and the respondents were asked whether the delay had been due to their own concerns or the restrictions applied by the hospital. They were also asked whether they had developed symptoms, or been diagnosed or hospitalized with COVID-19, whether their chemotherapy had been delayed due to a COVID-19 infection

and whether they had undergone chemotherapy in their home town to avoid attending the clinic.

Patients with COVID-19 infection

The patient medical files and laboratory records of all pediatric patients treated for cancer between March and June 2022 were analyzed for information on any COVID-19 infection. The severity of any COVID-19 infection was classified according to the US National Institutes of Health (NIH) guidelines as asymptomatic, mild, moderate or severe disease.

Patients in our department are tested for the SARS-CoV-2 through nasopharyngeal and oropharyngeal swabs using the reverse transcriptase polymerase chain reaction (RT-PCR) method before surgery, other procedures and admission. Patients who presented with febrile neutropenia were subjected to a PCR test, and they were followed up in the isolated ward until the results were obtained.

The study was approved by both the Turkish Ministry of Health and the ethics committee of Ankara City Hospital, and was carried out in accordance with the Declaration of Helsinki principles and all applicable regulations (19.08.2020/E1-20-1013).

Statistics

The statistical analysis of the study was carried out using IBM SPSS Statistics (Version 22.0. Armonk, NY: IBM Corp.). The normality of continuous variables was evaluated with a Shapiro-Wilk test, and since the data were not normally distributed, median (minimum-maximum) values were presented. Categorical variables were summarized with frequency (percentage) values.

RESULT

A total of 310 patients were hospitalized in our 45-bed oncology ward and 800 patients were followed up in the outpatient clinic between 11 March and 15 September, 2020, and 90 parents of patients whose treatment was continuing or who had been newly diagnosed with cancer were surveyed.

Delayed cancer diagnosis due to COVID-19

The median age of the 90 patients (38 female, 52 male) whose parents were surveyed was 11 (0.5–19) years, and 35 had been newly diagnosed and 55 were continuing chemotherapy after being diagnosed before the pandemic was declared. The primary diagnosis of the patients showed heterogeneity, with the most common being Ewing's sarcoma (16%) and Hodgkin lymphoma (15%) (Table I).

The cancer diagnosis was delayed in 13 of 35 newly diagnosed patients, with a median delay in 13 patients of 60 (14–150) days, all 13 of whom had delayed visiting the hospital due to fear of exposure to COVID-19. Although eight of these 13 patients attended hospital later, they were not admitted, three of whom visited the hospital 5 months after the first onset of complaints, one after 3 months, three after 2 months and six after 1 month. Of the 35 patients, the imaging of eight (23%) was delayed, and the biopsies of four (12%) patients were delayed for a month. Only five (14%) of the 35 patients reported visiting the clinic late, and none stated that the start of their oncology treatment was delayed.

Table I: Characteristics of 90 patients who answered the questionnaire

	New diagnosed, n=35 (%)	Under treatment, n=55 (%)
Gender		
Male	26 (74)	26 (47)
Female	9 (26)	29 (53)
Age		
Median (range)	12 (1-19)	11 (0.5-18)
Primary diagnosis		
Ewing's Sarcoma		14 (25)
Neuroblastoma	2 (6)	8 (15)
Hodgkin's Lymphoma	6 (17)	7 (13)
CNS Tumors	2 (6)	7 (13)
Soft tissue sarcoma	6 (17)	6 (11)
Non-Hodgkin's Lymphoma	8 (23)	4 (7)
Osteosarcoma	5 (14)	3 (5)
Other	6 (17)	6 (11)
Symptom of COVID-19		
No	28 (80)	43 (78)
Yes	7 (20)	12 (22)
COVID-19 positive		
No	28 (80)	44 (80)
Yes	7 (20)	11 (20)
Diagnosis delay/CT delay		
No	22 (62)	46 (84)
Yes	13 (38)	9 (16)
Telemedicine use		
No	15 (43)	16 (35)
Yes	20 (57)	36 (65)

CNS: *Central nervous system,* ***CT:*** *Chemotherapy*

One adolescent male patient with a vertebral fracture whose complaints included inability to walk and urinary incontinence was not admitted to the hospital as his respiratory symptoms suggested COVID-19, but was admitted to our clinic after lockdown was lifted with paraplegia, and was diagnosed with advanced stage rhabdomyosarcoma metastatic to both the lungs and bones. A Somalian male patient had been diagnosed with nasopharyngeal carcinoma in his hometown, but was not treated, and could travel to Türkiye only 6 months after his complaints started due to the travel restrictions in place. He was critically ill at the time of admission due to advanced-stage metastatic disease and respiratory failure and died in the 10th month of hospitalization.

Delayed cancer treatment due to COVID-19

Of the 55 patients whose chemotherapy treatments were continuing, nine delayed their hospital treatments due to a fear

Table II: Characteristics of patients with COVID-19

	n=58 (%)
Median age (range)(years)	12 (1-18)
Sex	
Male	33 (57)
Female	25(43)
Underlying cancer	
Bone tumors	15 (26)
Lymphomas (HL, NHL)	12 (22)
Brain tumors	11 (19)
Neuroblastoma	8 (14)
Other tumors	11 (19)
Disease status	
Active disease	52 (90)
Undergoing treatment but in remission	6 (10)
Diagnosis	
PCR, clinic positivity	30 (52)
PCR, screening before procedures and admission	28 (48)
Contact history	12 (21)
Symptoms and findings	
Fever	25 (45)
Cough	8 (15)
Dyspnea	4 (7)
Disease severity	
Asymptomatic	27 (47)
Mild	25 (43)
Moderate	3 (5)
Severe	3 (5)
Length of PCR positivity (median, range) (days)	15 (3-75)
Outcome	
Recovery	55 (95)
Death	3 (5)

HL: *Hodgkin's Lymphoma,* ***NHL:*** *Non-Hodgkin's Lymphoma,* ***PCR:*** *Polymerase chain reaction*

of exposure to COVID-19 in six patients and COVID-19 infection in the family in the three other patients. The median duration of delay in these 55 patients was 15 days (10–60 days).

All but two patients had undergone antineoplastic treatment within the last month. A patient with nasopharyngeal carcinoma and one with anaplastic large cell lymphoma tested positive for COVID-19 immediately after diagnosis before starting their chemotherapy treatment. Since the clinical course of the COVID-19 infection could not be followed in these two patients, their chemotherapies were begun only after a negative PCR test.

The primary surgery of one adolescent boy with Ewing sarcoma with no COVID-19 diagnosis was delayed for 2 months due to the restrictions in place within the surgical departments, and his tumor progressed.

A female patient with chromosome breakage syndrome and three different cancers (Wilms tumor, high-grade glioma and hepatocellular carcinoma) tested positive in a PCR test for COVID-19 in the first month of her allogenic stem cell transplantation treatment, and recovered within two weeks with mild symptoms and without specific antiviral therapy, but died 4 months later from brain metastasis.

A male Somalian patient with advanced-stage nasopharyngeal carcinoma whose COVID-19 PCR positivity persisted for 2.5 months underwent a single course of chemotherapy during the PCR test positivity period as his clinical condition was good except for a fever lasting for 3 days. No complications other than neutropenic fever developed after chemotherapy, but the patient ultimately died due to progressive cancer.

Patients who contracted COVID-19

During the first 2 years of the pandemic, 58 patients with cancer in the present study contracted COVID-19, the characteristics of whom are presented in Table II. At the time of their COVID-19 diagnosis, 53 patients were receiving intravenous chemotherapy, two patients were receiving maintenance therapy (T-lymphoblastic lymphoma and neuroblastoma), one patient was receiving radiotherapy and two patients were receiving targeted therapy (Sorafenib). The chemotherapy courses were continued during active infection in four (7%) patients, but were interrupted in the other patients. The median duration of PCR positivity was 14 (3–75) days, 29 patients (50%) were symptomatic, with the most common symptoms being fever (86%) and cough (30%), and 21 (36%) of the patients required hospitalization for reasons other than COVID-19, primarily febrile neutropenia. None of the patients received COVID-19-directed therapy. Of the 58 patients who contracted COVID-19, four (7%) required intensive care, due to diffuse lung metastasis of osteosarcoma in one and extensive lung involvement of Langerhans cell histiocytosis in another, in both of whom COVID-19 aggravated the pulmonary findings, while one required intensive care due to progressive glioma and another due to progressive nasopharyngeal carcinoma, both of whom were identified with severe pulmonary involvement due to COVID-19. Aside from the patient with osteosarcoma, no intubation was required in these patients.

All of the COVID-19-positive patients had relatively mild disease, with almost 90% being hospitalized for the close monitoring of chemotherapy complications, and all but three recovered without complications. The patient with progressive osteosarcoma and diffuse lung metastases tested positive on day one of their treatment for respiratory distress in the intensive care unit, and died on the second day. In the other two patients who died, the cause of death was not COVID-19 but the progression of their primary cancer.

Of the 90 patients, 56 (62%) reported receiving their blood and radiological test results through telemedicine. Only five patients opted to undergo chemotherapy in their home town rather than coming to Ankara.

DISCUSSION

It was found in the present study that the COVID-19 pandemic had led newly diagnosed cancer patients and their families to ignore serious complaints and to delay presentation to the hospital, and further, that the treatments of patients undergoing chemotherapy were sometimes delayed by COVID-19 infections, either in the patient or a family member, and the restrictions in place.

Restrictions on access to healthcare and delays in cancer diagnoses due to COVID-19 have been reported in various studies to date, affecting both children and adults (6-11). More specifically, there have been case series published reporting diagnosis and treatment delays in pediatric solid tumors due to the COVID-19 pandemic. In one such series, Offenbacher et al. reported that diagnoses of pediatric solid tumors have decreased during the COVID-19 pandemic, and patients tend to be admitted with more advanced stages of the disease.(12) Dvori et al. reported on 17 pediatric patients with solid tumors whose diagnosis and treatment for cancer were delayed by up to 8 months (13). The findings of these studies suggest that the detrimental effects of delaying the diagnosis and treatment of cancer may actually outweigh the risks associated with the COVID-19 pandemic.

In Türkiye, the first case of COVID-19 was reported on March 11, 2020, after which the number of reported cases and deaths witnessed a rapid increase. At the beginning of April 2020, strict restrictions on hospital visits and travel were imposed by the Turkish government, instilling a state of panic in the public, and leading to a reluctance to attend hospitals. Furthermore, many hospitals adopted a policy of not accepting patients with mild symptoms, and patients were advised not to come to the hospital unless absolutely necessary, although whether such restrictions would lead to a delay in the diagnosis of cancer patients was raised as a matter of concern.

Our results reveal that around one-third of parents delayed presenting to hospital with their children, even after they developed severe symptoms. One of the most striking examples of this involved a female patient with widespread metastatic osteosarcoma and with giant masses and severe pain in her leg whose family delayed visiting a doctor for 2 months for fear of infection. Another such example involved a young male patient with rhabdomyosarcoma who did not complete the last three cycles of chemotherapy, and who subsequently presented with severe neurological deficits and brain metastases in the third month of the pandemic and was started on radio-chemotherapy as a matter of urgency. We believe that the progression of the disease to an advanced stage or recurrence can certainly be attributed to such delays by parents. The median delay time in our series was 30 days (10–150), and most delays were due to the parents' concerns. One of the patients whose diagnosis was delayed was from Somalia while the other three were Syrian, which reflects the general patient composition of our hospital, which frequently accepts foreign patients and refugees.

The results of this study reveal that the fear of exposure to COVID-19 among families and the limited access to healthcare services led to significant delays in the diagnosis and treatment of cancer. In a nationwide study from Türkiye, delays in diagnosis and treatment were reported in 62.7% of patients, with a median delay of 15 (3–45) days (14). In one study, eight patients with hematological malignancies were reported to present to hospital 21–45 days after the first appearance of symptoms (9) In a study involving 12 patients by Lazzerini et al. (15), one of the two acute leukemia patients in the series was admitted to the emergency department after 7 days of high fever, while the other presented with severe anemia and respiratory distress. Of the 12 patients in the study, four ultimately died, and all 12 parents reported avoiding the hospital for fear of infection, similar to those in the present study.

In an international Pediatric Oncology East and Mediterranean (POEM) group study of 34 healthcare facilities in 19 countries, including three centers in Türkiye, restrictions on the acceptance of new pediatric oncology patients were reported by eight centers and delays in chemotherapy by 10 centers (16). The study also reported that 91% of the participating centers had placed restrictions on off-treatment visits, which was similar to the policy applied in our center, where long-term restrictions were applied to off-treatment visits to minimize their number. In contrast, most of the patients whose treatment had recently been completed continued to attend routine check-ups. As the pediatric hematology oncology clinic with the largest bed capacity in Europe, we continued to accept a large number of patients during the COVID-19 pandemic, including new oncology patients, unlike in other hospitals, and applied strict measures to reduce the spread of infections, such as allowing only one patient in each room, limiting parental access to pediatric wards to 1 parent only, and restricting changes in caregivers. Face masks were mandatory for all patients, caregivers and hospital staff, elevators were assigned for exclusive use by pediatric oncology staff and the playroom was closed. Outpatients were encouraged to use telemedicine to obtain the results of blood tests to reduce the number of people waiting, and 56 (62%) of the patients used telemedicine effectively. Patients whose treatments had been completed were advised to postpone routine check-ups unless they had any specific complaints, which led to a significant decrease in the number of patients in the outpatient clinic. No modifications were made to treatment doses or durations, and all myelosuppressive treatments were continued as planned. We also maintained tumor boards through teleconferencing.

In the present study, a high level of chemotherapy compliance (82%) was observed in patients whose treatments were continuing, and nearly all chemotherapy delays were due to COVID-19 infections. The treatment of only one case was discontinued for two weeks due to their contact with a COVID-

19-positive family member. Beypinar et al. (17) reported that in 108 adult cancer patients, delays in treatment for no reason during the COVID-19 pandemic were significantly higher than during the pre-COVID-19 period, with 51% of patients delaying their treatment without reason, although none had contracted a COVID-19 infection. In a study by Kebudi et al. (18) in Türkiye, chemotherapy was interrupted in 32 of 51 children with cancer and stem cell recipients with positive COVID-19 test results, with a median delay of 15 days reported. We believe this difference between pediatric and adult patients to be due to the fact that the treatment of children is under the control of their parents. Furthermore, the fact that cancer patients and their parents were already accustomed to such precautions as the use of masks, hygiene and social distancing during chemotherapy may have made it easier for them to adapt to the requirements of the pandemic.

While there were few studies published related to COVID-19 in pediatric cancer patients prior to mid-2020, this situation changed rapidly in the following months. In a study from China involving 171 children with COVID-19, it was reported that the disease had a milder prognosis in children than in adults (5). Among these patients, the single case with leukemia was one of only three patients in the entire group requiring mechanical ventilation support. In a study conducted in Italy, five pediatric cancer patients were reported with COVID-19, all of whom had mild symptoms and self-limited disease (19). The reason for the mild course of the disease in immunosuppressed children is still unknown. The mild course of COVID-19 in 58 patients in our study group is consistent with the findings of existing literature, and the deaths of all three patients who died were not attributable to COVID-19, but to the progression of the tumor. Our data show that among the children with no significant concomitant disease other than cancer, COVID-19 did not have serious consequences, and it was shown that myelosuppressive treatments can be continued in asymptomatic patients with careful, patient-specific evaluation.

Our study has several limitations, the most important of which are its retrospective design and the limited number of cases. Due to the small number of COVID-19-positive patients, it is difficult to comment on the course of the infection in pediatric oncology patients, so large prospective studies are needed. Furthermore, we did not have the opportunity to determine whether the delays in diagnosis were attributable to a fear of viral infection or a denial of symptoms. The majority of the patients in the study were from outside Ankara, and some had even come from abroad for treatment. Although the distance to our center from their home town may have affected the results, there is insufficient data to measure any influence on the results. Despite these limitations, we believe that the presented results contribute to literature by showing the social and physical effects of the COVID-19 pandemic on pediatric oncology patients and their parents and health professionals, while also providing information about the course of COVID-19 in immunosuppressed children undergoing chemotherapy.

CONCLUSION

The restrictions applied during the pandemic led to delays in the diagnosis and treatment of pediatric solid tumors. Delays in the diagnosis of cancer can be far more costly than the consequences of COVID-19 infection, as the disease may progress beyond a stage that can be cured in some patients. The continuation of the anticancer treatments of pediatric cancer patients who contract COVID-19 should be considered based on an evaluation of the clinical status of the patient.

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The Role of the AMH, SHBG, Free Androgen Index and LH/FSH Ratio in the Diagnosis of Polycystic Ovary Syndrome in Adolescent

Adölesanlarda Polikistik Over Sendromu Tanısında AMH, SHBG, Serbest Androjen İndeksi ve LH/FSH Oranının Rolü

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ABSTRACT

Objective: Polycystic ovary syndrome (PCOS) diagnosis is controversial in adolescents. Therefore, auxiliary markers are required for the diagnosis of PCOS. We aimed to evaluate whether luteinizing hormone (LH)/ follicle-stimulating hormone (FSH) ratio, free androgen index (FAI), anti-Mullerian hormone (AMH), and sex hormone-binding globulin (SHBG) levels are a useful test to screen adolescents with PCOS and to investigate which of them has more diagnostic value in the PCOS diagnosis.

Material and Methods: A total of 56 girls with PCOS and 70 healthy girls consisted in this study. Pediatric Endocrine Society criteria were used to diagnose PCOS. Clinical examinations and hormonal assays were performed.

Results: The LH/FSH ratio, and FAI levels were detected significantly higher, and SHBG levels were detected significantly lower in the PCOS group than in the control group ($p<0.001$). The best marker for PCOS diagnosis was found as AMH. In all adolescents with PCOS, irrespective of obesity/overweight, significantly higher AMH levels were observed compared to the control subjects ($p<0.001$). Also, we measured a LH/FSH ratio cut-off value of 1.48 ng/ml with 77% sensitivity and 77% specificity to differentiate cases with PCOS from healthy controls.

Conclusion: AMH, FAI, and LH/FSH ratio could be usefull and valuable tests for the PCOS diagnosis in the presence of the PCOS criteria. AMH was found to be the strongest diagnostic marker in patients with PCOS.

Key Words: Anti-Mullerian hormone, Free androgen index, LH/FSH ratio, Polycystic ovary syndrome, Sex hormone-binding globulin

ÖZ

Amaç: Adölesanlarda polikistik over sendromu (PKOS) tanısı tartışmalıdır. Bu nedenle PKOS tanısı için yardımcı belirteçlere ihtiyaç vardır. PKOS'lu adölesanları taramak ve PKOS tanısında hangisinin tanısal değerinin daha fazla olduğunu araştırmak için Luteinizan hormon (LH)/folikül uyarıcı hormon (FSH) oranı, serbest androjen indeksi (SAI), anti-

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

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müllerian hormon (AMH) ve seks hormon bağlayıcı globulin (SHBG) düzeylerinin yararlı ve değerli bir test olup olmadığını değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Bu çalışmaya PKOS tanılı 56 ve sağlıklı 70 kız dahil edildi. PKOS'u teşhis etmek için Pediatrik Endokrin Derneği kriterleri kullanıldı. Klinik muayeneleri ve hormon tahlilleri yapıldı.

Bulgular: PKOS grubunda kontrol grubuna göre LH/FSH oranı ve SAI düzeyleri anlamlı olarak yüksek, SHBG düzeyleri anlamlı olarak düşük saptandı (p<0.001). PKOS tanısı için en iyi belirteç AMH olarak bulundu. PKOS'lu tüm adölesanlarda, obezite/fazla kilodan bağımsız olarak, kontrol grubu ile karşılaştırıldığında anlamlı olarak daha yüksek AMH seviyeleri gözlendi (p<0.001). PKOS'lu vakaları sağlıklı kontrollerden ayırt etmek için LH/FSH oranı eşik değeri %77 duyarlılık ve %77 özgüllük ile 1.48 ng/ml ölçüldü.

Sonuç: AMH, SAI ve LH/FSH oranı, PKOS kriterlerinin varlığında PKOS tanısında yararlı ve değerli testler olabilir. AMH PKOS'lu hastalarda en güçlü tanısal belirteç olarak bulundu.

Anahtar Sözcükler: Anti müllerian hormon, Seks hormon bağlayıcı globülin, LH/FSH oranı, Polikistik over sendromu, Serbest androjen indeksi

INTRODUCTION

Polycystic ovary syndrome (PCOS), which is a current problem of reproductive age, affects 3.6-15% of women (1,2). Generally, Rotterdam consensus criteria are used for diagnosis. Rotterdam consensus criteria include a combination of anovulation, polycystic ovary, and hyperandrogenism (HA) in adults (3). Since ovarian physiology in adolescents is slightly different from that of adult women, different consensus criteria have been established to avoid underdiagnosis and overdiagnosis in adolescents (4). The menstrual cycles of adolescents differ from those of adults; therefore, anovulation criteria should be appropriate for the age and pubertal stage (5). Physiological anovulation in adolescents should not be confused with PCOS. Therefore, it is important whether menstrual irregularities continue or not. Clinical or biochemical HA is the diagnostic criterion for PCOS. Acne, hirsutism, alopecia, and menstrual irregularity are the findings of hyperandrogenism. Since acne and mild hirsutism are normal signs of puberty, mild hirsutism alone and isolated acne does not suggest hyperandrogenism (6). It has been reported that if mild hirsutism is detected in the presence of menstrual irregularity, this may be a marker of androgen excess (7). Modified Ferriman Gallwey (mFG) score was used for the evaluation of hirsutism (8). In addition, the free androgen index (FAI) is one of the methods used for the evaluation of hyperandrogenism, but studies on this subject in adolescents are rare (9). Polycystic ovarian morphology (PCOM) is not accepted as a criterion for PCOS, as PCOM is a normal finding in many healthy adolescents (10).

PCOS diagnostic criteria in adolescents were revised by the international pediatric subspecialty societies in the 2015 consensus by modifying the "National Institutes of Health criteria" according to age and stage (7). Therefore, PCOS in adolescents typically manifests with a combination of abnormal uterine bleeding patterns and evidence of hyperandrogenism (2,4,10). The difficulty of diagnosing PCOS in adolescents has encouraged studies to search for new markers. Therefore, it is important to understand the pathogenesis of PCOS.

The pathophysiology of PCOS is still not fully understood and it has been shown that disorders of the adrenal or hypothalamus-pituitary-ovarian axis have a major role in this topic. Secretion defects in gonadotropin-releasing hormone (GnRH) cause a relative increase in luteinizing hormone (LH) secretion (11). Studies demonstrated that the LH/ follicle-stimulating hormone (FSH) ratio increase in women with PCOS (12). Also, studies have suggested that serum anti-Mullerian hormone (AMH) level has increased significantly in women with PCOS compared to healthy women (13,14).

Human sex hormone binding globulin (SHBG), which binds androgens and estrogens with high affinity and specificity, is produced in the liver (15). It was demonstrated that binding and transporting sex steroids affect the bioavailability of these hormones (16). Meta-analysis showed that metabolic abnormalities in women with PCOS were associated with obesity, which was associated with low SHBG levels, and not with hyperandrogenism indices. This highlights the possibility that before increasing androgen levels in PCOS, decreasing SHBG levels occur (17).

The current study aimed to evaluate LH/FSH ratio, FAI, AMH, and SHBG levels to represent a useful and practical test to screen adolescents for PCOS and to investigate which of them has more diagnostic value in the diagnosis of PCOS

MATERIALS and METHODS

Adolescents diagnosed with PCOS and healthy control group between January 2020 and January 2023 were included in this retrospective study. The diagnosis of PCOS was made when two features of the syndrome were present: an abnormal uterine bleeding pattern consisting of oligo-amenorrhea or excessive uterine bleeding and clinical and/or biochemical signs of HA. Secondary amenorrhea was defined as follows: > 90 days without a menstrual period after initial menstruation; oligomenorrhea was defined as; 2nd year of menarche: average cycle length > 60 days; 3rd year of menarche: average cycle length > 45 days; 4th year of menarche: cycle length > 38 days. In the presence of a menstrual cycle with intervals of less than 21 days, or when menstruation lasts longer than 7 days, or having heavy menstruation (more than one pad needs to be changed every 1-2 hours, or clots) were defined as excessive

uterine bleeding (10,18). HA can be classified as clinically and biochemically. The presence of a mFG score ≥8 and/or moderately severe inflammatory acne vulgaris was evaluated as clinical HA. A score of 8 -15 indicates mild hirsutism and >15 indicates moderate or severe hirsutism. In premenopausal Caucasians, mFG score >8 is considered above the 95th percentile for the population in adult women (5).

Testosterone measured above adult norms was evaluated as biochemical HA. Over 50 ng/dL was accepted as high according to our laboratory. The additional inclusion criteria were: menstruation for at least 2 years after first menstruation, persistent symptoms for 1–2 years, absence of other endocrine diseases, inherited syndromes and congenital malformations, and not using drugs (including oral combined contraceptives) for 3 months before the study. The control group subjects were healthy adolescent girls without gynecological or endocrine pathology. The healthy patient group was selected from patients who were referred to endocrinology with complaints of menstrual irregularity in the history, increased hair growth, and cysts on ultrasonography, but whose menstrual cycle was found to be normal according to their gynecological age, who did not continue to have menstrual irregularities in their follow-up, and who did not have hyperandrogenism in the endocrine evaluation. This study was approved by the Ankara Bilkent City Hospital Ethics Committee with the decision no 23-3467 dated March 1, 2023.

Laboratory and clinical measurements

Anthropometric evaluations (body weight, height, body mass index (BMI)) were done by the same physician. The BMI was assessed using the ratio of weight (kg) to height squared (m2). Assessment of hirsutism was graded according to the mFG score by the same physician. After an overnight fast, fasting blood samples for glucose, insulin, LH, FSH, total testosterone, estradiol, progesterone, SHBG, and AMH were drawn between 08:00-09:00 a.m in the follicular phase 1-7 days after spontaneous menstruation for controls and at a convenient time for PCOS group. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated (HOMA-IR = fasting plasma insulin (μU/mL) × fasting plasma glucose (mmol/L)/22.5). The FAI was calculated with the following formula: total testosterone x 100/SHBG. The plasma glucose levels were measured by an enzymatic colorimetric method. Insulin, FSH, LH, testosterone, and estradiol levels were measured using a chemiluminescence immunoassay (Siemens Healthineers, Erlangen, Germany). The SHBG values were analyzed using an IMMULITE 2000 XPi (Siemens, Cary, NC, USA), and AMH levels were measured by an enzyme-linked immunosorbent assay by VIDAS AMH assay by bioMérieux (bioMérieux, Marcy L'Etoile, France). AMH values of > 9 were not measured in our hospital ELISA assay kit. This was defined as a score >9 in the laboratory. So, data of the patients with an AMH value >9 were entered as 9 in our study.

Statistical analysis

Statistical analyses and evaluations were performed with SPSS (version 24.0; IBM Corporation, Armonk, NY, USA). The mean, standard deviation (SD), median, and 1st (Q1) and 3rd (Q3) quartiles of the numerical variables were calculated. Categorical variables are expressed as numbers and percentages (%). The Shapiro-Wilk test was used to evaluate the normal distribution of variables. Furthermore, the variables with kurtosis and skewness values in the range of -1.5 to 1.5 were considered to have a normal distribution. Student's T-test was performed for groups with normal distribution, and the Mann-Whitney U test was performed for groups that did not comply with the assumption of normal distribution. Chi-square tests were performed for comparing categorical variables. The PCOS and control groups were divided into four groups according to whether they were overweight/obese or normal. One-way analysis of variance (ANOVA) was used to evaluate the statistical differences between groups with normal distribution, and Kruskal Wallis test was used to evaluate those who did not. Intra-group differences in AMH levels were evaluated using post-hoc analysis. Tamhane's T2 test was used for the analysis. Intra-group differences in LH/FSH ratios were evaluated using post-hoc analysis. Tukey test was used for the analysis. In addition, the laboratory markers used to predict the presence of polycystic ovary syndrome were analyzed using binary logistic regression analysis. Logistic regression model was used to identify predictors of the dependent variable, if more than one independent predictor variable was evaluated, p value <0.250 in univariate analysis, tested using multivariate logistic regression analysis of clinically significant variables. The LH/FSH ratio, FAI, SHBG, and AMH levels were evaluated with logistic regression analysis to predict the presence of polycystic ovary syndrome. For LH/FSH ratio, the best cut-off value that could be used to differentiate between children with PCOS and healthy controls was calculated using receiver operating characteristic (ROC) curve analysis. The p value for statistical significance was set at $p < 0.050$.

RESULTS

A total of 126 adolescents, 56 (44.4%) patients diagnosed with PCOS, and 70 (55.6%) healthy controls were included in our study. All pubertal patients were Tanner stage 5. In terms of mFG score, the cases were divided into subgroups according to clinical evaluation as mFG score <8, mFG score 8-15, and mFG score >15. In the healthy control group, the score of 69 (98.6%) cases was lower than 8, and the score of one case was 8-15. In the PCOS group; the score of 45 (80.4%) cases was 8-15, and the score of 11 (19.6%) cases was higher than 15.

Both PCOS and the healthy control group were similar age (p=0.429). The BMI standard deviation score (SDS) was significantly greater in the PCOS group than in the healthy

Table I: The clinical and laboratory characteristics of polycystic ovary syndrome group and healthy controls

	Polycystic ovary syndrome (n=56)		Healthy controls (n=70)		p
	Mean±SD	Median Q1–Q3	Mean±SD	Median Q1–Q3	
Age (years)	16.1±1.3	16 (15.1–17.4)	15.9±1.3	16.1 (14.8–17)	0.429
Weight (kg)	76.7±18.5	74.6 (61.5–91.3)	59.1±11.8	56.4 (50–70)	<0.001
Height (cm)	163.2±6.3	162.9 (159.3–168)	161.1±5.8	162 (156.1–165)	0.057
Height SDS	0.18±1.07	0.16 (-0.55–1.09)	-0.12±1.06	-0.06 (-1–0.74)	0.129
BMI (kg/m^2)	28.6±6	28.5 (23.3–33.8)	22.7±4	22 (20.1–24.9)	<0.001
BMI SDS	1.9±1.47	2.2 (0.74–3.1)	0.35±1.45	0.3 (-0.59–1.34)	<0.001
FSH (mIU/mL)	6.6±1.7	6.5 (5.2–7.9)	5.7±1.7	5.7 (4.7–6.7)	0.004
LH (mIU/mL)	13.8±7.3	12.5 (8.1–19.8)	6.1±5.6	4.6 (2.9–7.4)	<0.001
LH/FSH ratio	2.08±1.05	2 (1.5–2.6)	1.09±0.83	0.81 (0.52–1.44)	<0.001
Estradiol (pg/mL)	55.1±24.7	49.5 (39.3–66)	83±88.5	48 (34–102.3)	0.768^M
Testosterone (ng/dL)	49.3±20.8	49 (35–56)	25.9±8.5	24 (19–31.5)	<0.001^M
Progesterone (ng/mL)	0.98±1.1	0.74 (0.51–1.1)	1.89±3.1	0.73 (0.4–1.47)	0.854^M
SHBG (nmol/L)	24.4±14.1	20.5 (13–32.8)	47.3±19	45 (33–56.3)	<0.001^M
FPG (mg/dL)	86.6±7.5	87 (82.3–90)	84.9±6.3	85 (80–89)	0.179^M
Insulin (ng/mL)	21±13.1	17.7 (11.2–25.3)	11±5.4	9.4 (7.7–12.3)	<0.001^M
HOMA-IR	4.56±3.02	3.64 (2.38–5.75)	2.35±1.27	1.98 (1.68–2.63)	<0.001^M
FAI	2.81±2.16	2.15 (1.2–3.77)	0.63±0.3	0.51 (0.4–0.76)	<0.001^M
AMH (µg/l)	6.85±2.19	7.65 (5.18–9)	3.47±1.82	3 (2.08–4.4)	<0.001

Normally distributed variables were evaluated with Student's T test. ***M*** *symbol indicates that Mann Whitney U test was used.* ***SD:*** *standard deviation,* ***SDS:*** *standard deviation score,* ***BMI:*** *body mass index,* ***SHBG:*** *Sex hormone binding globulin,* ***FPG:*** *fasting plasma glucose,* ***HOMA-IR:*** *homeostasis model assessment of insulin resistance,* ***FAI:*** *free androgen index,* ***AMH:*** *anti-Müllerian hormone,* ***LH:*** *luteinizing hormone,* ***FSH:*** *follicle-stimulating hormone.*

Table II: Univariate binary logistic regression analysis results of factors that predict polycystic ovary syndrome presence

Predicting factors	*B*-value	Odds ratio	%95 Confidence interval		p
LH/FSH ratio	0.937	2.553	1.079	6.043	0.033
FAI	4.386	80.305	5.034	1281.044	0.002
SHBG	-0.017	0.983	0.917	1.054	0.637
AMH	0.716	2.046	1.373	3.050	0.001

FAI: *free androgen index,* ***SHBG:*** *Sex hormone binding globulin,* ***AMH:*** *Anti-Mullerian Hormone,* ***LH:*** *luteinizing hormone,* ***FSH:*** *follicle-stimulating hormone*

control group. The clinical and laboratory characteristics of the polycystic ovary syndrome group and healthy controls are presented in Table I. The LH, LH/FSH ratio, total testosterone, insulin, HOMA-IR, FAI, and AMH levels were measured significantly higher in the PCOS group (p<.001). While the AMH value was >9 in 15 patients in the PCOS group, the AMH value was >9 in 1 patient in the healthy control group. SHBG levels were found to be significantly lower in the PCOS group compared to the control group (p<0.001).

The effect of LH/FSH ratio, FAI, SHBG, and AMH levels on the likelihood that cases have PCOS was determined by logistic regression analysis. The logistic regression model was statistically significant ($\chi^2(5) = 122.597$, p<0.001). The model explained 87% (Nagelkerke R^2) of the variance in PCOS and correctly classified 95% of the cases. Of all cases predicted to have polycystic ovary syndrome, 91.8% were correctly predicted (The positive predictive value). Of all cases predicted to not have PCOS, 97.1% were correctly predicted (The negative predictive value). Increased FAI and AMH levels were associated with an increased likelihood of PCOS. The univariate binary logistic regression analysis results for factors that predict PCOS are shown in Table II.

We regrouped adolescents with PCOS and controls according to BMI as overweight/obese PCOS patients, normal-weight PCOS patients, overweight/obese controls, and normal-weight controls and again compared all variables (Table III). The BMI SDS measurement and FAI levels were detected significantly higher in the PCOS group with overweight/obese compared to the other 3 groups, and SHBG levels were found to be lower. In all adolescents with PCOS, irrespective of obesity/overweight, significantly higher AMH levels were found compared to the healthy control subjects (p<0.001). Among the children with PCOS, those who had normal-weight had higher AMH levels than those who were obese or overweight (p=0.005). Among

Table III: Differences in PCOS and control groups according to being overweight and obese, and not.

	Overweight/obese PCOS* (n=35)	Normal weight PCOS* (n=21)	Overweight/obese controls* (n=26)	Normal weight controls* (n=44)	p
Age (years)	16.2±1.4	16±1.3	15.9±1.3	16±1.4	0.842
Weight (kg)	87±14.5	59.6±9.3	71.6±7	51.2±5.8	<0.001
Height (cm)	163.3±6	163.1±7	163.9±5.5	159.4±5.3	0.004
Height SDS	0.2±1.03	0.16±1.17	0.44±1.05	-0.48±0.91	0.002
BMI (kg/m^2)	32.3±3.9	22.3±2.6	26.7±2.9	20.2±2	<0.001
BMI SDS	2.85±0.65	0.29±0.98	1.74±0.64	-0.56±1.05	<0.001
Basal LH	10.7±5.5	18.8±7.2	5±5.2	6.8±5.8	<0.001
LH/FSH ratio	1.76±0.76	2.62±1.25	0.92±0.7	1.19±0.89	<0.001†
SHBG	20.8±12.7	30.5±14.4	42.3±15.9	50.3±20.2	<0.001
FAI	3.26±2.3	2.09±1.73	0.71±0.33	0.57±0.28	<0.001†
AMH	6.14±2.3	8.02±1.41	2.95±1.64	3.78±1.88	<0.001

*One-way analysis of variance (ANOVA) was applied. *Mean ± SD, Those marked with the †symbol were analyzed with the Kruskal Wallis test.* ***PCOS:*** *polycystic ovary syndrome,* ***SD:*** *standard deviation,* ***BMI:*** *body mass index,* ***SDS:*** *standard deviation score,* ***SHBG:*** *Sex hormone binding globulin,* ***FAI:*** *free androgen index,* ***AMH:*** *Anti-Mullerian Hormone,* ***LH:*** *luteinizing hormone,* ***FSH:*** *follicle-stimulating hormone.*

healthy children, there was no statistically significant difference between the AMH levels of those who had normal-weight and those who were obese or overweight (p=0.472).

We detected an LH/FSH ratio cut-off value of 1.48 ng/ml with 77% sensitivity and 77% specificity, a 77% positive predictive value, and a 77% negative predictive value to differentiate cases with PCOS from healthy controls (Figure 1). The maximum area under the curve (AUC) for the mean LH/FSH ratio was 0.81 (95% CI:0.73-0.88; p<0.001).

Among the children with PCOS, those who had normal-weight had higher LH/FSH ratios than those who were obese or overweight (p=0.003). Among healthy children, there was no statistically significant difference between the LH/FSH ratios of those who had normal-weight and those who were obese or overweight (p=0.616).

DISCUSSION

We analyzed several biochemical variables that showed different results in PCOS diagnoses. Compared to controls, we report a higher FAI, LH/FSH ratio, AMH, and lower SHBG levels in adolescents with PCOS. The AMH has detected the best marker for PCOS diagnosis. We found higher FAI and lower SHBG levels in overweight/obese adolescents with PCOS than in the other three groups. Regardless of BMI, AMH levels were detected significantly higher in adolescents with PCOS than in healthy controls. Also, we found that the normal-weight group with PCOS had higher AMH levels than those who were obese/overweight group with PCOS. Interestingly, we demonstrated a higher LH/FSH ratio in the normal-weight group with PCOS than in the obese/overweight group with PCOS

As previously reviewed, PCOS diagnosis are controversial and may lead to misdiagnosis in adolescents. So, studies have been conducted to identify newer biomarkers to aid in diagnosis. AMH has been assessed for its possible use as a diagnostic criterion or auxiliary criterion for PCOS. Sahmay et al. showed that serum AMH measurement is precious for the diagnosis of women with PCOS. They detected higher serum AMH levels in women with PCOS compared to healthy controls (19). Another study from China suggested similar results. It has been reported that markers such as serum testosterone, serum AMH, LH/FSH ratio, and fasting insulin can be used in combination for accurate diagnosis of PCOS and to increase the specificity and sensitivity in the PCOS detection (20). Moreover, it was reported that AMH levels were higher in non-obese and obese adolescents with PCOS compared to the control group. It has been shown that AMH levels can decrease with weight loss or other treatments in adolescents diagnosed with PCOS (21,22). Also some studies demonstrated a significant negative relationship between BMI and AMH, some studies suggested that AMH was not statistically different for obesity but rather correlates with PCOS status (23-25).

Until now, different AMH cutoff values with various sensitivities and specificities have been proposed, but the optimal threshold is not known. In a meta-analysis, it was reported that the AMH threshold value of 4.7 ng/mL showed specificity and sensitivity of 79.4% and 82.8%, respectively, in women with PCOS (26). Another adolescent PCOS study found that AMH level > 7.20 ng/mL showed the highest sensitivity (76.0%) and specificity (89.0%) for PCOS diagnostics in adolescence (27). Since AMH values >9 could not be measured in our study, the cut-off value for AMH could not be calculated. This is one of the limitations of this current study. Although AMH values >9 were taken as the lowest value, such as 9, we detected significantly higher serum AMH levels in the PCOS patients compared to the healthy controls which is consistent with the literature. In our study, we also demonstrated that regardless of BMI, serum AMH levels were detected significantly higher in adolescents with PCOS.

Our study found AMH levels to be higher in normal-weight patients with PCOS than in obese/overweight patients with PCOS. However, no difference was found between the AMH levels of obese and normal-weight adolescents in the healthy control group.

Despite detecting high serum AMH levels in PCOS, using different AMH test techniques and different PCOS criteria in studies cause heterogeneity between studies. As well as heterogeneity between studies, it was found significant overlap in AMH levels (28). Evidence-based recommendations from a systematic review suggested that AMH value should not be used alone as an alternative for the diagnosis of PCOS and the detection of polycystic ovary morphology (26). AMH and LH/FSH ratio combination could be useful and practical as a criterion for the diagnosis of PCOS in the presence of the PCOS criteria mentioned above. Khashchenko et al. (27) reported that LH/FSH ratio >1.23 had high sensitivity and specificity in PCOS diagnosis. In another study, the LH/FSH ratio cut-off was found to be 1.33, with lower sensitivity but higher specificity. (65.76% and 95.24%, respectively). Also serum AMH level and LH/FSH ratio were found to be similarly effective in differentiating PCOS patients from controls in this study (12). In an another study evaluating the LH/FSH ratio according to BMI (normal-high) values in patients with PCOS, no difference was found between the two groups (29). In a study comparing obese/overweight and normal weight women with different PCOS phenotypes and obese and normal weight healthy control subjects, it was shown that LH, SHBG and AMH levels were significantly lower in obese and overweight women compared to normal weight women in all groups (23). In our study, similar to the literature, LH, AMH levels were found to be lower in the obese group with PCOS than in the normal weight group with PCOS, but no difference was found between the two groups in the healthy control group. In this case, it made us think that AMH, LH might be related to PCOS condition rather than BMI value.

The association between SHBG levels and PCOS is limited. Obesity, an increasing problem in adolescents, increases the risk of PCOS. SHBG synthesis and secretion decrease with obesity, and this is thought to trigger PCOS by increasing the bioavailability of androgens (30). Meta-analysis of SHBG and PCOS demonstrated that SHBG levels in controls were significantly higher than those in PCOS patients, with significant heterogeneity across studies. These meta-analyses reported a significant association between low SHBG and obesity, glucose intolerance, insulin resistance, hyperandrogenism, and type 2 diabetes in women with PCOS (31). In another study, in which two groups with similar BMI SDS were evaluated, low levels of SHBG and high levels of AMH were reported in the PCOS group compared to the healthy control group (32). Moreover, another study suggested that the combination of SHBG and AMH had higher sensitivity to diagnose PCOS when compared with AMH levels alone (33). Therefore, SHBG may be a beneficial biomarker to be used in the diagnosis and post-treatment follow-up of PCOS. In this current study, SHBG levels in the PCOS group were detected significantly lower than in the healthy control group. We also showed a negative association between SHBG levels and obesity. The serum SHBG levels decrease in individuals with obesity, and there are many studies in this direction in the literature. Therefore, we thought that it would not be appropriate to conduct a cut-off for SHBG directly and indirectly for FAI values.

Most of the data in the literature revealed that compared to controls, levels of testosterone, LH, LH/FSH, and FAI were detected higher in adolescents with PCOS (12,34). The important question is which one is superior to other endocrine variables in the diagnosis of PCOS. Khashchenko et al. (27) evaluated the AMH, testosterone, FAI, androstenedione, LH/FSH ratio, ovarian volume, and ovarian-to-uterine index for PCOS prediction. In this study, it was demonstrated that using four or more of the specified criteria to diagnose PCOS, had the highest accuracy of over 90%. Moreover, they showed that the rate of correct diagnosis decreased as the number of parameters used decreased, and diagnostic precision was 85% with the use of 3 parameters (27). Another study demonstrated that AMH, LH, total testosterone, hirsutism, antral follicle count, and acanthosis nigricans are important and helpful in the diagnosis of PCOS (35). In the logistic regression model, it was shown that with four parameters (LH/FSH ratio, FAI, AMH and SHBG), 95% of PCOS cases could be detected with 87% sensitivity. The parameters that were significant in the model were the LH/FSH ratio and AMH. These parameters differed significantly in subgroup analyzes, especially in the differential diagnosis of obesity and non-obese patients.

The homogeneity of our study population and the good and clear definition of the patient and control groups constitute the strength of this study. All participants were evaluated by the same physician. As for the limitations of the study, we could not measure the AMH value greater than 9. So the AMH cut-off value could not be calculated. Also, the control and PCOS groups included a relatively low number of participants.

In conclusion, this study's results suggest that serum increased AMH, FAI, and LH/FSH ratio could be helpful and handy tests for screening adolescents with PCOS. Among them, the best marker for PCOS diagnosis was found as AMH. Moreover, AMH levels and LH/FSH ratio are negatively affected by increased adiposity in adolescents with PCOS but not healthy group. Larger studies help us to reach more precise conclusions and increase our knowledge.

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The Impact of the COVID-19 Pandemic on the Educational Process of Children with Autism Spectrum Disorder and Effects on the Parental Quality of Life

COVİD-19 Pandemisinin Otizm Spektrum Bozukluğu Olan Çocukların Eğitim Süreçlerine ve Ebeveyn Yaşam Kalitesine Etkileri

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ABSTRACT

Objective: After the pandemic period, the daily routines changed, and this caused a significant decrease in families' quality of life. We aimed to show how the pandemic period and closure of educational institutions influenced children with autism spectrum disorder (ASD) and their families' quality of life.

Material and Methods: The study is a descriptive type of research. The study population consists of families of children aged between 3 and 16 diagnosed with ASD who attended special education and rehabilitation centers and educational practice schools in Trabzon for at least 6 months before the pandemic, registered with the Trabzon Autism Association, and were followed at the Karadeniz Technical University Faculty of Medicine Child and Adolescent Mental Health and Pediatric Neurology Polyclinic.

Families were asked to complete the questionnaire we designed. The data was collected face-to-face prospectively. The questionnaire consisted of six parts: sociodemographic and personal characteristics of children and parents; education problems during the pandemic period; the effect of daily routines during the pandemic period on both children and families; the Quality of Life in Autism Questionnaire-Parent Version; and the Parental Burnout Scale.

Results: We contacted 169 parents. Mothers were more likely than fathers to complete the questionnaire (73.1% vs. 26.9%). School attendance decreased by 11.9%, while regular education availability fell by 8.1%. The pandemic has caused changes in the daily routines of families and children in many areas of life, such as decreased physical activity, changes in sleep duration and time, and deterioration in regular eating habits (p = 0.035; 0.001; 0.004; 0.001,

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Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. This study was approved by Trabzon Karadeniz Technical University (2021/383-19.11.2023).

Contribution of the Authors / Yazarların katkısı*: *YILDIZ N: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Taking responsibility in the writing of the whole or important parts of the study. ***ÖZEN N:*** Constructing the hypothesis or idea of research and/or article, Taking responsibility in the writing of the whole or important parts of the study. ***ÖZKAN KART P:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***YILDIRIM S:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***KARADENİZ S:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***BİLGİNER Ç:*** Taking responsibility in necessary literature review for the study. ***ESENÜLKÜ G:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ŞAHİN S: Taking responsibility in necessary literature review for the study. ***ACAR ARSLAN E:*** Organizing, supervising the course of progress and taking the responsibility of the research/study. ***KAMAŞAK T:*** Organizing, supervising the course of progress and taking the responsibility of the research/study. ***ÖZKORUMAK KARAGÜZEL E :*** Taking responsibility in logical interpretation and conclusion of the results. ***TOPBAŞ M:*** Reviewing the article before submission scientifically besides spelling and grammar. ***CANSU A:*** Planning methodology to reach the Conclusions, Taking responsibility in logical interpretation and conclusion of the results, Reviewing the article before submission scientifically besides spelling and grammar.

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respectively). The QoL of parents whose daily schedules changed decreased as a result. Our study found that their levels of burnout significantly increased, and the PBS total score and the QoLA scores had a moderately significant correlation (rs = 0.411, p<0.001).

Conclusion: In this study, we showed that the COVID-19 epidemic negatively affected the education process of children with ASD. In order to improve the QoL of families and reduce burnout levels, we suggest providing additional service opportunities (parks, playgrounds, hobby centers, etc.) and special psychiatric services for children with ASD during pandemic periods.

Key Words: Autism spectrum disorder, Burnout, COVID-19, Parenting, Quality of life

ÖZ

Amaç: Pandemi dönemi sonrasında günlük rutinler değişti ve bu durum ailelerin yaşam kalitesinde ciddi bir düşüşe neden oldu. Pandemi döneminin ve eğitim kurumlarının kapatılmasının otizm spektrum bozukluğu (OSB) olan çocukların ve ailelerinin yaşam kalitesini nasıl etkilediğini göstermeyi amaçladık.

Gereç ve Yöntemler: Çalışma tanımlayıcı tipte bir araştırmadır. Araştırmanın evrenini, pandemi öncesinde en az 6 ay boyunca Trabzon ilindeki özel eğitim ve rehabilitasyon merkezleri ile eğitim uygulama okullarına devam eden, Trabzon Otizm Derneğine kayıtlı, 3-16 yaş arası OSB tanısı alan çocukların aileleri ve Karadeniz Teknik Üniversitesi Tıp Fakültesi, Çocuk ve Ergen Ruh Sağlığı ile Çocuk Nöroloji Polikliniğinde takipli olgular oluşturdu.

Tüm OSB'li ailelere ulaşılması hedeflenmiştir. Ailelerden tasarladığımız anketi doldurmaları istendi. Veriler prospektif olarak yüz yüze toplanmıştır. Anket altı bölümden oluşmaktadır: çocukların ve ebeveynlerin sosyo demografik ve kişisel özellikleri; pandemi döneminde yaşanan eğitim sorunları; pandemi döneminde günlük rutinlerin hem çocuklar hem de aileler üzerindeki etkisi; Otizmde Yaşam Kalitesi Anketi-Ebeveyn Versiyonu; ve Ebeveyn Tükenmişliği Ölçeği.

Bulgular: 69 veli ile iletişime geçildi. Annelerin anketi doldurma oranları babalardan daha yüksekti (%73.1'e karşı %26.9). Okullara devam oranı %11.9 azalırken, düzenli eğitime ulaşılabilirlik %8.1 azaldı. Pandemi, fiziksel aktivitede azalma, uyku süresi ve süresinde değişiklik, düzenli beslenme alışkanlıklarında bozulma gibi hayatın birçok alanında ailelerin ve çocukların günlük rutinlerinde değişikliklere neden olmuştur (sırasıyla p = 0.035; 0.001; 0.004; 0.001). Sonuç olarak günlük rutinleri değişen ebeveynlerin yaşam kalitesi azalmıştır. Tükenmişlik düzeylerinin anlamlı düzeyde arttığı ve PBS toplam puanı ile QoLA puanlarının orta düzeyde anlamlı bir korelasyona sahip olduğu bulunmuştur (rs = 0.411, p<0.001).

Sonuç: Bu çalışmada COVID-19 pandemisinin OSB'li çocukların eğitim sürecini olumsuz etkilediğini gösterdik. Ailelerin yaşam kalitesini artırmak ve tükenmişlik düzeylerini azaltmak amacıyla, pandemi dönemlerinde OSB'li çocuklara ek hizmet olanakları (parklar, oyun alanları, hobi merkezleri vb.) ve özel psikiyatri hizmetlerinin sağlanmasını öneriyoruz.

Anahtar Sözcükler: Otizm spektrum bozukluğu, Tükenmişlik, COVİD-19, Ebeveynlik, Yaşam kalitesi

INTRODUCTION

The coronavirus disease (COVID-19) emerged in 2019 and has significantly impacted people's lives worldwide. Isolation and social distance strategies have been developed to prevent the virus's spread and protect against infection (1). During this process, schools throughout Turkey were closed, and most extracurricular activities for children and adolescents, which typically occur outside the home and in group settings, were canceled (2). Additionally, regular education schools for children with Autism Spectrum Disorder (ASD) were shut down.

Families worldwide have been grappling with the question of how to best support their children in these circumstances. The epidemic has been even more devastating for children who need special health care. The epidemic's disruption of these children's education was observed to have a negative effect on both their physical and mental health as well as their skill levels (3).

It has been emphasized that the pandemic and the measures implemented cause psychosocial distress that jeopardizes family stability (4). Such a stressor exacerbated the symptoms of the pre-existing mental disorder, caused stress on families and children, and caused anxiety and feelings of helplessness (5). The pandemic has altered the daily routines of families. The fact that children with ASD remain at home has increased the burden of educational responsibility on families. Families in this situation have differentiated themselves with actions such as altering their lives both inside and outside the home. The changing physical and mental health of families has affected both their quality of life and burnout levels.

ASD is a neurodevelopmental disorder that is characterized by difficulties in social communication and the presence of constrained, repetitive behaviors or interests (6). During the pandemic, there have been some changes in individuals with ASD at home, at school, in rehabilitation centers, etc. Their educational processes were interrupted, and their developmental characteristics were at risk. Children with autism have difficulty adapting to rules that do not fit into their usual routines and are more likely to have co-occurring psychiatric disorders and behavior problems. In addition to keeping up with the pandemic period and measures, parents are attempting to support their children who need additional care and time, such as the development of their physical, mental, and spiritual health, as well as their formal education at home.

This study aims to investigate how the pandemic period affected the behaviors, daily lives, and neurological development of children with ASD whose educational processes were disrupted by the closure of educational institutions. Another aim

is to evaluate the family relationships of parents with children diagnosed with ASD, their sensitivity to both their own and their children's problems, their quality of life, and their burnout status as a result of the effects of the pandemic on both themselves and their children.

MATERIALS and METHODS

The population of the study consisted of families of children who were between the ages of 3 and 16, with a diagnosis of ASD, who were educated in the education and rehabilitation centers in Trabzon or were followed in the Child and Adolescent Psychiatric Health and Pediatric Neurology Outpatient Clinic of Karadeniz Technical University Faculty of Medicine. The Trabzon Directorate of National Education provided a list of schools that specialize in autism education. We visited every autism school in the heart of the city and spoke with the principals about the study. Families who agreed to take part in the research were enlisted. Because the study was descriptive research and intended to reach all families in the city center with children who had been diagnosed with autism, the sample size was not established. Families of 169 children with ASD were asked to complete the questionnaire we designed. Data were collected through face-to-face interviews with families without recording personal information, with the thought that families would express themselves more easily, provide reliable information, and reduce errors and ambiguity. Every participant who voluntarily answered the questionnaire was included in the study. The study did not include any families that did not volunteer. Surveys that provided incomplete answers to the questions in the data form were excluded from the study. Therefore, the statistical study was conducted on a total of 134 survey forms.

The questionnaire was divided into six sections, which were organized by the researchers after a review of the literature. In the first section, questions about some sociodemographic and personal characteristics of the child diagnosed with ASD, and in the second section, questions about some sociodemographic and personal characteristics of the parents were asked. In the third section, questions about the child regarding COVID-19 were asked. In the fourth section, there are questions for parents about COVID-19.

The Quality of Life in Autism Questionnaire-Parent Version (QoLA) was placed in the fifth section. The QoLA was a disorder-specific scale developed by Eapen et al. (8) to assess the quality of life (QoL) of parents of autistic children. Gürbüz B. et al. (9) conducted a Turkish validity and reliability study. It was divided into two parts. Part A includes 28 questions that assess parents' perceptions of their own QoL. Each question was scored on a five-point Likert scale from 1 to 5. Part B assessed parents' perceptions of how significant their child's autism-related difficulties were to them. There were 20 evaluation questions for this, which included the difficulties that children with ASD face. Part A of the questionnaire had a Cronbach alpha value of 0.93, and Part B had a Cronbach alpha value of 0.94. A high score indicated that parents had fewer issues with their autistic children's behaviors. The scale yielded a score ranging from 48 to 240; however, it was recommended that each section be scored and used separately.

The Parental Burnout Scale (PBS) was found in the sixth section. Kaner (10) created the PBS to assess the level of burnout experienced by parents in their marriage lives. Avşar A et al. (11) conducted a validity and reliability study of PBS in determining the burnout level of parents of children with ASD in 2019. It was a five-point Likert scale with 52 items and four subscales. The first PBS subscale was the "Negative Spouse and Marriage Relationship" subscale, which had 18 items. The "Emotional Burnout" subscale was the second, which had 17 items. The third subscale of PBS was "Sensitivity to Spouse and Children," which had 11 items. The final subscale of the PBS was the "Satisfaction with Marriage" subscale, which had six items (10,11). The scale score was proportional to the degree of burnout. Subscale Cronbach alpha coefficients were 0.94 for the Negative Spouse and Marriage Relationship subscale, 0.93 for the Emotional Burnout subscale, 0.84 for the Sensitivity to Spouse and Children subscale, and 0.89 for the Marriage Satisfaction subscale. As a result of the Cronbach's alpha internal consistency analysis performed on all of the scale's items, the scale's Cronbach's alpha coefficient was calculated as 0.89.

This study was approved by Trabzon Karadeniz Technical University (2021/383-19.11.2023).

Approval was received from the Ministry of Health, as it was a study conducted during the pandemic period, and from the Ministry of National Education, since access to the subjects and their families would be provided by schools. Informed consent was also obtained from families who volunteered to participate in the study.

For statistical analysis, SPSS 26.0 was used. Descriptive statistics of evaluation results were provided, including numbers, percentages, and mean, standard deviation, median, and minimum-maximum values for categorical variables, as well as mean, standard deviation, median, and minimum-maximum values for numerical variables. The normal distribution was tested using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Measures that conformed to the normal distribution were compared using the independent t-test or ANOVA, while measures that did not conform to the normal distribution were compared using the Mann-Whitney U test, Wilcoxon test, or Kruskal-Wallis Analysis of Variance. The McNemar test was used to compare these proportions before and during the pandemic. The Pearson-Spearman correlation test was used to determine whether there was a correlation between the measurement variables. The significance level was set at $p<0.050$ in all statistical analyses.

RESULTS

One hundred sixty-nine volunteer parents participated in the study, but 35 questionnaires were excluded due to a lack of data. Of the 134 people who answered the questionnaire completely, 73.1% (n= 98) were mothers. Males constituted 83.6% (n= 112) of children with ASD. The mean age of the children was 9.1±4.1 (3–16). The age at diagnosis of ASD was 3.3 ± 1.4 (1–10).

It was stated that 35.8% (n= 48) of the children had diseases accompanying the diagnosis of ASD. Concomitant diseases were attention deficit and hyperactivity disorder in 58.3% (n= 28), epilepsy in 27.1% (n= 13), mood disorders in 10.4% (n= 5), disruptive behavior disorders in 8.3% (n= 4), an oppositional defiant disorder in 6.3% (n= 3), obesity in 4.2% (n= 2), Down syndrome gait disturbance, Duchenne muscular dystrophy, solitary kidney, hypertension, hearing loss, cleft palate-lip, bipolar disorder, Tourette syndrome, speech disorder, and an obsessive-compulsive disorder in 2.1% (n= 1). While 81.3% (n= 109) of children with ASD were receiving education before the pandemic, only 69.4 (n= 93) of them continued education during the pandemic period, and the difference was statistically significant (p= 0.027). Before the pandemic, 121 children received face-to-face education in schools; 92 children were able to continue their education face-to-face during the pandemic. On the other hand, while the rate of children receiving special education at home before the pandemic was 6.4%, it was 9.7% during the pandemic period. While the rate of students receiving online education was 0.0% before the pandemic, it was 9.7% (n= 9) during the pandemic period. The data on children's education and therapy status before and during the pandemic are shown in Table I.

When the status of mothers working in an active income-generating job was examined, 75.4% (n= 101) did not work both before and during the pandemic, 17.2% (n= 23) continued to work in their pre-pandemic job, and 3.7% (n= 5) left their jobs during the pandemic process. 21.6% (n= 29) of fathers did not work both before and during the pandemic, 56.0% (n= 75) continued to work before the pandemic, and 8.2% (n= 11) left their jobs during the pandemic. The monthly income of 29.1% (n= 39) of the parents decreased compared to the pre-pandemic period. 14.2% (n= 19) of the parents made a change of place for the education of their child with ASD during the pandemic period.

When it was evaluated whether there was a change in the relationship between the parents (separation/divorce status) during the pandemic period, it was determined that 3% (n= 4) of the parents experienced separation.

When the pre-pandemic and pandemic periods were compared, it was determined that there was a significant increase in the playing time of children at home (p<0.001). Those who used drugs for ASD during the pandemic (38.1%) were significantly lower than before the pandemic (45.5%) (p= 0.002). Data on children's daily routines before and during the pandemic are shown in Table II.

Information about children's and parents' daily routines before and during the pandemic is shown in Table III. Children (33.6%) who ate irregularly by skipping meals during the pandemic period were found to be significantly more than those (26.9%)

Table I: Children's education and therapy situations before and during the pandemic (n=134)

	Before pandemic n(%)	During pandemic n(%)	p*
Educational status			
Continue education	109 (81.3)	93 (69.4)	0.027
Regular	85 (78.0)	65 (69.9)	0.004
Irregular	24 (22.0)	28 (30.1)	0.004
Not pursuing any formal education	25 (18.7)	41 (30.6)	0.027
Receiving therapy† outside of education			
Receiving therapy	40 (29.9)	36 (26.9)	0.584
Not receiving therapy	94 (70.1)	98 (73.)	

*****Mc Nemar Test was used,* †*Speech/language therapy, play therapy, music therapy*

Table II: Information about the daily routine of children before and during the pandemic period (n=134)

	Before pandemic	During pandemic	p†
Time spent on screen (television, computer, tablet, phone) excluding special education/therapy (hours)*	1.8 ± 1.6 (0-5)	1.6 ± 1.5 (0-5)	0.505
Time spent playing outside (garden, playground) (hours)*	1.4 ± 1.2 (0-5)	1.3 ± 1.1 (0-5)	0.009
Time spent playing at home (hours)*	1.9 ± 1.4 (0-5)	2.1 ± 1.4 (0-5)	<0.001
Drug use due to ASD‡			
Yes	61 (45.5)	51 (38.1)	0.002§
No	73 (54.5)	83 (61.9)	

*****Mean ± SD (min-maks),* †*Wilcoxon,* ‡*n(%),*§ *Mc Nemar Test was used,* ***SD:*** *standard deviation*

Table III: Information about children and parents' daily routines before and during the pandemic period

	Children			Mother			Father		
	Before the pandemic*	**During pandemic***	**p†**	**Before pandemic ***	**During pandemic***	**p†**	**Before pandemic***	**During pandemic***	**p†**
Nutrition									
Eating regularly without skipping meals	98 (73.1)	89 (66.4)	0.004	106 (79.1)	101 (75.4)	0.383	109 (81.3)	100 (74.6)	0.093
Eating irregularly by skipping meals	36 (26.9)	45 (33.6)		28 (20.9)	33 (24.6)		25 (18.7)	34 (25.4)	
Physical activity									
Yes	88 (65.7)	89 (66.4)	1.000	74 (55.2)	66 (49.3)	0.057	69 (51.5)	63 (47.0)	0.070
No	46 (34.3	45(33.6)		60 (44.8)	68 (50.7)		65 (48.5)	71 (53.0)	
Sleep on time									
Sleeping on time	102 (76.1)	99 (73.9)	0.678	100 (74.6)	88 (65.7)	0.017	108 (80.6)	95 (70.9)	0.004
Not sleeping on time	32 (23.99	35 (26.1)		34 (25.4)	46 (34.3)		26 (19.4)	39 (29.1)	
Sleep duration									
Enough sleep time	103 (76.9)	97 (72.4)	0.031	101 (75.4)	92 (68.7)	0.049	117 (87.3)	105 (78.4)	0.002
Not enough sleep time	31 (23.1)	37 (27.69		33 (24.6)	42 (31.3)		17 (12.7)	29 (21.6)	

** n(%), †Mc Nemar Test was used*

Table IV: Total scores of parents' parental burnout scale and quality of life in autism-parent edition sections according to the pandemic-related situations

	Parents' Parental Burnout Scale (n=132)		Quality Of Life Scale In Autism-Parent Edition Section (n=134)			
	Total scale score*	**p**	**Part A***	**p**	**Part B***	**p**
COVID-19 status of the child						
Infected	153.7 ± 36.3	0.443	88.1 ± 14.0	0.816	71.1 ± 19.6	0.248
Not infected	160.0 ± 24.5		89.8 ± 17.0		65.7 ± 16.9	
Quarantine status						
Imposed	155.8 ± 18.5	0.121	88.2 ± 15.9	0.595	65.7 ± 19.3	0.806
Not imposed	160.7 ± 28.5		90.2 ± 17.0		66.5 ± 16.5	
Changes in parental relationship (separation/divorce status) during the pandemic period n(%)		0.009				
Change in status	105.3 ± 46.1	(Posthoc	83.5 ± 13.9		77.8 ± 12.3	
No change in status	161.4 ± 23.4	p† 0.023)	90.0 ± 16.6	0.507‡	65.8 ± 17.4	0.365§
Separation/divorce status before the pandemic	137.5 ± 21.9		80.3 ± 23.5		70.3 ± 11.7	
Neurological development of the child with ASD						
A regression	153.3 ± 26.8	0.079	83.5 ± 13.5	0.007	63.4 ± 14.7	0.164
No change or progress	162.3 ± 25.2		92.6 ± 17.4		67.4 ± 18.3	

**Score (Mean ± SD), †(Bonferroni-adjusted p values) Posthoc Analysis Results Between* Groups, *‡Kruskal Wallis. others Mann Whitney U, §ANOVA.*

who were fed irregularly before the pandemic (p= 0.004). According to the results of the bedtime evaluation, mothers who did not sleep on time during the pandemic period (34.3%) were found to be significantly higher than mothers who did not sleep on time before the pandemic (25.4%) (p= 0.017). A similar relationship was discovered for fathers. In terms of sleep duration, the rate of children, mothers, and fathers who did not sleep enough during the pandemic period was found to be significantly higher than before the pandemic (p= 0.031; p= 0.049; p= 0.002, respectively).

It was determined that 11.2% (n= 15) of children diagnosed with ASD were infected with SARS-CoV-2, and 28.4% (n= 38) of the parents stated that they were quarantined because they were infected or had close/heavy contact with someone who was infected.

The parents' mean PBS scores were calculated as 159.3± 26.0, the QoLA Part A mean scores were 89.6±16.7, and the Part B mean scores were 66.3±17.3.

When the PBS scores were compared based on the change in the relationship between the parents during the pandemic period, those with a change (separation/divorce status) had significantly lower scale scores (105.3±46.1) than those who did not (161.4 ± 23.4) (posthoc p= 0.023).

During the pandemic period, 32.8% (n= 44) of the parents reported that their child with ASD regressed in neurological development. Regression was reported in 52.3% (n= 23) of those who had language/speech, 22.7% (n= 10) who had motor movement, 77.3% (n= 34) who had social communication, 22.7% (n= 10) who had self-care, 43.2% (n= 19) who obeyed commands, 38.6% (n= 17) who made eye contact, and 40.9% (n= 18) who had attention/focus/adaptive skills.

Table V: Total score of parents burnout scale and quality of life in autism-parent version sections according to the daily routine of parents

	Parents' parental burnout scale total score (n=132)				Quality of life scale in autism-parent edition section (n=134)							
	Total Scare Score				Part A				Part B			
	Mother*	p	Father*	p	Mother*	p	Father*	p	Mother*	p	Father*	p
Sleep on time												
Sleeping on time	164.1 ± 25.2	0.004	164.1 ± 26.6	<0.001	93.0 ± 16.8	0.001*	92.7 ± 16.6	<0.001	69.4 ± 16.6	0.003*	68.2 ± 17.1	0.039*
Not sleeping on time	150.1 ± 25.3		148.0 ± 20.8		83.2 ± 14.5		82.2 ± 14.6		60.3 ± 17.0		61.5 ± 16.9	
Sleep duration												
Enough sleep time	161.9 ± 27.7	0.052	162.2 ± 24.3	0.022	92.9 ± 16.8	0.001	91.8 ± 16.7	0.001*	69.8 ± 17.1	<0.001*	66.8 ± 16.8	0.507*
Not enough sleep time	153.5 ± 20.9		148.9 ± 29.5		82.4 ± 14.1		81.7 ± 14.3		58.5 ± 14.9		64.4 ± 19.0	
Nutrition												
Eating regularly without skipping meals	165.0 ± 23.3	<0.001	162.7 ± 23.4	0.002	91.8 ± 16.8	0.001*	92.1 ± 16.1	0.004	65.9 ± 17.8	0.634*	67.1 ± 18.0	0.335*
Eating irregularly by skipping meals	142.3 ± 26.7		149.6 ± 25.7		82.9 ± 14.6		82.4 ± 16.5		67.5 ± 15.5		63.8 ± 14.6	
Physical activity												
Yes	157.8 ± 27.2	0.716	158.4 ± 27.4	0.868	89.5 ± 14.5	0.760	89.8 ± 15.3	0.625	68.7 ± 17.0	0.113*	69.1 ± 18.1	0.035
No	160.7 ± 25.0		160.1 ± 24.9		89.7 ± 18.6		89.5 ± 17.9		63.9 ± 17.3		63.8 ± 16.2	

* **Score (Mean ± SD),** *Independent T-test, others Mann Whitney U

The QoLA Part A scores of parents who believed they had been regressed (83.5±13.5) were found to be statistically significantly lower than those who believed there had been no change or progress (92.6±17.4) (p= 0.007). The total scores of the Parent Burnout Scale and Autism Quality of Life Scale-Parent Edition sections based on the pandemic-related conditions of the parents are shown in Table IV.

The results of the PBS and the QoLA sections based on the parents' daily routines are shown in Table V. According to the findings of the time-to-sleep comparison, the mean PBS scores of both mothers and fathers who did not sleep on time during the pandemic period were statistically significantly lower

Table VI: The results of the correlation analysis between the PBS total score and sub-dimension scores and the QoLA Part A and Part B scores

	PBS total score		PBS "Negative spouse and marital relationship" sub-dimension		PBS "Emotional burnout" sub-dimension		PBS "Sensitivity to spouse and children" sub-dimension		PBS "Dissatisfaction with marriage" sub-dimension	
	rs	p	rs	p	rs	p	rs	p	rs	p
QoLA Part A scores	0.411	<0.001	0.086	0.327	0.108	0.217	-0.013	0.886	-0.01	0.851
QoLA Part B scores	0.421	<0.001	0.138	0.111	0.015	0.861	-0.056	0.521	-0.061	0.482
Child's age	0.412	<0.001	0.249	0.004	0.083	0.343	0.047	0.587	0.031	0.724
Age at which the child was diagnosed with ASD	0.009	0.920	-0.107	0.219	0.066	0.446	0.101	0.245	0.027	0.757
Number of Siblings of the child	-0.117	0.180	0.120	0.132	0.087	0.323	0.022	0.804	0.077	0.382

***QoLA**: Quality of Life in Autism Questionnaire-Parent Version, **PBS:** Parental Burnout Scale, **ASD:** Autism spectrum disorder, **rs:** Correlation Coefficient (Spearman)*

(p= 0.004; p<0.001, respectively). Similarly, the mean scores of both mothers and fathers in QoLA Parts A and B were statistically significantly lower (p= 0.001, p< 0.001, p= 0.003, and p= 0.039, respectively).

The results of the correlation analysis between the PBS total score and sub-dimension scores and the QoLA Part A and Part B scores are shown in Table IV. The PBS total score and the QoLA Part A scores had a moderately significant correlation (rs= 0.411, p<0.001), as did the QoLA Part A score and the PBS "negative spouse and marital relationship" sub-dimension score (rs= 0.421, p<0.001). A moderately significant relationship was discovered between the QoLA Part A score and the "emotional burnout" sub-dimension score (rs= 0.412, p<0.001). There was no statistically significant relationship between the parents' total ADS score and the age of the child with ASD, the age at which the child was diagnosed with ASD, or the number of children the parents had.

DISCUSSION

Education is an essential part of life for children with ASD. In this study, we found that the closure of schools during the pandemic process, as well as the deterioration of the education system's continuity and sustainability, had an impact on the quality of life of not only children but also families. As a result of the interviews with the families, the parents, particularly those who were suffering from severe psychological depression during the pandemic, declined to participate in the survey. We observed that burnout increased in families that reported intra-familial conflicts and more intense childcare during the pandemic period. We believed that if they had also participated, our outcomes would have been even more striking. We discovered that there was little job loss among parents during the pandemic. In light of all of this information, we discovered that the change in the educational process has resulted in an increase in behavioral disorders in children as well as a decline in their neuromotor, social, and cognitive skills. At the same time, the pandemic and the measures implemented both exhausted the parents and had a significant influence on their daily QoL. Again, families reported a significant change in their QoL as a result of the difficulties faced by children who were unable to attend school during the pandemic. Closure and quarantine practices had a significant impact on daily life during the pandemic period. It has resulted in a reduction in children's sleep duration and a deterioration in their eating habits. The daily routines of the families changed as a result of this process, and this change consumed the families with mental and emotional functions.

It has been predicted that both families and children with autism may be affected during the pandemic period, and various studies and practices regarding the precautions to be taken in this process have been developed (12). However, studies examining the relationship between educational limitations, family quality of life, and mental burnout during the pandemic period were rare in the literature. Here, we aim to show the impact of the education process on autism spectrum disorder children and families during the pandemic period.

It is difficult for parents to cope with difficult children and adolescents independently because they lack the professional expertise to overcome these challenges and must frequently rely on schools and therapists for assistance (13). In our country, children with ASD were enrolled in school two weeks after their diagnosis to begin receiving an education. Their life skills and development were aided by 2 hours of individual therapy and 3 hours of group therapy per week. During the pandemic, ASD couldn't have the opportunity to attend these hours, and the continuity of education during the pandemic process was provided both at home with private trainers and online.

It has been well known that families play an important role in education, especially during times of crisis, such as the pandemic. In our study, we found that behavioral disorders increase blindly in ASD children whose parents were burned out and had a high level of emotional incapacity and who continue their education at home. Again, the parents' separation/divorce during the pandemic process resulted in exhaustion as well as difficulties adapting the children to their routines. Our research revealed that the pandemic had significantly reduced educational intensity, that families had become exhausted during this time, that their quality of life had declined, and that their children's emotional, social, cognitive, and motor development had suffered.

When asked what their biggest concerns were about the epidemic and the emergency, families mentioned the infection due to changes in daily routines (e.g., school absenteeism, kindergarten, the constant repetition of infected information, etc.) that increased/intensified, and the child's previously acquired or learned skills. It was stated that they were concerned about losing their health (7,14). Similar to the literature, it was found that among the areas where families had the most common problems with not being able to attend school, there was a fear of interrupting education during the pandemic and spreading it to their children when they went to school. Other reasons included being unable to spare enough time for the child, which existed before the pandemic, as well as transportation and financial problems.

Given that institutional interventions in environments such as schools, hospitals, and workplaces had changed entirely, it was thought that individuals with ASD who had difficulties in social interaction and communication might find it difficult to establish social relations from a distance and that this may even cause regression or hesitation in some skills acquired by staying at home during the epidemic. This was one of the most pressing concerns for families (14). According to the observations of the parents in this study, there were losses in the performance areas of the children during the pandemic period, with

regression in the neuromotor developmental stages being the most common. Furthermore, families stated that their children were harmed in areas such as social communication, language speaking success, obeying commands, maintaining attention, and making eye contact during the pandemic. Throughout this time, the children's stagnation and regression in motor and cognitive achievements increased the family's stress and had a significant impact on their exhaustion. When we looked at the QoLA rating scale of families who noticed a decline in their children's performance, we saw that the burnout level of the families who thought that there was a decrease in performance was high.

Literature included habits about eating, nutrition, and sleep problems in ASD families and gave advice to use QoLA for daily routine activities (14,15,9). According to our findings, changes in the routine daily activities of the families, according to QoLA, caused a significant decrease in the families' quality of life. This demonstrates that the pandemic has had a significant impact on not only children's but also families' daily activities.

Given the possibility of education being disrupted in the future due to the emergence of different waves of the epidemic and similar situations (e.g., natural disasters such as earthquakes, floods, and so on), it was thought that better strategic plans for ASD may be required (3). As a result, it was critical to disclose the studies conducted by institutions directly dealing with ASD for these individuals and their families. It was necessary to emphasize the importance of continuity in the education of special children once more.

The number of participants was the most significant limitation of this study. The study's goal when it was created was to reach a larger audience. Some of the families did not want to fill out the form, thinking that such studies were not beneficial to their children or themselves and that the state did not care about such studies. In some families, they could not fill out the form even if they wanted to because their spouses did not give permission. Since the study was voluntary, the number of participants was insufficient. Since most educational institutions are in the center, transportation to the districts could not be provided due to both logistical difficulties and time constraints. Children with mild to moderate autism were included in the study, but because it was a survey study, a comparison of PBS and QoLA based on the children's autism severity could not be made to protect the data's confidentiality.

CONCLUSION

The COVID-19 pandemic has influenced all aspects of life. Children with ASD were reliant on routines and eager to improve their skills through education. Their patterns had an impact on both their families and themselves. Education was the basis of intervention for the clinical symptoms of autism. It was nearly impossible for a person with autism to survive without education. Even minor changes in this area could result in significant gaps in their world. To avoid deep gaps in cases such as pandemics, it should be ensured that services in the fields of education, social communication, and health care are provided continuously.

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Familial Mediterranean Fever and Accompanying Inflammatory Diseases: Effects on the Disease Severity Score

Ailevi Akdeniz Ateşine Eşlik Eden İnflamatuar Hastalıklar ve Hastalık Ağırlık Skoruna Etkisinin Değerlendirilmesi

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ABSTRACT

Objective: Familial Mediterranean fever (FMF) stands as the most prevalent autoinflammatory disorder in childhood. It is well-established that certain inflammatory conditions may accompanying with FMF. Within the scope of our research, we examined the inflammatory diseases accompanying FMF and their possible effects on the course of the disease in pediatric FMF patients.

Material and Methods: We retrospectively reviewed the medical records of 349 patients diagnosed with FMF based on the diagnostic criteria, who were followed between January 1, 2015, and December 31, 2020. The effect of inflammatory diseases associated with FMF on the Pras disease severity score was investigated.

Results: Among the patients included in the study, 45.85% exhibited mild disease, 42.98% had moderate disease, and 11.17% had severe disease. Among the study participants, 16% were found to have accompanying inflammatory diseases. Specifically, IgA vasculitis was present in 5.73% of cases, sacroiliitis in 3.72%, prolonged febrile myalgia in 2.00%, acute rheumatic fever in 1.71%, juvenile idiopathic arthritis in 0.85%, polyarteritis nodosa in 0.57%, inflammatory bowel diseases in 0.85%, Behçet's disease in 0.28%, recurrent optic neuritis in 0.28%. In some cases, more than one inflammatory disease has been observed in addition to FMF. It was observed that the disease severity score was higher in patients with accompanying inflammatory diseases (p=0.04). Additionally, the rate of severe disease was found to be increased in patients with accompanying inflammatory diseases (17.31%) (p=0.02).

Conclusion: Our study demonstrated that accompanying inflammatory diseases increase the disease severity score and the clinical severity of FMF. Furthermore, patients with accompanying inflammatory diseases showed higher erythrocyte sedimentation rate values during attack-free periods and an increased use of biological agents.

Key Words: Biological Agent, Disease Severity Score, Familial Mediterranean Fever, Inflammatory Diseases

ÖZ

Amaç: Ailevi Akdeniz ateşi (AAA), çocukluk döneminde en sık görülen otoinflamatuar hastalıktır. Bazı inflamatuar hastalıkların AAA'ya eşlik edebildiği bilinmektedir. Çalışmamızda AAA tanılı hastalarda eşlik eden inflamatuar hastalıkları ve hastalık seyrine etkilerini inceledik.

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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 research received approval from the Health Sciences University Ankara Children's Hematology and Oncology Training and Research Hospital Ethics Committee under the decision number 2019-069 dated March 25, 2019.

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

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Gereç ve Yöntemler: 1 Ocak 2015-31 Aralık 2020 tarihleri arasında klinik tanı kriterlerine göre AAA tanısı ile takip edilen 349 hastanın tıbbi kayıtları geriye dönük incelendi. AAA ile birliktelik gösteren inflamatuar hastalıkların Pras hastalık ağırlık skoruna etkisi araştırıldı.

Bulgular: Çalışmaya dâhil edilen hastaların %45.85'inde hafif, %42.98'sinde orta ve %11.17'inde ağır hastalık mevcuttu. Çalışmaya dâhil edilen hastaların %16'sında eşlik eden inflamatuar bir hastalık tespit edildi (%5.73 IgA vasküliti, %3.72 sakroileit, %2 uzamış febril miyalji, %1.71 akut romatizmal ateş, %0.85 juvenil idiyopatik artrit %0.57 poliarteritis nodosa, %0.85 inflamatuar barsak hastalıkları, %0.28 Behçet hastalığı, %0.28 tekrarlayan optik nörit). AAA'ya eşlik eden birden fazla inflamatuar hastalığın olduğu durumlar mevcuttu. Hastalık ağırlık skorunun, eşlik eden inflamatuar hastalığı olanlarda olmayanlara göre yüksek olduğu bulundu (p=0.040). Ek olarak eşlik eden inflamatuar hastalığı olan hastalarda ağır hastalık görülme oranının (%17.31) arttığı görüldü (p=0.020).

Sonuç: Çalışmamızda eşlik eden inflamatuar hastalıkların AAA hastalığı ağırlık skorunu yükselttiği, ağırlık şiddetini artırdığı, bu hastalarda ataksız dönemdeki eritrosit sedimentasyon hızı değerlerinin yüksek seyrettiği ve biyolojik ajan kullanımının arttığı gösterilmiştir.

Anahtar Sözcükler: Biyolojik Ajan, Hastalık Ağırlık Skoru, Ailevi Akdeniz Ateşi, İnflamatuar Hastalık

INTRODUCTION

Familial Mediterranean fever (FMF) is the most common autoinflammatory disease in childhood. It is characterized by recurrent attacks marked by fever, abdominal pain, joint pain, chest pain, and erysipelas-like erythema (ELE) (1).

The disease is caused by mutations in the MEFV gene, which encodes the pyrin protein involved in regulating inflammation (2). The most frequent mutations observed in our country are M694V, M680I, and V726A. It is known that M694V reflects the most severe clinical phenotype (3,4). Colchicine effectively controls the recurrent attacks of the disease. The use of colchicine has a dramatic impact on the course of the disease and prevents an increase in the number of patients with renal amyloidosis. In cases of colchicine resistance, biologic agents can be used (5-7).

It is well-established that certain inflammatory diseases can accompany with FMF. Investigating the possible accompanying diseases in FMF patients is essential to understand their clinical impact, determine if they share a common etiological pathway, and identify potential common treatment approaches. In particular, diseases such as IgA vasculitis, sacroiliitis, juvenile idiopathic arthritis (JIA), polyarteritis nodosa (PAN), inflammatory bowel diseases (IBD), prolonged febrile myalgia (PFM), acute rheumatic fever (ARF), and Behçet's disease can be seen alongside FMF (8). Accompanying diseases may adversely affect the quality of life of FMF patients and could be related to disease severity.

In our study, we aimed to evaluate the frequency of accompanying inflammatory diseases in FMF patients. We also evaluated the relationship between the presence of accompanying inflammatory diseases and the patients' mutations, disease severity, and colchicine resistance.

MATERIALS and MATERIALS

In this study, we retrospectively examined the medical records of 349 FMF patients according to the Yalçınkaya-Özen diagnostic criteria (5). The data were collected from January 2015 to December 2020 at the Pediatric Rheumatology Clinic of the Health Sciences University Ankara Children's Hematology and Oncology Training and Research Hospital. Patients who had not undergone mutation analysis, were followed up for less than 6 months, or had incomplete file data were excluded from the study. The research received approval from the Health Sciences University Ankara Children's Hematology and Oncology Training and Research Hospital Ethics Committee under the decision number 2019-069 dated March 25, 2019.

Patient characteristics including age at diagnosis and follow-up duration, family history, mutations, accompanying inflammatory diseases, time of onset of FMF in relation to the accompanying condition, colchicine dosage (mg/kg/day), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) during the attack-free period, yearly attack frequency before and after colchicine treatment, use of biologic agents in treatment, and treatments for accompanying inflammatory diseases were retrospectively reviewed. The Pras et al.(10) disease severity score was used to assess disease severity, and information related to disease onset age, monthly attack frequency, arthritis, ELE, amyloidosis, and colchicine dosage was analyzed (9).

The accompanying inflammatory diseases recorded in the study included IgA vasculitis, sacroiliitis, JIA, PAN, IBD [ulcerative colitis (UC), Crohn's disease (CD)], PFM, ARF, Behçet's disease, and ON.

Genetic mutations were grouped as M694V heterozygous, M694V homozygous, non-M694V homozygous, and non-M694V heterozygous, M694V compound heterozygous, as well as mutation-negative cases. This classification was designed with the aim of assessing the clinical implications of the M694V mutation, a mutation known to be associated with severe disease, in a subgroup-specific manner. The use of biologic agents for FMF treatment and the specific biologic agents used were queried.

The Pras et al. (10) disease severity score was categorized as mild (score 3-5), moderate (score 6-8), and severe (score 9 and above) (9) (Table I).

Statistical analysis was conducted using SPSS 23.00 software (IBM SPSS Statistics for Windows, Version 22.0, Armork, NY, USA). Descriptive statistics such as mean, standard deviation,

Table I: Severity score by Pras et al. (10) modified for children.

Parameter	Features	Score
Age of onset (years)	11-20	2
	6-10	3
	<6	4
Number of attacks per month	<1	1
	1-2	2
	>2	3
Arthritis	Acute	2
	Protracted	3
Erysipelas-like erythema		2
Amyloidosis		3
Dose of colchicine	Less than appropriate* dose	0
	Appropriate dose	1
	More than appropriate dose	2

minimum, maximum, percentage, and frequency were used for parametric and non-parametric data. The chi-square test was used for comparisons of categorical data. If significant results were observed in the chi-square test, the group responsible fort he difference was identified with a post-hoc multiple comparasion test. Independent sample t-tests were employed for binary group comparisons of parametric data, while ANOVA test was used for comparisons involving three or more groups. The critical significance level was set at 0.050 for all analyses.

RESULTS

Demographic characteristics:

Out of the 349 patients included in the study, 182 (52.14%) were female, and 167 (47.86%) were male. The mean age at diagnosis was 7.43±3.77 years, and the mean follow-up duration was 5.93±3.60 years. In 304 patients (87.11%), a clinically significant genetic mutation was detected in the MEFV gene, either homozygous, compound heterozygous, or heterozygous (Table II).

Disease severity and applied treatments:

The patients were grouped based on their disease severity scores, with 160 (45.85%) classified as having mild severity, 150 (42.98%) as moderate, and 39 (11.17%) as severe disease. The median ages for patients with mild, moderate, and severe disease were 8.63 years, 6.62 years, and 5.58 years, respectively. Patients with mild disease had a statistically significantly higher median age compared to those with moderate and severe disease (p=0.039).

All patients with FMF diagnosis were on colchicine treatment. Among them, 329 patients (94.26%) responded to colchicine, while 20 (5.74%) were colchicine-resistant and required the use of biologic agents alongside colchicine. It was observed that patients using biologic agents had significantly higher ESR levels (p=0.012), but there was no statistically significant difference in CRP values (p=0.532).

Association between accompanying inflammatory diseases and disease severity:

Out of the 349 patients, 52 (14.89%) had accompanying inflammatory diseases. The occurrence rates of accompanying inflammatory diseases are listed in Table III. IgA vasculitis was the most common accompanying disease with FMF, present in 20 patients (38.46%). Among these patients, 11 were diagnosed with IgA vasculitis before FMF, five were diagnosed with FMF before IgA vasculitis, and four were diagnosed simultaneously with both conditions.

Among the 20 patients with both IgA vasculitis and FMF, two had prolonged febrile myalgia, and one had sacroiliitis as accompanying diseases. One patient with accompanying FMF and ulcerative colitis also had sacroiliitis.

Upon analyzing disease severity scores, patients with accompanying inflammatory diseases had significantly higher scores (6.37±1.90) compared to those without accompanying inflammatory diseases (5.79±1.71) (p=0.038). Patients with accompanying inflammatory diseases had a higher proportion of severe disease (n=9, 17.30%), whereas patients without accompanying diseases had a higher proportion of mild disease (n=143, 48.14%) (p=0.019) (Table IV).

In patients with accompanying inflammatory diseases, 9 (17.30%) had an ESR value >20 mm/hour during the attack-free period, while this was observed in 17 patients (5.72%) without accompanying inflammatory diseases. The ESR levels during the attack-free period were significantly higher in patients with accompanying inflammatory diseases (p=0.011).

The average colchicine dose was 0.026±0.023 mg/kg in patients with accompanying inflammatory diseases and 0.029±0.011 mg/kg in patients without accompanying inflammatory diseases, with no statistically significant difference (p=0.310). The use of biologic agents was significantly higher in patients with accompanying inflammatory diseases (11.51%) (p=0.041).

Table II: Mutation Groups

Accompanying inflammatory diseases	None	M694V heterozygous	M694V homozygous	M694V compound heterozygous	non-M694V heterozygous	non-M694V homozygous	p
No*	41(13.80)	50 (16.83)	74 (24.91)	59 (19.86)	34 (11.44)	39 (13.13)	0.51†
Yes*	4 (7.69)	8 (15.38)	14 (26.92)	15 (28.84)	7 (13.46)	4 (7.69)	0.51†

** n(%), †Chi-square test was performed*

Table III: The occurrence rates of accompanying inflammatory diseases

Accompanying inflammatory diseases	of patients with accompanying inflammatory diseases*	of all patients*
IgA vasculitis	20 (38.46)	20 (5.73)
Sacroiliitis	13 (25.00)	13 (3.72)
Acute Rheumatic Fever	6 (11.53)	6 (1.71)
Prolonged Febrile Myalgia	7 (13.46)	7 (2.00)
Juvenile Idiopathic Arthritis	3 (5.76)	3 (0.85)
Poliarteritis Nodosa	2 (3.84)	3 (0.57)
Ulcerative Colitis	2 (3.84)	2 (0.57)
Crohn Disease	1 (1.92)	1 (0.28)
Behçet's Disease	1 (1.92)	1 (0.28)
Recurrent Optic Neuritis	1 (1.92)	1 (0.28)

**n (%)*

Table IV: The Relationship Between the Presence of Accompanying Inflammatory Disease and Disease Severity

FMF with Accompanying Inflamatory Disease	Disease Severity			p
	Mild	Moderate	Severe	
No*	143 (48.14.9	125 (42.08)	29 (9.76)	0.020†
Yes*	17 (32.69)	26 (50.00)	9 (17.31)	0.020†

**n (%), †Chi-square test was performed*

DISCUSSION

In this study, it was demonstrated that approximately 16% of FMF patients had an accompanying inflammatory disease, with IgA vasculitis being the most frequent among them. In FMF patients with accompanying inflammatory diseases, it was observed that there were higher ESR levels during the attack-free period and a higher of severe illness.

Familial Mediterranean fever is considered the prototype of autoinflammatory diseases resulting from dysregulations in the innate immune system. Identifying accompanying inflammatory diseases associated with this condition will enable the implementation of the most appropriate patient care by evaluating common points in their pathogenesis and treatment options. This study revealed a significant occurrence rate of approximately 16% for accompanying inflammatory diseases. In another study conducted in our country with 686 patients, the rate of accompanying inflammatory disease was found to be 18.9% (8). Yet another study from our country reported this rate as 12.8% (11). In both studies, vasculitis, IBD, sacroiliitis, and JIA were prominent. Among the diseases identified in association with FMF in our study, IgA vasculitis was the most common. In cases where the course of IgA vasculitis is more severe than expected, the possibility of accompanying FMF should be considered. Detailed anamnesis for diagnosis and MEFV gene analysis in suspected cases direct towards FMF diagnosis. In a study published in 1997 with 207 FMF patients, the frequency of IgA vasculitis was reported as 7% (12). IgA vasculitis is the most common initial diagnosis in over half of the patients. Cattan et al. (12), in 2004, reported that IgA vasculitis is frequently the initial diagnosis in the accompanying of both diseases and suggested that MEFV mutation analysis should be performed on patients diagnosed with IgA vasculitis in regions where FMF is common (13). Although the clinical manifestations of FMF start earlier, the more dramatic course of IgA vasculitis necessitates an earlier diagnosis. If IgA vasculitis presents with more severe symptoms than expected or if symptoms like rash and abdominal pain persist for an extended period, the possibility of accompanying FMF should be considered. In our study, three FMF patients were found to have other inflammatory diseases, and among them, IgA vasculitis was the most common. PFM was observed in association with IgA vasculitis in two patients, and sacroiliitis was seen in one patient on the background of FMF.

Poliarteritis nodosa is another vasculitis that can be accompanying with FMF. The prevalence of PAN is 9 per 1.000.000 adults. Several studies have highlighted the importance of variations in the MEFV gene as a significant susceptibility factor for PAN. In a study conducted by Tunca et al. (3) in 2005 with 2.838 patients, this rate was found to be 0.9%, and in another study by Barut et al. (1), it was 0.3%. Our study and other studies in the literature demonstrate an increased frequency of PAN in FMF patients (14). FMF and PAN can present with similar clinical manifestations, such as fever and abdominal pain. Therefore, diagnosing PAN in FMF patients can be challenging, and clinicians should have a high awareness of PAN in cases of fever and severe abdominal pain that exceed the typical attack duration for FMF. Vasculitis such as IgA vasculitis and PAN may be associated with inadequately controlled inflammation due to FMF. Although prolonged febrile myalgia is defined as a condition seen in FMF, it is more often considered as a vasculitic syndrome accompanying FMF (15). In a study on diseases associated with FMF, PFM was reported in 1.4% of patients (16). In our current study, PFM was observed in 2.00% of FMF patients.

Behçet's disease was another disease investigated in association with FMF. In a study by Schwartz et al. (17) involving 4,000 FMF patients, this rate was 0.9%, and another study reported a rate of 0.14% for Behçet's disease among 686 FMF patients (9). Behçet's disease is seen in our country at a rate of 1-3 per 10,000 individuals (17). The relationship between Behçet's disease and FMF is not as clearly understood as in other vasculitides, and further studies are needed in this regard (18).

It is known that the frequency of sacroiliitis increases in FMF. However, in some cases, it is challenging to distinguish whether sacroiliitis develops secondary to FMF or if it is part of enthesitis-related arthritis. The age of disease onset, clinical presentation,

ocular findings, and HLA B27 or MEFV gene analysis can be helpful in making this distinction. All sacroiliitis patients included in our study were distinguished from FMF-related sacroiliitis by the presence of HLA-B27 positivity, enthesitis, or uveitis. In our study, sacroiliitis was the second most common accompanying inflammatory disease. Additionally, one patient was diagnosed with sacroiliitis in association with IgA vasculitis, and another patient was diagnosed with sacroiliitis in association with ulcerative colitis (UC). In a study involving 392 patients, the rate of sacroiliitis in FMF patients was found to be 1.7% (19).

Inflammatory bowel diseases are another inflammatory disease that can accompanying with FMF (20). In our study, one of the patients with FMF had CD, and two had UC. One patient diagnosed with UC also had sacroiliitis. In a study presenting accompanying diseases, the rate of IBD in FMF patients was found to be 0.8% (21). Similar studies have reported the incidence of IBD-FMF accompanying as 1.45% and 1.16% (9). A study focusing on the frequency of IBD in FMF patients reported that the accompanying disease rate was higher than the prevalence of the individual diseases (20).

It is known that ARF can also accompanying with FMF . In a study conducted by Balcı-Peynircioğlu et al. (21) in 2015, this accompanying rate was found to be approximately 0.8%. The prevalence of ARF in our country was reported as 21 per 100,000 individuals in the most comprehensive study conducted between 2000 and 2009 (16). It should be noted that the Modified Jones criteria were revised in 2015, and the current prevalence may be higher. As arthritis is prominent in both diseases, correct diagnostic approaches for both conditions are crucial to demonstrate their accompanying and to avoid diagnostic challenges.

In some FMF patients, multiple inflammatory diseases were observed to co-occur. The presence of FMF-IgA vasculitis-sacroiliitis, FMF-sacroiliitis-UC and FMF-IgA vasculitis-PFM indicates the presence of more than one disease with FMF on the basis of inflammation.

In our study, there was no significant relationship between patients' mutations and the development of accompanying inflammatory diseases. However, the presence of at least one M694V mutation in patients with accompanying inflammatory disease is similar to the data in the literature. Ayaz NA. et al. (16) reported a rate of 72% in a study with 1687 patients.

Patients with accompanying inflammatory diseases had significantly higher disease severity scores compared to the group without accompanying diseases. When evaluating disease severity, the rate of severe disease was higher in patients with accompanying inflammatory disease and statistically significantly lower in patients without accompanying disease. Recently, a study with 1687 patients also indicated that accompanying conditions may be associated with disease severity (16). This relationship will guide clinicians in the clinical follow-up and treatment of FMF patients with accompanying inflammatory diseases. In cases of severe FMF grouped as severe disease, consideration should be given to possible accompanying inflammatory diseases that may develop and not conform to the course of FMF. Additionally, patients with accompanying inflammatory diseases during the attack-free period had significantly higher ESR levels. These parameters routinely used in the diagnosis and follow-up of FMF also provide insight into subclinical inflammation (22). Investigating the possible presence of other diseases that may cause subclinical inflammation in these patients can prevent unnecessary escalation of colchicine dosage.

In our study, no significant relationship was found between the presence of accompanying inflammatory diseases and the dosage of colchicine in FMF patients. However, patients with accompanying inflammatory diseases showed significantly higher rates of using biological agents. The response to colchicine dosage was not associated with the presence of accompanying inflammatory diseases in patients responding to colchicine. However, colchicine-resistant patients are at risk for the development of other inflammatory diseases. We believe that patients using biological agents, i.e., colchicine-resistant patients, need to be monitored for other inflammatory diseases.

The main limitation of this study is its retrospective and single-center design. Nevertheless, this study is important in drawing attention to the possible presence of accompanying inflammatory diseases in patients with FMF, the most common autoinflammatory disease in our country, where severe disease and high ESR during the attack-free period were observed.

In conclusion, various inflammatory diseases, including IgA vasculitis, sacroiliitis, and PFM, can accompanying in FMF patients. Accompanying inflammatory diseases can increase the disease severity score and severity of FMF, leading to higher ESR values during the attack-free period in these patients. The presence of an additional inflammatory disease alongside FMF may contribute to the severity of the disease, and the use of biological agents may be considered during follow-up.

The clinicians should be aware of the possibility of accompanying inflammatory diseases and the potential impact on disease severity in FMF patients. Close monitoring of FMF patients for potential inflammatory diseases, especially those using biological agents or resistant to colchicine, is crucial to provide appropriate management and ensure better patient outcomes.

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Demographic, Clinical and Radiological Characteristics of Pediatric Cases Diagnosed As Transient Intussusception As A Result of Spontaneous Reduction

Spontan Redüksiyon Sonucu Geçici İnvajinasyon Tanısı Alan Pediatrik Olguların Demografik, Klinik ve Radyolojik Özellikleri

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ABSTRACT

Objective: Transient intussusception (TI) is a condition in which part of the small intestine is identified to enter the anterior part of the intestine telescopically, but this condition spontaneously reduces during follow-up. The observation of this situation has increased with the widespread use of ultrasonography among diagnostic tools. In this study, the aim was to present cases of intussusception that resulted in spontaneous reduction in our clinic.

Material and Methods: The records of all cases diagnosed with intussusception between January 2014 and September 2022 were scanned. The files of the patients who were diagnosed with TI as a result of observation were investigated. Age, gender, clinical findings, duration of admission, ultrasonography findings, treatment options and results were analyzed retrospectively.

Results: A total of 71 cases diagnosed with intussusception included 50 boys and 21 girls, with a mean age of 22.3 months. Intussusception was ileo-colic in 36 patients, ileo-ileal in 32 patients, and jejuno-jejunal in three patients. Clinical observation with physical examination and ultrasonography was performed in 33 (21%) patients with SBI who did not have signs of peritoneal irritation and had short segment involvement. Surgical reduction was performed in four patients because intussusception persisted after observation. Control US performed on the remaining 29 patients showed that intussusception disappeared. The age range of 29 patients diagnosed with TI ranged from 10 to 122 months (mean 46.2 months). Of the cases, 19 (65.5%) were male and 10 (34.4%) were female. The length of the invaginated segment ranged from 1-2.2 cm (mean 1.8 cm).

Conclusion: Spontaneous reduction of SBI, which does not have acute abdominal findings and progresses with short segment involvement on US, may occur during clinical observation. For this reason, close follow-up of suitable cases that may develop spontaneous reduction is important to avoid unnecessary surgical interventions and consequences.

Key Words: Child, Intussusception, Transient, Spontan reduction

ÖZ

Amaç: Geçici invajinasyon, ince bağırsağın bir kısmının teleskopik olarak bağırsağın ön kısmına girdiğinin tespit edildiği ancak takip sırasında bu durumun kendiliğinden düzeldiği bir durumdur. Tanı araçları arasında ultrasonografinin yaygınlaşması ile birlikte bu durumun görünürlülüğü artmıştır. Bu çalışmada kliniğimizde spontan azalma ile sonuçlanan invajinasyon olgularının sunulması amaçlandı.

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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*: The study was approved by Health Sciences University in the Eskisehir City Hospital, Clinical Research Ethics Committee (Approval No: ESH/GOEK 2023/34, 20.06.2023)

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

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Gereç ve Yöntemler: Ocak 2014 ile Eylül 2022 tarihleri arasında invajinasyon tanısı alan bütün olguların kayıtları tarandı. Gözlem sonucunda geçici invajinasyon tanısı konulan hastaların dosyaları incelendi. Yaş, cinsiyet, klinik bulgular, başvuru süresi, ultrasonografi bulguları, tedavi seçenekleri ve sonuçları retrospektif olarak incelendi.

Bulgular: İnvajinasyon tanısı alan 50'si erkek, 21'i kız çocuğu olmak üzere toplam 71 olgunun yaş ortalaması 22.3 aydı. İnvajinasyon 36 hastada ileokolik, 32 hastada ileo-ileal ve 3 hastada jejuno-jejunaldi. Peritoneal irritasyon bulgusu olmayan ve kısa segment tutulumu olan 33 (%21) ince barsak invajinasyonlu hastaya fizik muayene ve ultrasonografi ile klinik gözlem yapıldı. Dört hastada gözlem sonrası invajinasyonun devam etmesi nedeniyle cerrahi redüksiyon uygulandı. Geri kalan 29 hastaya 12 saat sonra yapılan kontrol ultrasonunda invajinasyon görüntüsünün kaybolduğu görüldü. Geçici invajinasyon tanısı alan 29 hastanın yaş aralığı 10 ile 122 ay (ortalama 46.2 ay) arasında değişiyordu. Olguların 19'u (%65.5) erkek, 10'u (%34.4) kadındı. İnvaginasyonlu segmentin uzunluğu 1-2.2 cm (ortalama 1.8 cm) arasında değişiyordu.

Sonuç: Akut batın bulguları olmayan ve ultrasonda kısa segment tutulumu ile seyreden ince barsak invajinasyonlarında klinik gözlem sonucu spontan redüksiyon meydana gelebilir. Bu nedenle spontan redüksiyon gelişebilecek uygun vakaların yakın takibi, gereksiz cerrahi müdahalelerin ve sonuçlarının önlenmesi açısından önemlidir.

Anahtar Sözcükler: Çocuk, İnvajinasyon, Geçici, Spontan redüksiyon

INTRODUCTION

Intussusception is a serious condition in which part of the intestine invaginates into the intestine just in front of it (1). Incidence was reported as 0.2% (2). The mean age of children diagnosed with intussusception is between 6-18 months, and only 30% of the cases are seen in those older than two years (1,2).

The etiology of pediatric intussusception is usually idiopathic, and lead points are detected in only 10% of cases (3). Although the etiology has not been sufficiently clarified, Peyer's plaque hypertrophy, mesenteric lymph adenopathy and gastroenteritis due to rotavirus are thought to play a role (4,5). If treatment is delayed, intussusception may gradually cause vascular congestion, intestinal wall damage, tissue ischemia, necrosis, and intestinal perforation (5).

Intermittent colic abdominal pain, rectal bleeding in the form of currant jelly, and palpable abdominal mass are typical clinical signs of intussusception, but this clinical triad is seen in less than one-third of children with intussusception (6,7). The diagnosis of intussusception is made by the target sign and/or pseudokidney image detected on abdominal ultrasonography (US) performed by experienced radiologists, which is highly accurate (8-10).

Treatment in the pediatric population depends on the type of intussusception. For ileo-colic intussusception (IC), which is the most common type in children, if there are no signs of peritoneal irritation or intestinal perforation, ultrasound-guided or fluoroscopic pneumatic or hydrostatic enema reduction is attempted (11). If non-surgical reduction is not successful, a surgical procedure (manual reduction and/or resection or enterostomy) is performed.

Transient intussusception (TI) is a term used for spontaneous reduction of small bowel intussusception (SBI) during observation (9,12). There is no known non-surgical reduction method for SBI, but the possibility of spontaneous reduction during close follow-up was discussed in terms of criteria for determining treatment (surgery or follow-up).

In this study, the aim was to create an algorithm on this subject by discussing our cases diagnosed with temporary intussusception in the last 8 years in our clinic, in the light of the literature.

MATERIALS and METHODS

Between January 2014 and September 2022, 71 cases under the age of 18 who were followed up and treated with diagnosis of intussusception were analyzed retrospectively. The study was approved by Health Sciences University in the Eskisehir City Hospital, Clinical Research Ethics Committee (ESH/GOEK 2023/34, 20.06.2023).

Abdominal US and Doppler US were performed by a US team consisting of 8 faculty members in the radiology department, using high-frequency linear probes of 5-10 MHz. Intussusception was diagnosed with the appearance of a target sign (also known as a donut sign) and/or a pseudokidney sign on ultrasound. Additionally, the presence of lymph nodes (long axis greater than 1 cm) and/or other lead points within the intussusception were investigated. Invaginated segment length was measured. In the same session, the absence of blood flow to the intestines was checked using color Doppler US.

Patients diagnosed with invagination as a result of abdominal US were hospitalized. Among our patients diagnosed with ileo-ileal (IIL) and jejuno-ileal intussusception (JJ), those without acute abdomen findings (peritoneal irritation signs and intestinal perforation) were monitored. In these cases, a short invaginated segment (less than 3 cm) was found on abdominal US and there was no edema of the intestinal wall. Physical examination was performed at least once every 2 hours for our patients under observation. Abdominal US was repeated every 12 hours. Oral feeding was started in patients whose clinical findings regressed and with no invagination detected on repeated abdominal US. The patients whose clinical condition improved and symptoms disappeared after the second ultrasonographic evaluation were discharged 1 day later. Surgical reduction was performed in patients with clinical deterioration and/

or permanent US findings as a result of follow-up. Surgical reduction was performed in patients with clinical deterioration and/or permanent US findings as a result of follow-up and in patients with initial peritoneal irrigation findings.

Patients with ileocolic intussusception (IC) who were diagnosed with ileocolic intussusception and did not have acute abdominal symptoms underwent reduction with hydrostatic pressure enemas under fluoroscopy or ultrasound guidance. Surgical treatment (manual reduction and/or resection or enterostomy) was applied to irreducible cases and patients with signs of peritoneal irritation.

Age, gender, clinical findings, type of intussusception and treatment methods of the patients were recorded. Statistical assessment of data was conducted by the biostatistics department. SPSS software (version 28.0; SPSS Inc., Chicago, IL, USA) was used for data analysis. First, descriptive statistics were applied to all data of the study. Descriptive statistics for variables determined by measurement; given as mean and standard deviation. Firstly, the data used were tested for normal distribution (Shapiro-Wilk test). Kruskal-Wallis test was used for group comparisons. Categorical variables were compared with the Chi-square (Fisher's exact) test. P values <0.050 were considered statistically significant.

RESULTS

In the last 8-year period, 71 patients with diagnosis of intussusception were monitored and treated in the Pediatric Surgery Clinic, 50 male and 21 female. Mean age was 22.3 months (4–122 months). The common complaint of all patients was abdominal pain. Additional complaints included vomiting in 63 cases (88.7%), and blood in stool in 8 cases (11.2%). Abdominal mass was palpated in 7 cases (9.8%).

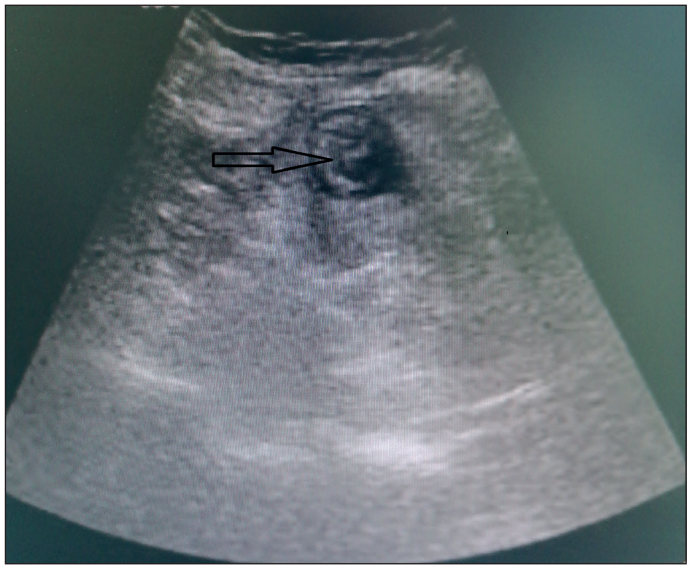

Figure 1: Ultrasonographic target sign of a patient with transient small bowel intussusception.

Table I: The management according to intussusception types

	Ileo-ileal	Jejuno-Jejunal	Ileo-colic
Hydrostatic reduction	-	-	21
Surgery	6	-	15
Follow-up	26	3	-
Total	32	3	36

The classic triad (colic pain, hematochezia, and palpable abdominal mass) was detected in only 7 (9.8%) patients. The diagnosis of intussusception was made by observing the target (donut) sign and/or pseudokidney findings on abdominal US (Figure 1). Based on USG findings, 3 types of intussusception were detected: IC, IIL, and JJ. Intussusceptions were IC in 36 patients, IIL in 32 patients, and JJ in 3 patients. No patient had colo-colonic intussusception (CC).

In addition, the presence or absence of lead points, which may predispose to intussusception, were screened. Enlarged lymph nodes (over 1 cm) were present in 22 (30.9%) patients. In the same session, Doppler US was performed in patients diagnosed with intussusception, and intestinal wall blood flow was evaluated. Intestinal wall vascularization was decreased in 5 (7%) patients with IC and 2 (2.8%) patients with IIL. Types of intussusception according to management is presented in Table I.

Emergency surgical procedures were performed in 2 patients with IIL whose invaginated segment was longer than 3 cm (4 and 7 cm) and with edema detected in the intestinal wall. Thirty-three patients with other SBI were observed. As a result of clinical follow-up, spontaneous reduction was detected in 29 patients on abdominal US performed 12 hours later, and they were diagnosed with TI. Manual surgical reduction was performed in 4 patients with persistent intussusception on US, and no resection was required in any of these cases. The mean age of our patients diagnosed with TI was 46.1 months (range 10-122 months). Of the cases, 19 were boys and 10 were girls. Palpable abdominal mass was detected in 12 patients (41.3%). Rectal bleeding was not present in any patient. The mean length of the invaginated segment, which was detected by abdominal US at the time of diagnosis and spontaneously reduced during follow-up, was calculated as 1.8 cm (range 1-2.2 cm). There was no edema in the intestinal wall in these patients and no lead point was detected in any of the patients. The duration of hospital admission was more than 24 hours in patients who underwent surgical reduction for small bowel intussusception.

Four of the 36 IC intussusception cases underwent immediate surgery due to acute abdomen. In 32 (45% of total) of the remaining cases, hydrostatic reduction was ensured with fluoroscopy. Surgery was performed as needed following unsuccessful hydrostatic reduction attempts in 11 IC intussusception cases. Mean age of patients who underwent surgery was 16.4 months (4-46 months). Manual reduction was performed in 21 patients

who underwent surgery, with intussuscepted segments ranging from 4 to 12 cm. Bowel resection or enterostomy was not required in any of the patients.

DISCUSSION

Intussusception is a major abdominal emergency in children with serious consequences if not diagnosed and treated in time. The etiology is not clear in most cases, but it is thought to develop secondary to lymphoid hyperplasia due to a nonspecific infection caused by adenovirus, enterovirus and rotaviruses (5,13). It is the most common cause of bowel obstruction in infants (under the age of three) and is more common in boys (14). In our study, the mean age was 22.3 months, and 50 of our cases were male.

The clinical manifestation of intussusception is variable, but patients usually present with colic abdominal pain, pulling the knees to the chest, excessive irritability, and crying (15). The child may return to normal activities between episodes of pain but may appear listless and lethargic as the pain becomes more intense. Vomiting may occur shortly after the onset of pain. Although clinical manifestations of intussusception are well defined, they do not cover all cases of intussusception. The classic pediatric triad of intermittent abdominal pain, palpable abdominal mass, and bloody stool is present in only 15% of cases (16). The classical triad was seen in 7 (9.8%) of our patients diagnosed with intussusception. Currant jelly stools were not detected in any of the patients diagnosed with TI.

While plain X-ray films are considered useful for the diagnosis of obstruction, they lack sensitivity and specificity for the diagnosis of intussusception. Therefore, abdominal US, barium radiography and computed tomography (CT) can be used for diagnosis (5). The sensitivity and specificity of US for the diagnosis of intussusception is close to 100%, especially in children (8-10). All of our patients were diagnosed with abdominal US. In 29 of the 33 patients under observation, intussusception findings disappeared on control abdominal US performed 12 hours later. Thus, unnecessary surgical procedures were avoided.

Considering the differences in clinical findings and treatment approach, childhood intussusceptions of IC/CC can be considered as 2 separate subgroups of intussusceptions and SBI (17). IC and CC cases can be easily treated with non-surgical (hydrostatic or pneumatic reduction) methods (18). However, the surgical approach is indicated by the failure of non-surgical methods or in patients with signs of intestinal perforation and peritoneal irritation. In a study that included patients from 14 countries, Tran et al. (19) reported the rates of surgically-treated intussusception ranged between 2.5% and 95%. Hydrostatic reduction was performed in 32 of our patients with IC, and reduction was achieved in 21 (65.6%) patients. Surgical reduction was performed in 11 patients (34.3%) who could not be reduced by non-surgical methods. Although CC transient intussusception cases were reported in the literature, it is very rare in children (20). There was no CC intussusception among our cases.

SBI is less common than IC intussusception and there is no known non-surgical reduction method (17). There are two different options in the approach to these patients; clinical and radiological follow-up of cases that are likely to develop spontaneous reduction or surgical manual reduction (21). During follow-up, patients with spontaneous reduction of intussusception are diagnosed with TI. There is no standard algorithm for the clinical and radiological findings of pediatric cases with TI and the general course of the disease. Therefore, the selection of patients for whom clinical follow-up is required should be done carefully. It was reported that SBIs without acute abdominal findings may spontaneously reduce and these cases should be observed and followed closely (22). We monitored patients with involvement of a short segment of the small intestine (less than 2.5 cm) and no intestinal wall edema. In the current study, ultrasonographic findings disappeared and clinical improvement was observed in 29 of the 33 patients under observation. The mean invaginated segment length in these cases was 1.8 cm. The mean age of these cases was higher than the treated group (46.1 months). Surgery may seem like the only treatment option, as there is no known non-surgical reduction method for SBI. However, close follow-up in appropriate cases, detection of spontaneously reduced cases, and avoidance of unnecessary surgical procedures are extremely important. In the literature, the rate of TI was reported as 84-96.2% (22,23). In the current study, the spontaneous reduction rate of the patients with SBI under observation was calculated as 87.8%.

The limitation of this study is that the data are retrospective. All procedures were performed in a single institution and the number of patients was limited, allowing descriptive rather than comparative analyses. US was performed by a team of academic staff in the radiology department with similar experience and educational background. The relatively specific and easily detectable signs of intussusception on US minimized potential radiologist-dependent variation in US accuracy.

CONCLUSION

For SBIs without signs of peritoneal irritation and no lead points, close observation is required if the segment length is less than 3 cm and the intestinal wall blood flow is normal on Doppler US. In these cases, disappearance of clinical findings during follow-up and detection of spontaneous reduction in abdominal US will prevent unnecessary surgical procedures. SBIs with no clinical improvement during the follow-up period and persistence of intussusception on ultrasound should be treated with surgical methods. The increase in publications

about spontaneous reduction of SBI necessitates a separate and more careful algorithm for the approach to these cases.

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Effects of Hormone Replacement Therapy on Autoimmune Markers and Clinical Outcomes in Pediatric Patients with Hashimoto's Thyroiditis

Hashimoto Tiroiditli Pediatrik Hastalarda Hormon Replasman Tedavisinin Otoimmün Belirteçler ve Klinik Sonuçlar Üzerindeki Etkisi

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ABSTRACT

Objective: Hashimoto's Thyroiditis (HT), a chronic autoimmune thyroiditis, is the predominant cause of hypothyroidism in regions without iodine deficiency. HT is characterized by the loss of immunological tolerance of the thyroid gland, leading to autoimmune attacks. This study aimed to compare the autoantibody profiles, along with clinical and laboratory findings, of patients diagnosed with Hashimoto's disease who were either receiving treatment or followed without treatment.

Material and Methods: Clinical manifestations, laboratory data, and thyroid ultrasonography (USG) findings of patients diagnosed with Hashimoto's thyroiditis receiving hormone therapy and those followed without treatment were compared in our clinic.

Results: Among a total of 249 patients, 116 received hormone replacement therapy, while 133 were followed without treatment. The mean age of all patients was 13.91±3.71 years, with a mean age at diagnosis of 11.51±3.79 years. After twelve months of follow-up, the untreated group showed an increase in serum fT4 and antiTPO levels (p=0.012 and p=0.001), with no significant difference found in serum TSH, fT3, and antiTG levels. Those receiving treatment exhibited a significant decrease in serum TSH levels and a significant increase in serum fT4 levels (p=0.002 and p<0.001, respectively). Although there was an increase in serum antiTPO and antiTG levels over time, no change was detected in serum fT3 levels. Clinical improvement was significantly greater in the treatment group (p=0.044).

Conclusion: It has been concluded that early initiation of hormone replacement therapy in Hashimoto's thyroiditis can mitigate negative clinical effects during follow-up, contributing to patient comfort and alleviating clinical complaints.

Key Words: Hashimoto Thyroiditis, Hormone Replacement Therapy, Pediatrics, Thyroid Autoantibodies

ÖZ

Amaç: Hashimoto Tiroiditi (HT), (kronik otoimmün tiroidit) iyot yetersizliği görülmeyen bölgelerdeki hipotiroidizmin en sık görülen nedenidir. HT otoimmün saldırıya karşı tiroid bezinin immünolojik toleransının kaybolması olarak karşımıza çıkmaktadır. Çalışmamızda hashimoto hastalığı tanısı alan hastalar, tedavi verilen ve tedavisiz izlenen gruplar olarak

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Ethics Committee Approval / *Etik Kurul Onayı*: The study was approved by Ankara Bilkent City Hospital, Clinical Research Committee No. 1 (14.10.2020- E1-20-1041).

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

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ayrılmıştır. Tedavi verilen ve tedavisiz izlenen grupların otoantikor seyri, hastanın klinik ve laboratuvar bulgularıyla birlikte karşılaştırılması amaçlanmıştır.

Gereç ve Yöntemler: Kliniğimizde hashimoto tiroiditi tanısı alan hormon tedavisi alan ve tedavisiz izlenen hastaların klinik bulguları, laboratuvar verileri ve tiroid ultrasonografi (USG) bulguları karşılaştırıldı.

Bulgular: 116'sı hormon replasman tedavisi alan, 133'ü tedavisiz izlenen toplam 249 hastanın ortalama yaşı 13.91±3.71 yıl, ortalama tanı yaşları ise 11.51±3.79 yıldı. On iki aylık izlem sonunda tedavisiz izlenen gruptaki hastaların serum sT4 ve antiTPO değerlerinde artış saptanırken (p=0.012 ve p=0.001), serum TSH, sT3 ve anti TG düzeylerinde anlamlı bir fark bulunmadı. Tedavi alanların serum TSH düzeylerinde anlamlı gerileme, serum sT4 düzeylerinde ise anlamlı bir artış olduğu görüldü (sırayla p=0.002 ve p<0.001). Ayrıca serum antiTPO ve antiTG düzeylerinde zamanla artış olmakla birlikte, serum sT3 düzeylerinde değişiklik saptanmadı. Klinik bulgularda gerileme, tedavi alan grupta anlamlı düzeyde daha fazlaydı (p=0.044).

Sonuç: Hashimoto tiroiditinde, erken dönemde başlanan hormon replasman tedavisinin izlemdeki olumsuz klinik etkileri azaltabileceği, hastanın konforu ve klinik şikayetlerini yatıştırma açısından önemli olabileceği kanısına varılmıştır.

Anahtar Sözcükler: Hashimoto Tiroiditi, Çocuklar, Hormon Replasman Tedavisi, Tiroid Otoantikorları

INTRODUCTION

Hashimoto's thyroiditis (chronic autoimmune thyroiditis) stands as the primary cause of hypothyroidism in long-term patients. The prevalence of autoimmune hypothyroidism in childhood is approximately 1-2%, with a female predominance of 4:1. Positive family history is evident in about 50% of cases. Individuals with Hashimoto's thyroiditis face an elevated risk of other autoimmune conditions such as diabetes, alopecia, vitiligo, and celiac disease (1). The characteristic feature of Hashimoto's thyroiditis is the presence of autoantibodies against the thyroid, leading to diffuse lymphocytic infiltration of the thyroid gland by thyroid-specific B and T cells.

The pathogenesis of the disease involves autoreactivation of T and B lymphocytes, their infiltration into the thyroid gland, and the development of antibodies against three primary thyroid antigens—thyroid peroxidase (TPO), thyroglobulin (TG), and thyroid-stimulating hormone receptor (TSHR) (2, 3).

Several studies on adults have shown that prophylactic levothyroxine (LT4) treatment in euthyroid patients diagnosed with Hashimoto's thyroiditis aids in the regression of serological or cellular markers and goiter (4-6). However, there is currently no study demonstrating the impact of initiating levothyroxine treatment at TSH levels below the upper limit of 10 µU/ml on growth, development, and cognitive functions.

In our study, we aimed to assess the autoantibody levels, thyroid ultrasonographic findings, thyroid hormone levels, and clinical manifestations of patients diagnosed with Hashimoto's thyroiditis, whether they were monitored with or without levothyroxine treatment. Consequently, we sought to evaluate the influence of hormone replacement therapy on the autoimmune-induced damage to the gland and the clinical course of the disease.

MATERIAL AND METHODS

In this study, retrospective analysis was performed on the medical records of a total of 249 patients diagnosed with Hashimoto's thyroiditis. Among them, 133 were monitored without treatment, and 116 received hormone replacement therapy due to the presence of AntiTPO and/or AntiTG autoantibody positivity at Ankara Bilkent City Hospital Child Health and Diseases Clinic. The study was approved by Ankara Bilkent City Hospital, Clinical Research Committee No. 1 (14.10.2020- E1-20-1041).

Serum TSH was measured using the SIEMENS® Healthlineers Atellica IM Thyroid Stimulating Hormone 3-Ultra (TSH3-UL), fT4 with SIEMENS® Healthlineers Atellica IM Free Thyroxine FT4*A, and antiTPO and antiTG autoantibodies with SIEMENS® Healthlineers Atellica IM AntiThyroglobulin (aTgII) and SIEMENS® Healthlineers Atellica IM AntiTPO kits.

The evaluation encompassed patient demographics, including age and gender, clinical or biochemical status regarding hypothyroidism, euthyroidism, or hyperthyroidism, dosage and duration of LT4 hormone replacement therapy, clinical characteristics, and serum levels of antiTG, antiTPO, fT3, fT4, and TSH.

Patients with serum TSH levels >6.5 mU/L and normal fT4 values were classified as having subclinical hypothyroidism. Clinical, laboratory values, and ultrasonographic findings were assessed at baseline, 6th, and 12th months. Patients without regular outpatient follow-up and those with missing file data were excluded from the study.

LT4 hormone replacement therapy was initiated in patients with goiter and clinical manifestations of Hashimoto's thyroiditis (HT), or serum TSH levels >10 mIU/L with normal fT4 values. It was also initiated in cases of overt hypothyroidism with high serum TSH levels (>10 mIU/L) and low fT4 levels (<0.7 mIU/L), as well as in patients with normal serum TSH and fT4 levels but markedly elevated thyroid antibodies (antiTPO and/or antiTG) exceeding 1000 IU/ml.

Statistical Analysis

Data IBM SPSS Statistics 18© Copyright SPSS Inc. Analyzed using 1989, 2010 software. The suitability of continuous variables to normal distribution was examined with the Kolmogorov-Smirnov test. Categorical variables in the study were presented with frequency and percentage, and continuous variables were presented with mean, standard

deviation, median, minimum and maximum values. Chi-square and Fisher Chi-square significance tests, Yates and post hoc Bonferroni correction were performed in the analysis of categorical variables. Since parametric test assumptions were not met, the Mann Whitney U test was used for independent two-group mean comparisons, the Wilcoxon Signed Rank test was used for dependent two-group mean comparisons, and Friedman and post hoc pairwise comparison tests were used for repeated measurements analysis. In the study, the statistical significance level was accepted as 0.05.

RESULTS

The mean age of the total 249 patients enrolled in the study was 13.91±3.71 years, with an average age at the time of diagnosis being 11.51±3.79 years. Among these, 116 patients (46.6%) belonged to the group monitored without treatment (Mean age 13.97 ± 3.71), and 133 patients (53.4%) were in the group receiving treatment (Mean age 14.02 ± 3.41) (Table I).

At the time of diagnosis, clinical findings were present in 35.34% (88 patients) of the individuals, with the following frequency: menstrual irregularity, hair loss, constipation, weakness, palpitations, tremor, headache, loss of appetite, obesity, short stature, learning disability, edema, inguinal hernia, exophthalmus, burning on the soles of the feet, chills, and hirsutism.

Throughout the follow-up period, it was observed that clinical findings persisted in 63 patients (25.30%), improved in 11 patients (4.42%), and regressed in 10 patients (4.01%). In the group monitored without treatment, clinical findings were present in 24.14% of cases, and clinical regression was noted in 0.86% during follow-up. Among those receiving hormone replacement LT4 therapy, the average treatment dose was 1.55±4.32 mcg/kg/day, and the average treatment duration

Table I: Age analyzes by treatment groups

	Treatment (-)		Treatment (+)		p
	mean±std	Median (min-max)	mean±std	Median (min-max)	
Age (years)	13.97 ± 3.71	15.1 (3.5-19.7)	14.02 ± 3.41	14.7 (3.7-19.9)	0.823
Age at diagnosis (years)	11.6 ± 3.97	12 (3-17)	11.44 ± 3.64	12 (1-17)	0.476
Weight (kg)	51.34±20.42	50.2 (14-108.3)	49.6 ± 16.23	50.2 (16-112)	0.524
Weight (percentile)	52.95±34.22	53 (3-99)	49.86 ± 34.14	48 (3-99)	0.501
Height (cm)	152.63±20.5	159 (94-187)	152.18 ± 15.6	156.4 (95-184.5)	0.206
Height (percentile)	49.92±30.08	51 (2.7-99)	46.94 ± 30.1	45 (3-99)	0.347

Mann Whitney u test was performed and the data are shown with mean and median (min-max) values

Table II: Clinical findings characteristics according to treatment groups

Variable (n:249)	Treatment (-)*		Treatment (+)*		p
Initial clinical findings					
No	78	67.24	83	62.41	0.426
Yes	38	32.76	50	37.59	
Clinical findings during follow-ups					
No	87	75.0	89	66.92	0.044
Yes	28	24.14	35	26.32	
Regressed‡	1	0.86	9	6.76	

Chi-square test was performed and the data are shown with frequency and column percentage values. n(%), ‡The regression was significantly higher in the treatment (+) group (p=0.044). (Chi-square, post hoc Bonferroni correction made)*

Table III: Goiter stages according to treatment groups

Stages	Treatment (-)*		Treatment (+)*		p
0	94	81.03	94	70.68	0.163
1	1	0.86	4	3.01	0.163
1a	6	5.17	3	2.26	0.163
1b	8	6.90	16	12.03	0.163
2	6	5.17	12	9.02	0.163
3	1	0.86	4	3.01	0.163
Total	116	100.0	133	100.0	0.163

*****n(%), Chi-square test was performed and the data are shown with frequency and column percentage values*

Table IV: Change in laboratory values of patients over time

		0th month	6th month	12th month	p
No treatment					
TSH (n:92)	Mean ±sd	4.04±4.36	3.68±5.17	3.22±1.96	0.544
	Median (min-max)	3 (0.01-29)	2.8 (0.03-48.3)	3 (0-10.2)	
sT4 (n:90)	Mean±sd	1.26±1.60	1.30±1.04	1.38±1.61	0.012[a]
	Median (min-max)	1.12 (0.6-16)	1.17 (0.6-10)	1.19 (0.88-16.40)	
sT3 (n:21)	Mean ±sd	4.82±3.59	4.56±2.51	3.99±1.09	0.953
	Median (min-max)	4.30 (2.40-20)	4.20 (2.16-14.40)	3.80 (2.90-8.08)	
Anti TG (n:37)	Mean ±sd	708.40±2790.94	210.39±444.53	737.04±2140.01	0.936
	Median (min-max)	48.9 (0.10-16972)	50 (0.9-2130)	83 (13.5-11962)	
Anti TPO (n:44)	Mean ±sd	888.41±2741.24	915.57±1957.78	1488.46±2780.01	0.001[a]
	Median (min-max)	90.5 (0.4-17005)	173 (0.7-11529)	196 (28-11983)	
With treatment					
TSH (n:115)	Mean ±sd	97.70±829.711	11.40±24.84	6.26±14.84	0.002[a]
	Median (min-max)	7.7 (0-8908)	5.8 (0-150)	3.8 (0-150)	
sT4 (n:113)	Mean ±sd	1.12±0.77	1.23±1.20	1.27±0.34	<0.001[c]
	Median (min-max)	0.94 (0.25-4.89)	1.13 (0.3-13.5)	1.20 (0.7-3.29)	
sT3 (n:37)	Mean ±sd	6.14±4.76	4.86±3.51	4.18±1.72	0.584
	Median (min-max)	4.36 (0.62-20)	3.80 (0.65-19.70)	3.70 (1.02-11.50)	
Anti TG (n:50)	Mean ±sd	496.44±846.73	731.26±1706.25	2158.38±6214.94	0.246
	Median (min-max)	116.2 (0.5-4193)	125.7 (0.9-10000)	174.5 (3.4-39000)	
Anti TPO (n:59)	Mean ±sd	2422.69±4364.44	2942.19±4385.35	3904.47±4692.24	0.196
	Median (min-max)	708 (2.5-23108)	951 (1.4-19831)	1562 (30-13000)	

Friedman test and post hoc pairwise comparisons were performed. ***a:*** *There is a significant difference between the 0th month and the 12th month.* ***b:****The 12th month is significantly different from the others.* ***c:*** *All groups are significantly different from the others.*

was 2.21±9.41 years. Clinical findings were present in 26.32% of cases in the treatment group, with clinical regression observed in 6.76% during follow-up (p=0.044) (Table II). Additionally, during the follow-ups, it was observed that there was no significant change in goiter staging between the two groups that were monitored without treatment and those that received treatment (Table III).

When evaluating laboratory findings within each period, TSH and anti-TPO values were significantly lower (p<0.001 to p<0.001), and fT4 values were significantly higher in the untreated group at the beginning of the follow-up compared to the treated group (p=0.008). In the 6th month of follow-up, TSH, anti-TG, and anti-TPO levels in the untreated group were found to be lower than those in the treated group (p<0.001, p=0.044, and p=0.001). In the 12th month of follow-up, anti-TG and anti-TPO levels in patients without treatment were significantly lower than those in the treated group (p=0.036 and p<0.001) (Table IV). When all patients, whether untreated or treated, were evaluated, a decrease in TSH levels and an increase in anti-TPO values were observed at the 12-month follow-up (p=0.004 and p=0.001). Additionally, serum fT4 levels in all patients at the 12th month were higher than at other times (p<0.001). No significant change was observed in serum fT3 and anti-TG levels over time during follow-up (p=0.723 and p=0.379) (Table IV).

In the follow-up of patients in the untreated group, significant increases were detected in serum fT4 and anti-TPO values (p=0.012 and p=0.001). However, there was no significant difference in serum TSH, fT3, and anti-TG levels over time (p=0.544, p=0.953, and p=0.936) (Table IV).

Among the patients, those who received LT4 hormone replacement therapy showed a significant decrease in serum TSH levels and a significant increase in serum fT4 levels during their 12-month follow-up (p=0.002 and p<0.001, respectively). Additionally, although there was an increase in serum anti-TPO and anti-TG levels over time, no change was detected in serum fT3 levels (Table IV).

The changes in the initial and follow-up thyroid ultrasound findings of patients receiving and not receiving thyroid hormone replacement therapy are presented in Table V.

DISCUSSION

The aim of this study was conducted to evaluate the effect of hormone replacement therapy in patients with Hashimoto's thyroiditis, also known as chronic autoimmune thyroiditis, on autoimmunity damage in the thyroid gland. A total of 249 patients were evaluated in this study. In our study, similar to the literature. the diagnosis of Hashimoto's thyroiditis was found to be more common in female gender (78.31%) than in male gender (21.69%).

In an Italian study encompassing 715 patients and evaluating both the adult and pediatric populations, a significant reduction

Table V: Change in USG findings according to treatment groups

Group	First USG	Second USG			p
		(-)	(+)	Total	
Colloid cyst					
Treatment (-)	(-)	48 (90.56)	5 (9.43)	53 (100.0)	0.106
	(+)	3 (60.00)	2 (40.00)	5 (100.0)	
	Total	51 (87.93)	7 (12.10)	58 (100.0)	
Treatment (+)	(-)	54 (80.59)	13 (19.40)	67 (100.00)	0.132
	(+)	4 (50.00)	4 (50.00)	8 (100.00)	
	Total	58 (77.33)	17 (22.67)	75 (100.00)	
Heterogeneous parenchyma					
Treatment (-)	(-)	9 (69.23)	4 (30.77)	13 (100.00)	<0.001
	(+)	0 (0.00)	54 (100.00)	54 (100.00)	
	Total	9 (13.43)	58 (86.57)	67 (100.00)	
Treatment (+)	(-)	5 (55.56)	4 (44.44)	9 (100.00)	<0.001
	(+)	4 (5.33)	71 (94.67)	75 (100.00)	
	Total	9 (10.71)	75 (89.28)	84 (100.00)	
Nodul					
Treatment (-)	(-)	47 (87.03)	7 (12.96)	54 (100.00)	<0.001
	(+)	4 (30.77)	9 (69.23)	13 (100.00)	
	Total	51 (76.12)	16 (23.88)	67 (100.00)	
Treatment (+)	(-)	75 (97.40)	2 (2.60)	77 (100.00)	<0.001
	(+)	3 (42.86)	4 (57.14)	7 (100.00)	
	Total	78 (92.86)	6 (7.14)	84 (100.00)	
Increased blood flow					
Treatment (-)	(-)	47 (79.66)	12 (20.34)	59 (100.00)	0.001
	(+)	1 (14.29)	6 (85.71)	7 (100.00)	
	Total	48 (72.73)	18 (27.27)	66 (100.00)	
Treatment (+)	(-)	47 (73.44)	17 (26.56)	64 (100.00)	0.001
	(+)	6 (30.00)	14 (70.00)	20 (100.00)	
	Total	53 (63.09)	31 (36.91)	84 (100.00)	
Fibrous band					
Treatment (-)	(-)	53 (88.33)	7 (11.67)	60 (100.00)	0.057
	(+)	3 (50.00)	3 (50.00)	6 (100.00)	
	Total	56 (84.85)	10 (15.15)	66 (100.00)	
Treatment (+)	(-)	58 (81.69)	13 (18.31)	71 (100.00)	0.208
	(+)	8 (61.54)	5 (38.46)	13 (100.00)	
	Total	66 (78.57)	18 (21.43)	84 (100.00)	
Pseudonodul					
Treatment (-)	(-)	42 (82.35)	9 (17.65)	51 (100.00)	0.020
	(+)	3 (37.50)	5 (62.50)	8 (100.00)	
	Total	45 (76.27)	14 (23.73)	59 (100.00)	
Treatment (+)	(-)	43 (76.79)	13 (23.21)	56 (100.00)	0.002
	(+)	10 (38.46)	16 (61.54)	26 (100.00)	
	Total	53 (64.63)	29 (35.37)	82 (100.00)	

Chi square (exact) test was performed and the data are shown with frequency and line percentage values.

in serum anti-TPO levels was observed after a 12-18 month follow-up period among patients undergoing L-thyroxine treatment (7). Contrary to these findings, our study did not detect a significant change in serum anti-TPO levels within the treatment group during the follow-up period (p=0.196). However, we observed a significant increase over time in the untreated group (p=0.001). These outcomes suggest that, despite the persistent nature of the autoimmune condition, it can be partially managed with treatment.

Another study reported that, during an average follow-up of 22.5 months, 8% of 181 patients with Hashimoto's thyroiditis developed subclinical hypothyroidism, 13% developed overt hypothyroidism, and 6% exhibited nodule formation (8). Similarly, in a comparable study, it was documented that LT4 hormone replacement therapy was initiated in 13 out of 37 initially euthyroid patients who were followed without treatment, owing to the development of subclinical or overt hypothyroidism during the follow-up period (9). This underscores the notion

that, even though an individual may be euthyroid at the time of Hashimoto's thyroiditis diagnosis, hypothyroidism may evolve over time. Consequently, regular outpatient clinic follow-ups and thyroid function tests at predetermined intervals become essential.

In another study investigating patients with Hashimoto's thyroiditis (HT), both those under monitoring with or without treatment, it was observed that the group without treatment exhibited the highest serum anti-TPO levels. However, no significant correlation was identified between measured serum anti-TPO levels and serum fT4 and TSH levels (10). In our study, when we analyzed the initial, 6th, and 12th month controls separately, we observed lower antibody titers in the group without treatment.

A 2019 single-center study involving 83 cases, with 46.8% euthyroidism, 33.7% subclinical hypothyroidism, 17.7% hypothyroidism, 2.5% overt hyperthyroidism, and 2.5% subclinical hyperthyroidism, found higher serum anti-TPO and antiTG antibody levels in the treatment-initiated group, similar to our findings (p=0.01, p=0.051) (9).

In a Danish study examining retrospective data from 4649 HT-diagnosed patients, it was reported that initial thyroid autoantibodies were higher in patients who developed thyroid dysfunction during follow-up (12). These findings suggest that greater gland damage may occur when high autoantibody titers are present. Consequently, we propose that initial serum autoantibody levels may serve as a valuable predictor of the likelihood of developing hypothyroidism during follow-up.

A study aiming to elucidate the impact of prophylactic LT4 treatment on the prognosis of Hashimoto's thyroiditis reported the benefits of early replacement therapy in euthyroidic patients. While a decrease was noted in serum anti-TPO levels in cases diagnosed with HT receiving LT4 treatment, no decrease in antibody titers was observed in the untreated group (12).

Multiple studies have established a robust relationship between elevated serum TSH levels, increased serum thyroid autoantibodies, and augmented thyroid volumes (12-14). This observation reaffirms the association between high autoantibody levels and glandular damage, underscoring the importance of understanding the thyroid dysfunction that leads to clinical responses. In our study, we observed no significant changes in the ultrasound findings of patient groups diagnosed with HT, whether they received treatment or were monitored without treatment, during the first and second evaluations at the sixth month.

However, when evaluating patients undergoing treatment, this observation turned negative in 30% of those with increased blood flow in the initial ultrasound (p=0.001) (Table V). Additionally, it was noted that only 38.46% of the 13 treated patients exhibited a positive fibrous band in their initial ultrasound, and the majority of patients (61.54%) showed a negative result in the subsequent ultrasound (p=0.104) (Table V). In patients monitored without treatment, none of those with heterogeneous parenchyma observed in the initial ultrasound showed a negative result.

A study by Romaldini et al. (15), investigating the effects of LT4 treatment on autoantibody levels, lipid profile, and thyroid volume, revealed an 81% decrease in the thyroid volume of 10 patients after 6 months of levothyroxine treatment (15). The ultrasonographic changes detected in the follow-up of patients initiating treatment suggest that HT treatment may shield the gland from autoimmune damage. However, in our study, we observed no significant change in goiter staging between the two groups followed with or without treatment.

In a Korean study involving 153 patients (139 female and 14 male, ratio 9.9:1), the most common presenting complaint was thyroid gland enlargement (71.9%), followed by weight gain or fatigue (20.9%). For the remaining patients, it was detected during routine screening in the absence of thyroid dysfunction or other autoimmune diseases (16). In a study covering 102 cases diagnosed with Hashimoto's thyroiditis between 2005 and 2010 in our country, the most common complaints were neck swelling (41.1%), fatigue (12.7%), dry skin (11.7%), growth retardation (11.7%), hair loss (11.7%), and decreased academic success (10.7%), along with irritability (8.8%), cold intolerance (7.8%), and constipation (3.9%) (17).

Another study conducted in our country evaluated 41 female patients diagnosed with Hashimoto's thyroiditis, aiming to uncover the relationship between psychiatric disorders (depressive disorder, generalized anxiety disorder, ADHD, and social phobia) and Hashimoto's thyroiditis (18). In our study, the majority of patients belonged to the asymptomatic silent group, with only 35.34% (88 patients) exhibiting clinical findings.

In the follow-up of the group receiving treatment, it was observed that the clinical findings did not improve in 66.92% of the patients. the clinical complaints continued in 26.32% and the clinical findings regressed in 6.76% (p=0.044). In a study between 2012 and 2019 in our country that included patients diagnosed with Hashimoto's thyroiditis and receiving hormone replacement therapy it was reported that serum antiTPO levels decreased after LT4 treatment (19). In another study, it was observed that serum antiTG levels were high at the beginning and serum antiTPO levels increased progressively during follow-up (12,13).

In conclusion, considering the detrimental impact of autoimmunity in Hashimoto's thyroiditis (HT), regular patient follow-ups are deemed crucial. Drawing upon the findings of our study, the initiation of hormone replacement therapy, particularly in the presence of elevated autoantibody levels, especially anti-TPO, and in cases where serum TSH levels are mildly elevated, may be considered beneficial. Early commencement of hormone replacement therapy in Hashimoto's thyroiditis holds

the potential to alleviate adverse clinical effects during follow-up, enhance patient comfort, and mitigate clinical complaints.

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A Rare Cause of Chronic Pyelonephritis: Xanthogranulomatous Pyelonephritis

Kronik Piyelonefritin Nadir Bir Nedeni: Ksantogranulomatöz Piyelonefrit

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ABSTRACT

Xanthogranulomatous pyelonephritis (XGP) is a chronic, destructive, granulomatous inflammation of the renal parenchyma leading non-functioning kidney. Contrast-enhanced computed tomography (CT) is the most useful diagnostic method. A 6-year-old female patient admitted to us with complaints of abdominal pain, fever, fatigue, weakness. Recurrent urinary tract infection was present in her history. The patient's urine specimen revealed leukocyturia, hematuria, positive for nitrite and bacteria, white blood cell: 12.7x10^3 /microl, hemoglobin: 6.2 g/dl and C-reactive protein (CRP): 101 mg/dl. In the urinary system Ultrasound (US) imaging, the contours of the left kidney were irregular and lobulated, and medullary punctate echogenicity and calcifications were present. Contrast-enhanced abdominal CT showed increased left kidney size and opacities suggestive of stone in the collecting system; pararenal area was heterogeneous. Although the patient's gentamicin treatment was completed in 7 days and meropenem treatment in 14 days, acute phase reactants did not regress. No activity uptake was observed in the left kidney lodge in renal cortical scintigraphy. Left total nephrectomy was performed with the diagnosis of non-functioning left kidney and chronic pyelonephritis. Kidney biopsy material were reported as XGP. XGP is a rare and aggressive cause of chronic pyelonephritis with serious consequences such as nephrectomy requirement.

Key Words: Chronic pyelonephritis, Pyelonephritis, Urinary tract infections, Xanthogranulomatous pyelonephritis, XGP

ÖZ

Ksantogranülomatöz piyelonefrit (XGP), böbrek parankiminin fonksiyon kaybına yol açan kronik, yıkıcı, granülomatöz bir enflamasyonudur. Kontrastlı bilgisayarlı tomografi (BT) en yararlı tanı yöntemidir. Bu yazıda karın ağrısı, ateş, halsizlik şikayetleri ile başvuran ve XGP tanısı alan altı yaşında kız hastadan bahsedildi. Özgeçmişinde tekrarlayan idrar yolu enfeksiyonu öyküsü mevcuttu. İdrar incelemesinde lökositüri, hematüri, nitrit ve bakteri pozitifliği mevcuttu. Laboratuvar analizinde beyaz kan hücresi: 12.7x10^3 /mikrol, hemoglobin: 6.2 g/dl ve C-Reaktif Protein (CRP): 101 mg/dl saptandı. Üriner sistem ultrasonda sol böbreğin konturları düzensiz ve lobüler olup, medüller punktat ekojenite ve kalsifikasyonlar mevcuttu. Kontrastlı abdominal BT'de sol böbrek boyutunda artış ve toplayıcı sistemde taşı düşündüren opasiteler görüldü; pararenal alan heterojendi. Hastanın gentamisin tedavisi 7 güne, meropenem tedavisi 14 güne tamamlanmasına rağmen akut faz reaktanlarında gerileme olmadı. Renal kortikal sintigrafide sol böbrek lojunda aktivite tutulumu gözlenmedi. Fonksiyone olmayan sol böbrek ve kronik piyelonefrit ön tanıları ile hastaya total nefrektomi uygulandı. Böbrek biyopsi materyali XGP ile uyumluydu. XGP, nefrektomi gereksinimi gibi ciddi sonuçları olan kronik piyelonefritin nadir ve agresif bir nedenidir. Akut faz reaktanlarında beklenen düşüş sağlanamayan ve piyürisi devam eden çocuklarda ayırıcı tanıda düşünülmelidir.

Anahtar Kelimeler: Kronik piyelonefrit, Piyelonefrit, Üriner sistem enfeksiyonu, Ksantogranulomatöz Piyelonefrit, KGP

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INTRODUCTION

Xanthogranulomatous pyelonephritis (XGP) is a chronic, destructive, granulomatous inflammation of the renal parenchyma leading non-functioning kidney. The most frequently associated conditions are chronic urinary tract obstruction or ongoing infections due to kidney stones (1,2). Recurrent urinary tract infections due to Escherichia coli and Proteus mirabilis are frequently present in the history (3). The disease develops when renal or perirenal tissue is replaced by granulomatous tissue filled with lipid-laden macrophages due to a defect in macrophage-mediated bacterial degradation (4). Contrast-enhanced computed tomography (CT) is the most useful diagnostic method, demonstrating multiloculated abnormal kidney tissue consisting of dilated collecting systems surrounded by multiple hypoechoic areas with contrast enhancement. In addition, it can demonstrate the stones in the collecting system and the dissemination of the lesion in the kidney (5,6). XGP may imitate other neoplastic and inflammatory kidney diseases (7). It is a rare condition seen in 0.6% of histological examinations of chronic pyelonephritis and 19.2% of pyelonephritis resulting in nephrectomy (8). In this paper, we aimed to present our case, which is rare in childhood and treated with unilateral total nephrectomy, in the light of radiological findings and literature.

CASE

A 6-year-old, 8-month-old female patient applied to our emergency outpatient clinic with complaints of weakness that lasted for about 1 month and abdominal pain, fever, and fatigue for a week. She was born 2750 gr at 33 weeks, and she had no history of hospitalization before. It was learned from her history that she had occasional abdominal pain and that she had been treated with antibiotics several times with the diagnosis of urinary tract infection. She had no regular medication. On physical examination, weight: 17.5 kg (3-10p), height: 114 cm (10-25 p), cardiac pulse: 124/min, Blood Pressure: 108/66 mm/Hg, temperature was 38.2ºC. The skin and conjunctiva were pale and there was widespread tenderness in the abdomen. Other systemic examination was normal.

In laboratory analysis, white blood cell: $12.7x10^3$ /microl, hemoglobin: 6.2 g/dl, hematocrit 22.6%, MCV: 52 fL, RDW:21.7% (12.2-14.4), reticulocyte 2.3%, C-reactive protein (CRP): 101 mg/dl (0-8), procalcitonin 0.09 mcg/dl, iron 10 mcg/dl (50-120), total iron-binding capacity 222 mcg/dl (50-120), ferritin 16.9 mcg/L (11-307), urea: 22 mg/dl (17-47), creatinine:0.23 mg/dl (0.24-0.73), uric acid: 3.8 mg/dl, (2.5-7.2), albumin 33.1 g/L (35-55). Direct Coombs was negative, and distribution of hemoglobin electrophoresis was normal. The patient's urine specimen revealed a density of 1033, pH: 6.5, positive for nitrite and bacteria. There were 92 WBCs/hpf, 32 RBCs/hpf. Kidney functions, liver tests, serum electrolyte levels, and B12 levels were within normal limits. In the peripheral smear, neutrophil dominance (65%) was present, and no atypical cells and blasts were observed. Hypochromic microcytic erythrocytes were seen. The erythrocyte suspension was transfused to the patient. Empirical ceftriaxone treatment was initiated, and symptoms regressed within 48 hours and fever control was achieved. Urine culture was negative. At the 72nd hour of treatment, the patient was consulted with pediatric nephrology and pediatric infection, with an increase in CRP (132 mg/dl and 147 mg/dl, respectively) and ongoing leukocyturia in the control urinalysis. Her treatment was changed to meropenem and gentamicin.

In the urinary system Ultrasound (US) imaging, the long axis of the left kidney was 10 cm, the parenchyma thickness was 13 mm, and the Antero-posterior (AP) diameter was 11 mm. The contours of the left kidney were irregular and lobulated, and medullary punctate echogenicity and calcifications were present. Corticomedullary differentiation was lost. Dilatation and heterogeneous appearance were observed in the pelvicalyceal structures, and there was thickening of the calyx walls. The left pararenal area was heterogeneous and edematous. The long axis of the right kidney was 103 mm, the parenchyma thickness was 12 mm, and its parenchymal echogenicity was normal. Contrast-enhanced abdominal CT showed increased left kidney size and 7 mm diameter opacities suggestive of stone causing artifacts in the collecting system, and moderate to severe ectasia in the left kidney. The left pararenal area was heterogeneous, and the left ureter was dilated (Figure1). There was no vesicourethral reflux in the voiding cystourethrogram.

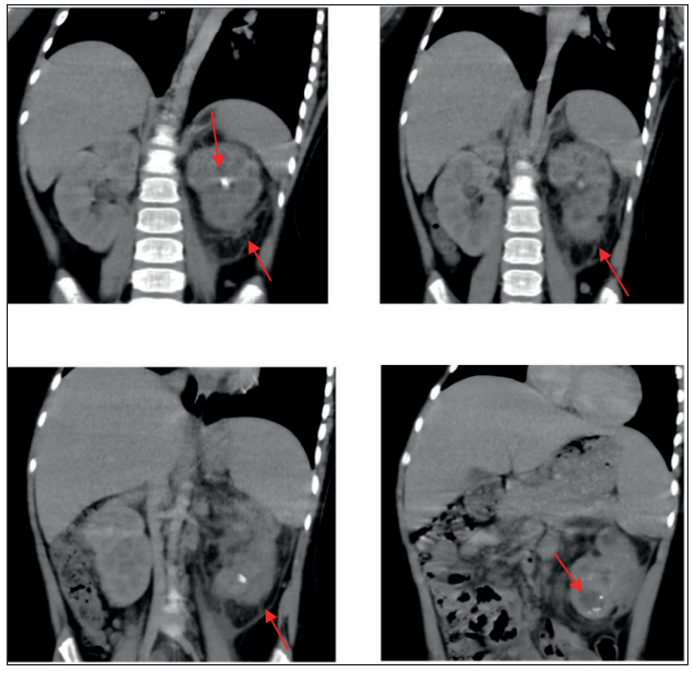

Figure 1: Contrast-enhanced abdominal computed tomography showing multiloculated appearance, ectasia, stones in the collecting system and heterogenous pararenal area of the left kidney

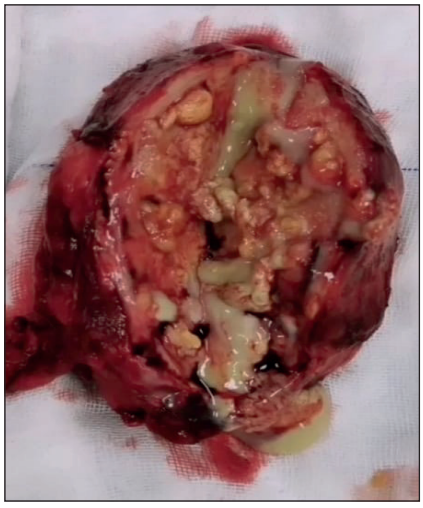

Figure 2. Nephrectomy material of non-functioning left kidney with yellow-green abscess areas in the cortex

Although the patient's gentamicin treatment was completed in 7 days and meropenem treatment in 14 days, acute phase reactants did not regress. In renal cortical scintigraphy with technetium-99m (Tc-99m) dimercaptosuccinic acid (DMSA), right kidney contours and size was normal, parenchymal uptake was homogeneous. No activity uptake was observed in the left kidney lodge. Left total nephrectomy was performed to the patient with the diagnosis of non-functioning left kidney and chronic pyelonephritis. Kidney biopsy material with yellow-green abscess areas in the cortex and the presence of pancytokeratin (-) and CD68 (+) staining were reported as XGP (Figure 2). The patient was discharged with oral cefixime on the 7th postoperative day without any complications. Acute phase reactants turned negative on the post operative 6th day. The patient is currently being followed up as an outpatient with normal renal function 4 months after surgery.

DISCUSSION

XGP is the chronic inflammation of renal parenchyma, causing non-functional kidney (1). The most common symptoms in children are fever, abdominal or flank pain and growth retardation. Urinary system symptoms such as dysuria, frequency and bloody urine may also be seen (3). Physical examination may reveal fever, pallor due to anemia, palpable unilateral or bilateral renal mass, costovertebral angle tenderness, nephrocutaneous fistulas, and rarely hepatomegaly due to liver invasion (3). Karabulut et al. (9) reported abdominal pain, weight loss and pallor; and Caixeta et al. (10) reported fever, pallor, and abdominal distension in their papers. In our patient, the initial complaints were fever, abdominal pain, weakness, and pallor, similarly. In patients with XGP, leukocytosis, anemia, increase in erythrocyte sedimentation rate, CRP, urea, and creatinine, as well as abnormalities in liver function tests due to mild biliary retention may be observed (11,12).

Urinalysis may reveal pyuria, bacteriuria, or hematuria. It has been reported that organisms such as Escherichia coli, Proteus mirabilis, Pseudomonas spp., Enterococcus faecalis and Klebsiella spp. grow in urine culture (11,12). In our case, resistant pyuria was present, and no microorganism growth was detected in the urine culture. Previously used antibiotics and the intense infection in the perinephric area were thought to be the cause of negative urine culture.

Staghorn stones can be shown radiologically on abdominal plain radiographs. CT is the most useful imaging in the diagnosis of XGP cases. With contrast-enhanced imaging, abnormal kidney tissue consisting of dilated collecting system with multiloculated appearance, multiple hypoechoic areas with contrast uptake around it, stones in the collecting system and the spread of the lesion in the kidney can be shown (5,6). Magnetic resonance imaging (MRI) can be performed in patients with contrast material allergy. Reduced kidney function can be demonstrated with Tc-99m DMSA scan. Biopsy and immunohistochemical staining (PAS positive staining) are other diagnostic methods (11,12). Karabulut et al. (9) reported parenchymal loss in the kidney, contamination in the perirenal fat planes, and nephrocalcinosis in their cases. Contrast-enhanced CT in our patient supported the diagnosis with a similar radiological appearance in the left kidney and pararenal region, and complete loss of function in the left kidney was revealed by renal parenchymal scintigraphy.

XGP is seen in 3 forms: diffuse, segmental, and focal. While segmental involvement is seen in the segmental type, there is localized cortex involvement not associated with the pelvic region in the focal type (13). The most common type is diffuse and has been divided into 3 stages by Malek and Elder. These stages are;

- Stage 1 (nephritic): Disease limited to the kidney
- Stage 2 (Peri-nephric): Disease with renal pelvis and perirenal fat involvement that has progressed into Gerato's fascia.
- Stage 3 (Paranephric): It is a disease with adjacent organ or retroperitoneal involvement (14).

Complications of XGP are psoas abscess, perinephric abscess, nephro-cutaneous fistula, intestinal fistulas, secondary amyloidosis, nephrotic syndrome, and sepsis (15). In our case, the abscess in the renal parenchyma opened to the calyces, causing sterile pyuria, and spread to the peri-nephritic and retroperitoneal areas with perforation of the renal parenchyma. Preoperative antibiotics and percutaneous drainage have a place in the treatment of cases with focal or segmental XGP. Partial or total nephrectomy can be performed in cases unresponsive to treatment (16). While Caixeta et al. (10) reported a complete recovery with antibiotic treatment in their pediatric case, nephrectomy was required in both cases of Karabulut et al. (9).

In conclusion, XGP is a rare and aggressive cause of chronic pyelonephritis with serious consequences such as nephrectomy

requirement. It should be considered in the differential diagnosis of patients who do not have the expected decrease in acute phase reactants and in children whose pyuria continues. The follow-up and treatment of these patients should be carried out in a multidisciplinary manner with the cooperation of pediatric nephrology, pediatric infectious diseases, oncology, urology/ pediatric urology, and radiology.

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Nintedanib Treatment in a Child with Pulmonary Fibrosis

Pulmoner Fibrozis Gelişen Bir Çocukta Nintedanib Deneyimi

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ABSTRACT

Pulmonary fibrosis (PF) in children is a very rare, progressive, and life-threatening condition. There are advances in the treatment of idiopathic PF in adults with the approval of antifibrotics like nintedanib. However, PF treatment in children is still an inconclusive area that needs to be studied further. Here, we present the nintedanib experience in a child with PF.

Key Words: Bleomycin, Child, Interstitial, Lung disease, Nintedanib, Pulmonary fibrosis, Radiotherapy

ÖZ

Çocuklarda pulmoner fibrozis (PF) çok nadir görülen, ilerleyici ve yaşamı tehdit eden bir durumdur. Nintedanib gibi antifibrotiklerin onaylanmasıyla erişkinlerde idiyopatik PF tedavisinde ilerlemeler kaydedilmiştir. Bununla birlikte, çocuklarda PF tedavisi hala daha fazla çalışılması gereken sonuçsuz bir alandır. Burada, PF'li bir çocukta nintedanib deneyimini sunuyoruz.

Anahtar Kelimeler: Bleomisin, Çocuk, İntersitisyel, Akciğer hastalığı, Nintedanib, Pulmoner fibrozis, Radyoterapi

INTRODUCTION

Pulmonary fibrosis (PF) is a rare condition that has been described in some form of interstitial lung disease (ILD) in children, such as surfactant disorders, hypersensitivity pneumonitis and drug-induced pneumonitis. In children, drug-induced lung fibrosis is usually associated with the drugs used in many cancer treatments (1). One well-known drug for this is bleomycin. Bleomycin is a chemotherapeutic used to treat Hodgkin's lymphoma (2). The most important limitation of bleomycin therapy is the potential risk of developing PF (1). Since there is no effective treatment for bleomycin-induced pulmonary fibrosis, it is usually treated symptomatically. Another factor contributing to lung injury is thoracic irradiation. It has been shown that radiation in combination with bleomycin increases the fibrogenic effect (3).

The main treatments for PF in children are corticosteroids and hydroxychloroquine. Corticosteroids have a beneficial effect on surfactant disorders, pulmonary hemosiderosis and in severe cases of neuroendocrine cell hyperplasia of infancy. Hydroxychloroquine is an alternative to steroids (4). If there is no response to these treatments, antifibrotics may be the treatment of choice for PF. One of the antifibrotics is nintedanib, a tyrosine kinase inhibitor approved by the US Food and Drug Administration (FDA) for idiopathic pulmonary fibrosis (IPF) and other chronic progressive ILDs in adults. A recent study

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of nintedanib in children and adolescents reported the safety profile of the drug (5). There is not enough data yet on the effectiveness of the drug in children.

Here, we present a 36-week experience with nintedanib in a boy who developed PF after treatment with a bleomycin-containing regimen and thoracic radiotherapy for Hodgkin lymphoma.

CASE REPORT

An 11-year-old boy with Hodgkin lymphoma had a history of 8 cycles of adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) protocol in 2020. His treatment continued with radiotherapy to the right upper hemithorax between February and March 2021 at a centre other than our hospital. One month after his last radiotherapy, he presented with cough, tachypnoea and dyspnoea on moderate exercise. His initial clinical evaluations were made in the hospital for the first 8 months, where he was treated for lymphoma. He was inititally treated with antibiotics. He also received inhaled beta-agonists and inhaled corticosteroids for three months. As there was no improvement in his cough and dyspnoea, systemic corticosteroids (1 mg/kg/day methylprednisolone) were started. An improvement in the percentage of predicted forced vital capacity (FVC) values (from 43% to 56%) achieved with systemic corticosteroid treatment. After the resolution of the tachypnoea, steroid doses were gradually reduced and discontinued after 5 months. Despite systemic steroids, the persistent cough became productive and he described progressing exercise intolerance. Flexible bronchoscopy was performed at the other hospital and showed normal macroscopic findings. Bronchoalveolar lavage fluid was free of malignant cells and microorganisms. At the follow-up visit, decreased breath sounds were noted on the right side compared to the left side. A chest computed tomography (CT) was performed because of the blunting of the right costophrenic angle on the chest X-ray. There was no pleural effusion, but blunting of the costophrenic angle was noted. Eight months after his last course of radiotherapy, the patient was admitted to our hospital. He presented with progressive productive cough, shortness of breath and exercise intolerance. He was not taking any medications for his symptoms at presentation. His body weight was 26 kg (5p-10p), and his transcutaneous saturation was 94% on room air. Physical examination revealed decreased breath sounds in the right hemithorax. The patient was unable to perform spirometry due to a severe cough. In the 6-minute walk test (6-MWT), he walked 396 meters (below the 3rd percentile estimated for his height) and there was a rapid drop in saturation with a minimum saturation of 80%. Routine blood tests such as complete blood count, liver and kidney function tests and blood gas analysis were normal. The first chest CT scan performed before hospitalization showed minimal traction bronchiectasis in the upper and lower lobes of the right lung, thickening of the right major fissure and subpleural reticular densities in both lungs, more prominent in the right lung. The remission of the Hodgkin lymphoma was confirmed by the oncology department of our hospital. Evaluation of the lymphoma protocol showed that bleomycin doses were higher than the accepted cumulative doses for children. Fifteen days after admission to our hospital, oral nintedanib (75 mg twice daily) was started due to a deterioration in his clinical condition, with the approval of the off-label committee of the Ministry of Health and the decision of a multidisciplinary meeting. The 75 mg dose of nintedanib was chosen based on the InPedILD study, which recommended weight-based dosing. Following the initiation of nintedanib, the patient was re-evaluated at the 1st, 2nd, 4th, 6th and 9th month of treatment. The patient did not receive any other medication during this period. Body weight, transcutaneous saturation, pulmonary function tests (PFT) and 6-MWT evaluated at each visit are shown in Table I. Six month after nintedanib therapy, respiratory symptoms and signs worsened, oxygen requirements increased and non-invasive ventilation began. He lost weight despite caloric support. He had two pulmonary exacerbations requiring hospitalisation in the last 3 months of the treatment. In addition to the clinical deterioration, chest CT and chest X-ray (CXR) showed progression of the parenchymal findings. A comparison of serial chest CT scans and CXR taken before starting nintedanib and

Table I: Clinical follow-up characteristics

Nintedanib treatment duration	Body weight	Saturation (%) (at rest in the room air)	Predicted FVC(%)*	Predicted FEV1 (%)*	Predicted FEV1/FVC (%)*	6-minute walking test (distance in meters /Percentile of the estimated to the height† minimum SpO2)
The first admission	26 kg	94	N/C ‡	N/C	N/C	396 /<3rd percentile / 80%
Before the treatment	24 kg	91	N/C	N/C	N/C	Not performed
First month	24.5 kg	93	23	21	83	310 /<3rd percentile / 80%
2nd month	23.5 kg	94	N/C	N/C	N/C	286 /<3rd percentile / 74%
4th month	23.5 kg	95	N/C	N/C	N/C	Not performed
6th month	23 kg	85	12	14	118	165 /<3rd percentile / 68%
9th month	22 kg	65	N/C	N/C	N/C	476 / <3rd percentile /78% (under the 3lt/min oxygen)

**Spirometry results, †Based on standardized reference values, ‡No cooperation*

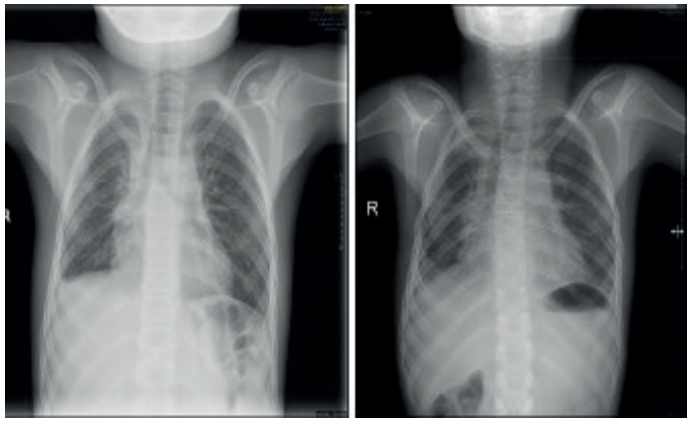

Figure 1: Chest X-ray at the first admission (before the nintedanib treatment:on the right side; 6th months of nintedanib treatment: on the left side)

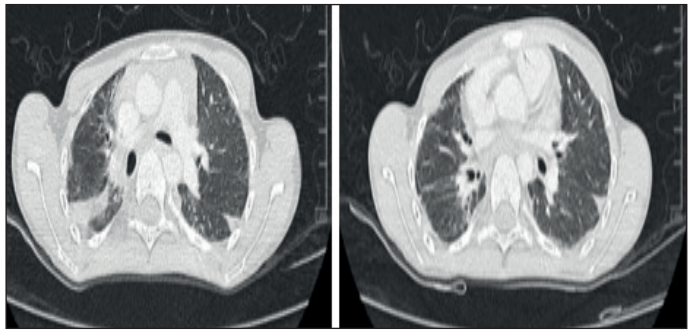

Figure 2: Chest CT performed before nintedanib treatment. Axial CT images show bronchiectasis, peribronchial thickening and reticulation consistent with pulmonary fibrosis.

at month 6 is shown in Figures 1 and 2. In the 9th month of treatment, mild nausea and vomiting due to nintedanib were observed. As there was no improvement or stabilisation of clinical and radiological findings, nintedanib treatment was considered ineffective in our patient and was discontinued in the ninth month of the treatment.

After discontinuation of treatment, the patient was referred for lung transplantation as he was considered to be a suitable lung transplant candidate. While waiting for transplantation, the patient's clinical condition deteriorated rapidly and ECMO was initiated for respiratory failure. The patient died after 40 days of ECMO.

DISCUSSION

Nintedanib is a tyrosine kinase inhibitor approved for IPF and other chronic progressive ILDs in adults, but there is limited experience in children (6). Here we report our experience with nintedanib in a child with PF following bleomycin and radiotherapy. In the early period after completing chemotherapy and radiotherapy, he had pneumonitis that did not respond to steroid treatment, and fibrosis developed in the lungs. For the antifibrotic effect, treatment with nintedanib was initiated. During 9 months of nintedanib, there was no objective improvement in overall clinical status and treatment was discontinued.

Lung fibrosis can be triggered by drugs such as chemotherapeutics. One of these is bleomycin, which is used in treatment protocols for Hodgkin's lymphoma. It is poorly metabolised in the lung due to low levels of bleomycin hydrolase. This poor metabolism leads to accumulation of bleomycin in the lung and causes vascular and cellular damage, leading to fibrosis in the lung parenchyma by induction of an inflammatory process in fibroblasts and macrophages (7-9). Another factor in PF is thoracic irradiation, which acts by causing oxidative damage to DNA, leading to cell damage and apoptosis of pneumocytes. The inflammatory response and subsequent repair process leads to lung fibrosis (10). Steroids and hydroxychloroquine are common treatments for children with PF (11). However, in the subacute or early phase of bleomycin-induced toxicity, good clinical responses to these two treatments may be seen. The success of these therapies is less likely to be achieved in the case of established fibrosis in the lungs (12). Many treatment options such as imatinib, pirfenidone for bleomycin-induced pneumonitis have been described in the literature (13,14). However, none of these have been studied for their efficacy and safety profile in children. In an adult population with IPF, randomised controlled trials of nintedanib showed that it significantly reduced the rate of decline in FVC in progressive pulmonary fibrosis, and fibrosing ILD associated with systemic sclerosis. Its effects have not yet been comprehensively studied in fibrosing ILD in children. However, the safety profile of nintedanib in children at the end of 24 weeks has been demonstrated in a recently published phase 3 randomised, placebo-controlled, double-blind study (the InPedILD study). In this study, the adjusted mean changes in FVC were not statistically significant between the nintedanib and placebo groups, but the changes with nintedanib at 24 weeks were similar to those seen in studies of adults with fibrosing ILD. It was showed that stabilisation in the decline in FVC and resting oxygen saturation was established at the end of 24 weeks of the treatment in children (5). At the time of the patient's admission to our clinic, pulmonary fibrosis was diagnosed according to the chest CT scan. Because, his clinical condition precluded lung biopsy. Due to the rapid progression of the disease and the lack of other promising treatment options, nintedeanib was chosen in this case.

Given that there is limited information in the literature on assessing PF in children, our patient's clinical outcome is controversial. A review of cases with PF of various aetiologies found that the outcomes of PF were not encouraging and resulted in end-stage respiratory failure or death according to Nadia et al. (11). In the literature, systemic corticosteriods and nintedanib treatment given early in the course of bleomycin-induced pulmonary toxicity has been shown to produce favourable results (15). In this report, we were not able to assess the effect of nintedanib in our case as no matched case has

been reported to date. Whether nintedanib treatment slowed disease progression in our patient is therefore unknown. In contrast to the results of the InPEDILD study, there could be many possible explanations for the treatment failure observed in our patient. First, the InPEDILD study allowed patients with an FVC% over 25%, but our patient was unable to perform PFT, suggesting that his clinical stage was worse than that of the patients included in the study. Therefore, the treatment may not have had a significant effect because it was started in the late fibrotic phase of the disease. Secondly, the aetiology of fibrosis in this case cannot be attributed to chemotherapy alone; high-dose radiotherapy may have had an additional contribution. It should be noted that there were multiple factors causing pulmonary fibrosis in this patient, making it difficult to draw direct conclusions about the effect of nintedanib. Clinicians should consider the aetiology of pulmonary fibrosis and the clinical stage of their patients before starting antifibrotic therapy.

As shown in the InPedILD study, gastrointestinal side effects were observed in our patient (5). Nausea and vomiting disappeared after discontinuation of the drug.

To our knowledge, this is the first paediatric case in the literature to report experience with nintedanib in a child with combination drug- and radiation-induced pulmonary fibrosis. This case is interesting because it would be a real-life experience of nintedanib in a child, resulting in failure to treat the fibrotic process in our patient.

CONCLUSION

In such complicated cases, it may be advisable to have this case reviewed before making a decision about treatment with nintedanib. Despite its safety profile in children, comprehensive studies are urgently needed to evaluate its effectiveness in children.

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Overview of Skeletal Dysplasias

İskelet Displazilerine Genel Bakış

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ABSTRACT

Skeletal dysplasias are quite a heterogeneous group of disorders, characterized by bone and cartilage abnormalities. Although each of them is individually rare, collectively the birth incidence is approximately 1 in 5000 live births. Due to the clinical heterogeneity, patients with skeletal dysplasias can apply to different departments with many different complaints or even lethal in the perinatal period. The establishment of a precise diagnosis provide proper clinical management of the patient, and a confirmed molecular diagnosis can prevent the recurrence of the disorder in the next generations. However, determining a spesific diagnosis is not always easy, yet a multisystemic, comprehensive, and stepwise approach to the patients with skeletal dysplasias, at least allows clinicians to classify into a specific group. In this review, general approach to patients with skeletal dysplasias, and some of the clinical and radiographic clues helpful in the diagnostic process are briefly summarized.

Key Words: Genetic disorders, Osteochondrodysplasias, Short stature, Skeletal dysplasias

ÖZ

İskelet displazileri kemik ve kıkırdak anormallikleri ile karakterize oldukça heterojen bir hastalık grubudur. Tek tek ele alındığında oldukça nadir olmakla birlikte bütüncül bakıldığında sıklığı yaklaşıl olarak 5000 doğumda 1'dir. Klinik heterojeniteye bağlı olarak hastalar farklı bölümlere farklı şikayetlerle başvurabilir ya da hastalar perinatal dönemde kaybedilebilir. Doğru tanı koymak, hastanın klinik takibinin uygun yapılmasını sağlar ve doğrulanmış moleküler tanı ile hastalığın sonraki nesillerde ortaya çıkmasının önüne geçilmiş olur. Ancak spesifik bir tanı koymak her zaman kolay değildir, ama multisistemik, kapsamlı ve basamaklı bir yaklaşım en azından spesifik bir grup içinde sınıflandırmayı sağlar. Bu yazıda iskelet displazili hastalara genel bir yaklaşım ve tanısal süreçte yardımcı olabilecek klinik ve radyolojik ipuçları kısaca özetlenmiştir.

Anahtar Kelimeler: Genetik hastalıklar, Osteokondrodisplazi, Boy kısalığı, İskelet displazisi

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INTRODUCTION

Skeletal dysplasias, also known as osteochondrodysplasias, are a large heterogeneous group of disorders, characterized by abnormal growth, differentiation, and development of bone and cartilage (1). Skeletal dysplasias are generally caused by variants in different genes, but they can also be related to extrinsic factors including maternal diseases and maternal drug use (2).

These disorders are individually rare, but the overall birth incidence is estimated to be about 2.4 to 4.5 per 10,000 live births, and represent %5 of all birth defects (2-4). Thanks to the advancements in the era of molecular genetics, and the development of genomic tools, many genes in the etiology of skeletal dysplasias have been delineated. It helps to understand the underlying pathophysiology and provides new therapeutic approaches. According to the Nosology of Genetic Skeletal Disorders, 2023 revision, genetic skeletal disorders encompass 771 entries resulting from variants in 552 known genes, and they are classified into 41 groups (Table I) (3). Due to clinical diversity, genetic heterogeneity, and individually rarity, recognizing them is not always easy (5,6). Obtaining a medical history, drawing a pedigree, physical examination, and assessment of radiographs in detail are essential in the evaluation of the patients with skeletal dysplasias.

CLINICAL EVALUATION

Skeletal dysplasias are quite a heterogeneous group of disorders, and patients with skeletal dysplasias can present with a wide variety of clinical findings. While some patients with skeletal dysplasia present with mild signs of osteoarthropathy starting in adolescence, some skeletal dysplasia can be lethal prenatally or life-limiting (2, 7-9). Even different variants in the same gene can cause quite different phenotypes. Loss of function variants in the FGFR3 gene cause CATSHL syndrome, a skeletal dysplasia with “tall stature”; while gain of function variants in the same gene cause Achondroplasia with “dwarfism”, Hypochondroplasia with “mild short stature” or Thanatophoric dysplasia that is usually “lethal” in the perinatal period (10).

To reach an accurate diagnosis or to narrow the differential diagnosis, a detailed clinical and radiographic evaluation is important, a stepwise aproach is essential (11, 12).

Medical history

Obtaining a detailed medical history of the patient is the first step in the assessment. The “onset of the symptoms” and “progression” should be asked. Medical history should include prenatal and natal history. Maternal illness, infections, and drug use during pregnancy should be noted. For example, maternal autoimmune disorders and exposure to warfarin prenatally cause chondrodysplasia punctata, and it is important to

Table I: Classification of skeletal dysplasias in the nosology of genetic skeletal disorders

Group 1	FGFR3 chondrodysplasias
Group 2	Type 2 collagen disorders
Group 3	Type 11 collagen disorders
Group 4	Sulfation disorders
Group 5	Dysplasias with multiple joint disloactions
Group 6	Filamins and related disorders
Group 7	Proteoglycan core protein disorders
Group 8	TRPV4 disorders
Group 9	Pseudoachondroplasia and multiple epiphyseal dysplasias
Group 10	Skeletal disorders caused by abnormalities of cilia or ciliary signaling
Group 11	Metaphyseal dysplasias
Group 12	Spondylometaphyseal dysplasias
Group 13	Spondyloepi(meta)physeal dysplasias
Group 14	Severe spondylodysplastic dysplasias
Group 15	Mesomelic and rhizo-mesomelic dysplasias
Group 16	Acromesomelic dysplasias
Group 17	Acromelic dysplasias
Group 18	Brachydactylies (isolated)
Group 19	Brachydactylies as part of syndromes
Group 20	Bent bone dysplasia group
Group 21	Primordial dwarfism and slender bones group
Group 22	Lysosomal storage diseases with skeletal involvement
Group 23	Chondrodysplasia punctata group
Group 24	Osteopetrosis and related osteoclast disorders
Group 25	Osteosclerotic disorders
Group 26	Osteogenesis imperfecta and bone fragility group
Group 27	Disorders of bone mineralisation
Group 28	Skeletal disorders of the parathyroid hormone signaling cascade
Group 29	Osteolysis group
Group 30	Disorganized development of skeletal components group
Group 31	Overgrowth (tall stature)syndromes and segmental overgrowth
Group 32	Genetic inflammatory or rheumatoid-like osteoarthropathies
Group 33	Cleidocranial dysplasia and related disorders
Group 34	Syndromes featuring craniosynostosis
Group 35	Craniofacial dysostoses
Group 36	Vertebral and costal dysostoses
Group 37	Patellar dysostoses
Group 38	Limb hypoplasia- reduction defects group
Group 39	Split hand/foot with or without other manifestations
Group 40	Polydactyly-syndactyly-triphalangism group
Group 41	Defects in joint formation and synostoses

Table II: Examples of clinical diagnostic clues in skeletal dysplasias

Physical examination	
Skull	Macrocephaly (Achondroplasia, Hypochondroplasia, Mucopolysaccahoridosis, Cole-Carpenter syndrome, Cranio-diaphyseal dysplasia, Cousin dysplasia) Cloverleaf skull (Tanatophoric dysplasia type 2) Large fontanelle (Osteogenesis imperfecta, Cleidocranial dysplasia, Opsismodysplasia) Triangular face (Kenny-Caffey syndrome)
Hair / Eyebrow	Sparse hair /eyebrow (Cartilage-hair hypoplasia) Alopecia (Chondrodysplasia punctata- Conradi Hunerman type) Light pigmentation of hair (AEC syndrome, EEC syndrome)
Eye	Blue sclera (Osteogenesis imperfecta) Wide palpebral fissures (Robinow syndrome) Hypertelorism (Robinow syndrome, Pfeiffer syndrome, Muenke syndrome, Saethre Chotzen syndrome) Otopalatodigital syndrome, Frank-Ter Haar syndrome, Lenz Majewski Hyperostotic dysplasia) Hypotelorism (Oculodentoosseous dysplasia) Microcornea (Oculodentoosseous dysplaia, Carpenter syndrome) Microphthalmia (Osteocraniostenosis, Kenny-Caffey syndrome) Proptosis (Thanatophoric dysplasia, craniosynostosis syndromes, Raine dysplasia) Blepharophimosis (Osteocraniostenosis, Schwartz Jampell syndrome) Buphthalmos (Melnick-Needles osteodysplasty) Lower eyelid coloboma (Nager syndrome) Ptosis (Baller-Gerold syndrome)
Nose	Depressed nasal bridge (Achondroplasia, Omodysplasia, Opsismodysplasia) Nasal bone hypoplasia (Keutel syndrome) Saddle nose (Sponastrime dysplasia) Pear-shaped nose (Tricho-rhino-phalangeal syndrome) Thin nose (Oculodentoosseous dysplasia) Hypoplastic ala nasi (Oculodentoosseous dysplasia) Parrot-like nose (Pyknodysostosis) Broad nose (Lenz-Majewski hyperostotic dysplasia) Thick bony wedge over glabella (Craniometaphyseal dysplasia) Prominent nose (MOPD) Midface hypoplasia (Achondroplasia, Stickler syndrome, craniosynostosis syndromes, Sponastrime dysplasia)
Chin	Rethrognathia (Stickler syndrome) Micrognathia (Cerebro-costo-mandibular syndrome) Prominent chin (Cartilage-hair hypoplasia) Prominent chin crease (Weaver syndrome)
Oral cavity	Cleft palate (Type 2 collagenopathies, Campomelic dysplasia, Catel-Manzke syndrome, Otopalatodigital syndrome) Multiple frenulum (Ellis-van Creveld syndrome) Alveolar ridge deformity (Robinow syndrome)
Teeth	Dentinogenesis imperfecta (Osteogenesis imperfecta, Odontochondrodysplasia) Supernumerary teeth (Cleidocranial dysplasia) Delayed eruption, enamel hypoplasia (Pycnodysostosis) Microdontia (Ellis van Creveld syndrome, Oculodentoosseous dysplasia, MOPD) Anodontia (AEC syndrome, EEC syndrome) Peg shaped teeth (Ellis van Creveld syndrome)
Ear	Cystic ear swelling (Diastrophic dysplasia) Petrified ears (Keutel dysplasia) Prominent ear crus (Saethre-Chotzen syndrome) Low-set ear (Roberts phocomelia syndrome, Baller-Gerold syndrome, Bent Bone dysplasia, Otopalatodigital syndrome, Spondylo-ocular dysplasia) Auditory canal atresia (SAMS syndrome)
Nail	Split nails (Condrodysplasia punctata- Conradi Hunerman type) Hypoplastic nails (Chondrodysplasia punctata- Brachytelephalangic type, Ellis-van Creveld dysplasia) Nail dysplasia (Nail-Patella syndrome, Yunis-Varon syndrome) Triangular lunula (Nail-Patella syndrome)
Spine	Cervical kyphosis (Larsen syndrome, Atelosteogenesis) Thoracolumbar kyphosis (Achondroplasia) Kyphoscoliosis (Osteogenesis imperfecta, Linkeropathy syndromes, Desbuquois dysplasia, Metatropic dysplasia) Increased lomber lordosis (Mucopolysaccharidosis, Achondroplasia) Short spine (SED congenita, Brachyolmia)

Physical examination	
Long bones	Bowing (Osteogenesis imperfecta, Stuve-Wiedeman syndrome, Campomelic dysplasia) Rhizomelic shortness (Achondroplasia, Hypochondroplasia, Boomerang dysplasia, Rhizomelic type Chondrodysplasia Punctata) Mesomelic shortness (Robinow syndrome, Leri Weill syndrome, Mesomelic dysplasia Langer type, AMDM) Rhizo-mesomelic dysplasia (Omodysplasia) Phocomelia (Roberts syndrome, Holt Oram syndrome, Tetra amelia syndrome)
Hands	Trident hand (Achondroplasia) Hitchikker thumb (Diastrophic dysplasia) Preaxial polydactyly (Townes Brock syndrome, Werner type mesomelic dysplasia) Postaxial polydactyly (Short rib polydactyly syndrome, Ellis van Creveld syndrome) Absent thumb (Yunis-Varon syndrome, Holt Oram syndrome, Duane Radial ray syndrome) Oligodactyly (Cornelia de Lange syndrome, Roberts syndrome, Fatco syndrome, Al Awadi syndrome) Syndactyly (Apert syndrome, Oculodentoosseous dysplasia, Werner type mesomelic dysplasia, Endosteal Hyperostosis Van Buchem type) Ectrodactyly (AEC syndrome, EEC syndrome) Cylindiric digits (Larsen syndrome) Crooked fingers (Tricho-rhino-phalangeal syndrome) Short hands (Geleophysic dysplasia, Acromicric dysplasia, Myhre dysplasia) Pudgy hands (Cartilage hair hypoplasia)
Feet	Club feet (Larsen syndrome, Diastrophic dysplasia, Achondrogenesis type 1B) Lateral deviation of fifth toe (IMPAD1 related dislocaiton syndrome) Short great toe (Fibrodysplasia ossificans proggressiva) Preaxial polydactyly (Carpenter syndrome)
Genital	Cryptorchidism (Robinow syndrome, Roberts syndrome, Al awadi syndrome) Ambiguous genitalia (Robinow syndrome, Campomelic dysplasia, Antley-Bixler syndrome, Short rib-polydactyly syndrome) Bifid scrotum (CDAGS) Hypospadias or micropenis (Robinow syndrome, IMAGE syndrome, Antley Bixler syndrome Cliteromegaly (Antley Bixler syndrome, Roberts syndrome) Large phallus (Roberts syndrome)
Skin	Achantosis nigricans (SADDAN dysplasia) Dimple at lower extremities (Campomelic dysplasia) Ichtiosiform erythrodermia (Chondrodysplasia punctata- Conradi Hunerman type) Erythroderma (EXTL3 deficiency) Thickened skin (Geleophysic dysplasia, Hyaline fibromatosis syndrome) Skin hyperextensiblity (B4GALT7 deficiency, B3GALT6 linkeropathy syndrome) Subcutaneous nodules (Hyaline fibromatosis syndrome, Winchester Torg syndrome) Skin rash- heterotopic ossification (Progressive osseous heteroplasia) Hypertrichosis/ hirshutism (Frank-Ter Haar syndrome, Diaphanospondylodysostosis syndrome, Bent bone dysplasia) Wrinkling of skin (Geroderma osteodysplasticum)
Systemic evaluation	
Cardiac system	ASD, VSD (Ellis-van Creveld syndrome, Holt Oram syndrome) Aortic root dilatation (B3GAT3-related linkeropathy syndrome) Thickening of heart valves (Geleophysic dysplasia)
Nervous system	Myotonia, contractures (Schwartz – Jampel syndrome) Decreased pain sensation, dysautonomia (Stüve-Wiedemann syndrome) Intellectual disability, developmental delay (Dyggvie-Melchior-Clausen dysplasia, Desbuquois dysplasia, Trichorhinophalangeal dysplasia type 2, NANS deficiency Microcephaly (MOPD)) Seizure (SADDAN)
Endocrine system	Hypocalcemia (Kenney-Caffey syndrome, Osteocraniostenosis, Albright hereditary osteodystrophy) Hypercalcemia (Hypophosphatasia, IMAGE syndrome, Metaphyseal chondrodysplasia Jansen type) Diabetes mellitus (Fibrous dysplasia (Mc-Cune Albright syndrome), MOPD, Wolcott-Rallison syndrome) Autoimmune tyhroiditis (SPENCD) Cushing disease, Hypertyhroidism (Fibrous dysplasia (Mc-Cune Albright syndrome)) Obesity (Carpenter syndrome, Albright's hereditary osteodystrophy) Adrenal insufficiency (IMAGE syndrome, Antley-Bixler syndrome)
Immunological system	Immune deficiency (Cartilage hair hypoplasia, EXTL3 deficiency, Schimke immuno-osseous dysplasia, SPENCD)

Systemic evaluation	
Renal system	Renal failure (Nail-Patella syndrome) Renal cysts (Asphyxiating thoracic dysplasia, Short-rib polydactyly syndromes) Nephrocalcinosis (Metaphyseal dysplasia- Jansen type)
Gastrointestinal system	Exocrine pancreatic insufficiency, pancreatic lipomatosis (Scwachman Diamond syndrome) Pancreatic cysts (Asphyxiating thoracic dysplasia, Short-rib polydactyly syndromes, Cranioectodermal dysplasia) Hepatosplenomegaly (Infantile osteopetrosis) Splenic hypoplasia/aspleni (Osteocraniostenosis) Liver fibrosis (Asphyxiating thoracic dysplasia)
Respiratory system	Laryngotracheomalacia (Campomelic dysplasia, Diastrophic Dysplasia, Atelosteogenesis type 3) Choanal stenosis/ atresia (Marshall Smith syndrome, Raine dysplasia, Lenz Majewski hyperostotic dysplasia)
Hematologic system	Cytopenia, anemia (Cartilage-Hair hypoplasia, Scwachman Diamond syndrome, Infantile osteopetrosis) Autoimmune hemolytic anemia (SPENCD)
Audiologic evaluaution	Hearing loss (Osteogenesis imperfecta, Type 2 collagenopathies, Stickler syndrome, Otopalatodigital syndrome, Myhre syndrome, Spondylo-ocular dysplasia, CATSHL syndrome)
Ophthalmological evaluaution	Miyopia, retinal detachment (Type 2 collagenopathies, Stickler syndrome) Hypermetropia (Kenny-Caffey syndrome, B4GALT7 deficiency) Cataract (Type 2 collagenopathies, Stickler syndrome, Spondylo-ocular dysplasia, osteocraniostenosis, Sponastrime dysplasia, CODAS syndrome, B4GALT7 deficiency, Chondrodysplasia punctata- Conradi Hunermann type and rhizomelic type) Microcornea (Oculodentoosseous dysplasia) Retinal pigmentary dystrophy (Mainzer-Saldino syndrome, Axial spondylometaphyseal dysplasia)
Ophthalmological evaluaution	Miyopia, retinal detachment (Type 2 collagenopathies, Stickler syndrome) Hypermetropia (Kenny-Caffey syndrome, B4GALT7 deficiency) Cataract (Type 2 collagenopathies, Stickler syndrome, Spondylo-ocular dysplasia, osteocraniostenosis, Sponastrime dysplasia, CODAS syndrome, B4GALT7 deficiency, Chondrodysplasia punctata- Conradi Hunermann type and rhizomelic type) Microcornea (Oculodentoosseous dysplasia) Retinal pigmentary dystrophy (Mainzer-Saldino syndrome, Axial spondylometaphyseal dysplasia)

question the mothers of the infants with stippling in this regard (10).

Short stature is one of the most common findings among patients with skeletal dysplasia, and it is important to know when it was noticed. For example, while the patients with 3M syndrome present with severe intrauterine growth restriction prenatally, and the birth length is approximately 40-42 cm; patients with pseudoachondroplasia are generally in normal length at birth, and short stature is detected at about 2 years (13). Patients with multiple epiphyseal dysplasia may not have short stature or height may be mildly shortened. These patients generally present with joint pain, waddling gait, and fatigue after long-distance walking in early childhood. Joint deformities and pain progress over time, and early-onset osteoarthritis requiring joint replacement can develop (14). PPRD (Progressive pseudorheumatoid dysplasia) is a skeletal dysplasia generally confused with Juvenile rheumatoid arthritis. Patients with PPRD are also normal at birth, and symptoms of arthropathy begin between three and six years with interphalangeal joint involvement. Large joints are also affected over time and progressive joint contractures develop (10). It is important to keep in mind skeletal dysplasias in patients presenting with joint pain.

Clinical findings may reverse over time, and the most typical example is Metatropic Dysplasia ("metatropos" means "changing pattern" in Greek) (15). While the patients with Metatropic Dysplasia have a short-limbed type of short stature at birth; in childhood, platyspondyly and kyphoscoliosis become more evident, and the trunk becomes shorter than the limbs (short-trunked short stature) (15).

Severe developmental delay and intellectual disability are not common among patients with skeletal dysplasia, but these patients may have delays at motor milestones due to discrepancies in body parts, bone deformities, or joint laxity (9). Neuromotor milestones should be noted. Only a few skeletal dysplasia including Dyggve-Melchior-Clausen dysplasia and NANS deficiency may have severe developmental delay and cognitive impairment (10). Patients should be asked about recurrent fractures or dislocations, time of teeth eruption, hearing loss, ophthalmologic problems, and diseases related to other systems. When evaluating a patient with short-limbed short stature, noticing the sparse-thin hair and eyebrows, and knowing the accompanying immune deficiency and cytopenia will be very helpful in the diagnosis of Cartilage hair hypoplasia.

Some of the diagnostic clinical clues in skeletal dysplasias are shown in Table II.

Family history

A detailed family history is essential, and it should be asked whether there are similar family members. Other affected patients in the family may help for the diagnosis. Height of the

parents should be noted and parents should be evaluated for skeletal deformities.

Physical examination

After obtaining a detailed medical and family history, a comprehensive physical examination may give many clues to determine the clinical diagnosis. Evaluation of facial dysmorphic features, head shape, joint, chest, spine, long bone, hand, and feet deformities should be noted. Clinical findings that can help to narrow the differential diagnosis are summarized in Table II. Anthropometric measurements should include head circumference, height, weight, arm span, and upper /lower segment ratio (6,12). Armspan and upper/lower segment ratio are important to determine whether the short stature is proportionate or disproportionate. Armspan is the distance between the tips of the middle fingers when the patient is standing upright against the wall (16). Although the arm span/ height ratio varies depending on age, gender, and ethnicity, it is approximately 1, and there should not be more than a 5 cm difference between height and arm span (7). The lower segment is the distance between the floor and the top of the symphysis pubis. The upper segment is calculated by subtracting the lower segment from the height. Age-related curves of the arm span- height difference and US/LS ratio are used for ethnicity and each sex. The normal upper/lower segment (US/LS) ratio is about 1.7 in newborns and decreases with age. At about 10 years old upper and lower segment lengths are equalized (7). Spondyloepiphyseal dysplasia congenital and Brachyolmia are examples of short-trunked skeletal dysplasias (10).

If the limbs are involved, segments of the extremities should be measured to detect which segment is primarily affected (upper segments (femur and humerus): rhizomelic; middle segments (radius, ulna, tibia, and fibula): mesomelic; and distal segments (hands and feet): acromelic). Achondroplasia, the most common skeletal dysplasia, is an example of rhizomelic short stature (17). Patients with Robinow syndrome, characterized by fetal face appearence, genital anomalies and costovertebral segmentation defects, exhibit mesomelic brachymelia (10). Geleophysic dysplasia is one of the acromelic dysplasias, characterized by happy-natured appearence, joint contractures and short hands and feet (10).

Radiologic evaluation

The majority of skeletal dysplasias have a distinguishable pattern of skeletal changes, and radiological evaluation of skeletal dysplasias depends on pattern recognition (18). A systematic stepwise radiographic approach can provide a specific diagnosis with the clinical details (1,18, 19). To determine which parts of the skeleton are mainly affected, a comprehensive skeletal survey including anteroposterior (AP) and lateral view of the skull, spine, and foot, AP view of thorax, pelvis, left hand and wrist, unilateral tubular bone graphies is needed (6, 12, 19). In case of limb asymmetry or suspicion of epiphyseal stippling, both upper and lower limb graphies should be obtained (20).

If the patient has previous graphies, they should be evaluated since the radiographic findings may change over time. In Chondrodysplasia punctata, epiphyseal stippling can not be seen after age two or three (10). In Pseudoachondroplasia, the finding of “anterior beaking” in vertebrae in early life changes to platyspondyly over time (10). Moreover, recognition of many skeletal dysplasias becomes challenging after epiphyseal fusion, and in adults, it is very important to obtain prepubertal skeletal graphies. In patients with multiple epiphyseal dysplasias, degenerative joint disease is progressive and results in early-onset osteoarthritis (14). In these patients, it is not easy to make a diagnosis of multiple epiphyseal dysplasia either in adults since epiphyses are fused, or in infants before epiphysis appear (14). Repeating the skeletal survey later in undiagnosed patients may be helpful (20).

Assessment of the radiographies includes evaluation of bone age, mineralization, structure, size, shape, and epiphyseal - metaphyseal – diaphyseal ossification (20). Some of the radiographic clues for skeletal dysplasias are shown in Table III.

Bone Age

Although there are various methods to determination the bone maturation, the most widely used one is hand and wrist radiograph of the non-dominant hand. Bone age is generally normal in patients with skeletal dysplasia, but can be delayed in epiphyseal dysplasias or advanced in Larsen syndrome or Desbuquois syndrome (9, 10).

Mineralization

Imbalance between bone formation and bone resorption causes osteopenia or osteosclerosis resulting with recurrent fractures. Osteogenesis imperfecta is a heterogeneous group of disorders characterized by decreased bone density, and it is the most common form of hereditary bone fragility disorder (22). Clinical severity is quite variable, and it may be lethal in perinatal period. Hypophosphatasia is another example of hypomineralization, and in severe lethal form, bones may be almost completely unossified (boneless fetus) (1,23). Metaphyseal lucencies and mid-diaphyseal spurs (Bowdler spurs) are other characteristic features of Hypophosphatasia (23). Osteosclerosis, increased bone formation, may be generalized (Osteopetrosis, Pyknodysostosis); may appear as bone islands (Osteopoikilosis) or metaphyseal striations (Sponastrime dysplasia, Osteopathia striata) (10). As well, graphies should also be evaluated for heterotopic calcifications in soft tissues, as in the Fibrodysplasia ossificans progressiva (10).

Calvarium

General ossification, shape and thickness of the skull, sizes of fontanelles, presence of wormian bones should be evaluated (24). In Achondroplasia an enlarged skull vault, frontal bossing,

Table III: Examples of radiographic diagnostic clues in skeletal dysplasias

Skull	Wormian bones (Osteogenesis imperfecta, Hajdu Cheney syndrome, Cleidocranial dysplasia) Thick skull (Myhre syndrome, Mucopolysaccahoridosis) Copper-beaten appearence (Hypophosphatasia, Cole-Carpenter syndrome) J sella (Geleophysic dysplasia, Mucopolysaccahoridosis) Obtuse mandibular angle (Pyknodysostosis) Intracranial calcification (Dysosteosclerosis, Osteopetrosis with renal calcification, Raine dysplasia)
Vertebrae	Decreased interpedicular distance in lumbar vertebrae (Achondroplasia) Dorsal hump (SED Tarda) Double hump (Dyggvie-Melchior-Clausen syndrome) Coronal clefts (SED congenita, Kniest dysplasia) Diamond-shaped vertebra (Pseudoachondroplasia) Pear shaped vertebra (SED congenita) Anisospondyly (Dissegmental dysplasia) Absent thoracic vertebral pedicles (Campomelic dysplasia) Cobra sign spine (Achondrogenesis type 1B) Sandwich appearence -sclerotic endplates- (Osteopetrosis) Codfish vertebra (Osteogenesis imperfecta, Cole Carpenter syndrome) Irregular endplates (Brachyolmia, Mucolipidosis type 3…) Overfaced pedicle (Metatropic dysplasia) Segmentation defects (Spondylocostal dysostosis)
Scapulae	Hypoplastic scapula (Campomelic dysplasia) Plump scapula (Mucopolysaccharidosis) Small misshapen scapula (Achondrogenesis) Hypoplastic scapula (Campomelic dysplasia, Cousin dysplasia, Cleidocranial dysplasia)
Ribs	Thick ribs (Mucopolysaccharidosis) Thin ribs (3M syndrome) Unossified rib gaps (Cerebro-costo-mandibular syndrome) Posterior rib gaps (Ischiospinal dysostosis) Ribbon-like ribs (Melnick Needle syndrome) Short ribs (SRPS, ATD) Wavy ribs (Bent bone dysplasia) Coat hanger ribs (Cranioectodermal dysplasia)
Clavicles	Hypoplastic/aplastic clavicle (Cleidocranial dysplasia) Thick clavicles (Mucopolysaccharidosis) Mustache-shaped small clavicles (Bent Bone dysplasia) Ram-horn bowing of the clavicles (SADDAN dysplasia) Handle-bar clavicle (Ellis van Creveld dysplasia, ATD, SRPD)
Pelvis	Square shape iliac bones (Achondroplasia) Small iliac wings (Achondrogenesis, Campomelic dysplasia, Cleidocranial dysplasia) Absent pubic ossification (SED congenita, Achondrogenesis, Hypochondrogenesis) Widely spaced pubic bones (Cleidocranial dysplasia) Trident pelvis (Achondroplasia, Tanataphoric dysplasia, Short-rib polydactyly syndromes) Champagne glass (Achondroplasia) Iliac horns (Nail-patella syndrome) Snail-like pelvis (Scneckenbecken dysplasia) Lacy appearance of iliac crests (Dygvie-Melchior-Clausen syndrome, Smith McCort syndrome) Hypoplasia of ischial rami (Ischio-pubic-patellar dysplasia) Unossified ischial rami (Ischiospinal dysostosis) Wide ischiopubic syndchondrosis (Cleidocranial dysplasia)
Long bones	Madelung deformity (Leri Weil dysostosis) Absent Radius (TAR syndrome, Holt Oram syndrome) Radio-ulnar synostosis (Nager syndrome, linkeropathy syndromes, Humeroradial synostosis (Cousin dysplasia) Hypoplasia of distal humeri (Diastrophic dysplasia, Larsen syndrome) Bifid distal humeri (CHST3 related dislocation syndrome) Ovoid lucency of proximal femur (Achondroplasia) Swedish key / Monkey wrench appearance (Desbuquois syndrome) Chevron deformity (Achondroplasia) Dumbell shape (Metatropic dysplasia, Kniest dysplasia, Fibrochondrogenesis Periost reaction (Hyaline fibromatosis syndrome)

Long bones	Gracile bones (3M syndrome, Osteocraniostenosis) Bowing (Osteogenesis imperfecta, Hypophosphatasia, Campomelic dysplasia, Thanatophoric dysplasia type 1, Melnick Needle syndrome) Accordion like tubular bones (Osteogenesis imperfecta type 2) Popcorn-like calcification (Osteogenesi imperfecta type 3) Ossification of the forearm interosseous membrane (Osteogenesi imperfecta type 5) Dripping candle wax (Melorrheostosis) Fibular aplasia (Nager syndrome)
Hands / Feet	Advanced bone age (Larsen syndrome, Desbuquois dysplasia) Delayed bone age (Multiple epiphyseal dysplasia) Bifid thumb (Desbuquois dysplasia, Robinow syndrome, Holt Oram syndrome) Bullet-shaped phalanges (Mucopolysaccharidosis) Cone shaped epiphysis (Cartilage-hair hypoplasia) Bifid distal phalanx of the thumb (Larsen syndrome) Proximal metacarpal pointing (Mucopolysaccharidosis) Ball in socket appearence (Pseudoachondroplasia) Acroosteolysis (Pyknodysostosis, Hajdu Cheney syndrome, Mandibuloacral dysplasia) Angel-shaped phalanges (ASPED dysplasia, Bent bone dysplasia, Spondylo megaepi-metaphyseal dysplasia) Chevron-shaped epiphysis (Acrodysostosis) Multiple ossification centers in calcaneus (Larsen syndrome) Supernumerary carpal and tarsal bone ossification centers (Larsen syndrome) Macroepiphysis (Spondylomegaepiphyseal metaphyseal dysplasia, OSMED)
Patella	Patellar hypoplasia (Nail-patella syndrome, Meier-Gorlin syndrome, Genitopatellar syndrome, Ischiopatellar dysplasia) Double-layered patella (SLC26A2-related multiple epiphyseal dysplasia)

*****For abbreviations: Bone Dysplasia, 4th edition*

midface hypoplasia and short skull base are observed. In Frontometaphyseal dysplasia, torus-like overgrowth of the supraorbital ridges and sclerosis of the skull base are typical (10). Large fontanelle and delay in its closure are seen in Osteogenesis imperfecta, Hypophosphatasia, Cleidocranial dysplasia, Pyknodysostosis (10). Premature fusion of cranial sutures result with abnormal skull shape (brachycephaly, dolichocephaly, plagyocephaly, turricephaly, trigonocephaly). Thanatophoric dysplasia type 2 is associated with cloverleaf skull. Turribrachycephaly is seen in Cole-Carpenter syndrome (10). Wormian bones are abnormal new bones developing from extra ossification centers, and they are located within the lambdoid or coronal sutures generally. Up to ten wormian bones are consider as normal variant, but more than ten wormian bones are seen in many conditions including Osteogenesis imperfecta, Cleidocranial dysplasia, Pyknodysostosis, Hajdu Cheney syndrome (24). Craniovertebral junction anomalies may cause significant morbidities and mortality in skeletal dysplasias such as foramen magnum stenosis in Achondroplasia or atlanto-axial instability due to odontoid hypoplasia in SED congenita (24, 25). So it is important to evaluate the skull graphies carefully.

Chest

Assesment of clavicles, ribs and scapula may give significant clues in the diagnosis of skeletal dysplasias. For example, the finding of hypoplastic scapula is very helpful in diagnosing Campomelic dysplasia. Absence or hypoplasia of clavicles with small and deformed scapulae is a clue for Cleidocranial dysplasia.

Rib assessment includes assesment of ossification, number, length, thickness, shape, fractures or fusion. Rib fusion with vertebra segmentation defects is typical for Spondylocostal dysostosis (crab-like chest). Paddle-shaped ribs are observed in mucopolysaccharidosis, wavy ribs are seen in Melnick Needle syndrome (26). Beaded ribs are a feature of Achondrogenesis type 1A and osteogenesis imperfecta type 2A. In Asphyxiating thoracic dysplasia, formerly known as Jeune syndrome, ribs are short, and the narrow thorax result with respiratory problems (10).

Spine

Dorsolumbar spine radiographs are essential part of the skeletal survey (27). In spine assessment, general shape of vertebral bodies (anisospondyly, platyspondyly, square / foreshortened / ovoid vertebra, hemivertebra, irregular enplates), posterior scalloping, ossification defects, stippling, notching, coronal or sagital clefts, pedicles, interpedicular distance, presence of kyphoscoliosis, increased or decreased lordosis should be evaluated.

Platyspondyly means flattened vertebra and can be seen in many skeletal dysplasias. In Thanatophoric dysplasia, vertebral bodies are strikingly flat (wafer-thin vertebral bodies) and in a H-shaped configuration. In Osteogenesis imperfecta codfish vertebrae (biconcave appearance of vertebrae) may be seen. In Achondrogenesis, vertebral body ossification is poor, but pedicle ossification is preserved (27). In osteopetrosis, sclerotic endplates give a sandwich-like appearence. The interpedicular distance expands caudally, but patients with Achondroplasia do not exhibit interpedicular widening.

Pelvis

Pelvis is constituted by pubic, iliac, ischial bones and sacrum (28). Detailed assesment of pelvic bones may provide many clues for skeletal dysplasia.

Ilium: Ilium should be assessed for shape (flared, square, hypoplastic, foreshortened, tombstone-like, crescent-shaped, halberd-shaped, snail-like appearance notching, lacy crest, iliac horns, champagne glass appearence…), osteopenia or sclerosis (bone-in-bone appearance, sunburst appearance, sclerotic oval focuses). Acetabular roofs may be flat, horizontal, sloping, irregular, or trident-shaped.

Pubis: Thickness and ossification of the pubis should be noted. Absent or retarded pubic ossification is an important finding in the diagnosis of SED congenita, achondrogenesis, and hypochondrogenesis.

Ischium: Thickness, tilt, and ossification of ischial bones should be assessed. Detecting an ischial anomaly can narrow the differential diagnosis (Ischiospinal dysostosis, Ischio-patellar syndrome).

Long Tubular Bones

Tubular bone assessment includes length, shape, mineralization, epiphysis, metaphysis, diaphysis, presence of bowing, exostoses, and enchondromas. In short-limbed skeletal dysplasias, it is important to determine which segment is more prominently affected to classify the skeletal dysplasia. It should be noted that the radiological evaluation of the segmental shortness of the long tubular bones (rhizomelic/ mesomelic/ acromelic) is more correct than clinical visualization (21). Achondroplasia, the most common skeletal dysplasia, is an example of rhizomelic shortness.

Likewise, determining the involvement of the epiphysis, metaphysis or diaphysis is also very important for classification. These regions can be affected isolated or in different combinations, and grouped according to the affected regions (Multiple epiphyseal dysplasias, metaphyseal dysplasias, spondyloepiphyseal dysplasias, spondylometaphyseal dysplasias, spondyloepimetaphyseal dysplasias). In multiple epiphyseal dysplasia, before the clinical symptoms appear, delayed ossification of the epiphysis is observed. Later epiphyses appear small and flat with irregular contours (14). Metaphyseal irregularities in metaphyseal dysplasias include flaring, splaying and cupping. Cartilage hair hypoplasia is an example of metaphyseal dysplasia, and knee metaphyses are most prominently affected (29). Camurati Engelman disease is a progressive diaphyseal dysplasia and characterized by hyperostosis primarily affecting the long bones and skull (10). Endosteal and periosteal proliferation, cortical thickening and patcy sclerosis are observed in diaphyses (10).

Hands and Feet

In hand graphies, overall morphology, length, shape, number of bones, mineralization, epiphysis, metaphysis, and diaphysis of the tubular bones, joint configuration, and presence of brachydactyly, syndactyly, oligodactyly, polydactyly (preaxial/ mesoaxial/ postaxial), ectrodactyly, symphalangism, pseudo epiphysis, carpal and tarsal bone fusions, stippling, osteolysis, exostoses, and Madelung deformity are evaluated (30). In a patient with spine malsegmentation, detecting carpo-tarsal coalition may be very helpful in diagnosing Spondylocarpotarsal synostosis syndrome. Cone-shaped epiphysis with metatarsal shortening in a patient with sparse hair, eyebrow and pear-shaped nose is helpful for Tricho-rhino-phalangeal syndrome. In Mucopolysaccharidoses, trabeculation is coarsely laced, tubular bones of the hands are short, wide, and deformed, proximal and middle phalanges are in bullet shape, second to fifth metacarpal bones are tapered proximally (10). Foot graphies are also evaluated similarly.

GENETIC EVALUATION

The last part in the assessment is genetic evaluation. With the advances in the field of genetics, many genes in the etiology of disorders including skeletal dysplasias have been identified. Due to clinical overlapping and heterogeneity, it is not easy to recognize a specific skeletal dysplasia type, with the clinical and radiographic findings. One of the most common skeletal dysplasia, Osteogenesis imperfecta, is caused by 21 known genes so far, the most common being COL1A1 and COL1A2 (22). While some of the subtypes of osteogenesis imperfecta are inherited autosomal dominantly, some of them are inherited autosomal recessively or X-linked recessively. Making a clinical diagnosis of Osteogenesis imperfecta without genetic tests, can not provide enough information for the family about the risk of recurrence. So it is important to have a confirmed molecular diagnosis, even if the clinical diagnosis is certain.

Different variants in the same gene may cause different disorders, and the typical example is the COL2A1 gene. In the OMIM database, 15 different entities related to COL2A1, with clinical findings ranging from mild osteoarthrosis to lethal achondrogenesis, have been reported (25).

If the patients have a specific clinical diagnosis, sanger sequencing and MLPA analysis of the relevant gene may be performed, but due to clinical and genetic heterogeneity, and rarity of the disorders, in many centers skeletal dysplasia gene panels or whole exome sequencing and microarray analysis (for suspected copy number variants) are being performed. In some centers, optical genome mapping and whole genome sequencing are performed, and they increase the diagnostic yield. Analysis of the genetic tests should be performed by specialist experienced in this field. A genetically confirmed diagnosis provide an improved clinical care for the patient, and genetic counseling to the family to prevent the disorder in the next generations (31).

MANAGEMENT

Management of the skeletal dysplasias is generally symptomatic and supportive, and still largely rehabilitation and surgical intervention. Patients should be assessed regularly in a multisystemic way. In skeletal dysplasias affecting spine, clinicians should be careful about spine compression and should perform neurologic assessment for myelopathy, regularly. To assess the instability of the occipito-cervical junction, flexion-extension cervical films are necessary (32). Patients with a high risk of airway obstruction (mucopolysaccharidosis, achondroplasia) should undergo polysomnography. Severe kyphoscoliosis cause respiratory failure and requires regular respiratory function tests. In Geleophysic dysplasia, progressive cardiac valvular disease is observed, and echocardiography is important in the follow-up (10). Eye examination is important in patients with SED congenita, as miyopia, retinal detachment, and cataract may develop over time (10). An accurate diagnosis in patients with skeletal dysplasia ensures appropriate medical follow-up.

The development of genomic technology enabled to understanding the pathophysiology of the disorders, and allowed new approaches such as pharmacological theraphy, cellular theraphy, or gene therapy (31). In Hypophosphatasia and Morquio A, enzyme replacement therapy (asfotase alfa and elosulfase alfa, respectively), in Osteogenesis imperfecta biphosphonates and in Achondroplasia vosorotide (CNP analog, BMN111) treatments are used currently, and many new treatment options in Achondroplasia, Osteogenesis imperfecta, osteopetrosis, Fibrodysplasia ossificans progressiva and hereditary multiple exostosis are about to complete phase 2 and 3 studies (4,31). In the near future, it is hoped to be used personalized gene theraphy and cell therapy safely and widely (33).

CONCLUSION

Skeletal dysplasias are clinically, genetically, and radiologically quite heterogeneous disorders. A multisystemic and comprehensive approach (detailed medical and family history, pedigree, physical examination, appropriate radiographs and genetic tests) is required. An accurate diagnosis is essential for the management of the patient, genetic counseling, and future treatment options in skeletal dysplasias.

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