Original Articles / *Özgün Araştırmalar*

- Accidental Home Injuries in Children in The Second Wave Of COVID-19: A Single Center Experience
  COVİD-19 Enfeksiyonunun İkinci Dalgasında Çocuklarda Ev Kazaları: Tek Merkez Deneyimi
- Frequency of Low Immunglobuline level in Pre-School Recurrent Wheezing
  Okul Öncesi Tekrarlayan Vizing ile İzlenen Hastalarda İmmünglobulin Düşüklüğü Sıklığı
- The Clinical and Molecular Cytogenetic Analyses of Six Patients with Pelizaeus-Merzbacher Disease From Four Families
  Dört Aileden Pelizaeus-Merzbacher Sendromlu Altı Hastanın Klinik ve Moleküler Sitogenetik Analizleri
- Outcomes of Video-Assisted Thoracoscopic Decortication in Pleural Empyema in Children
  Çocuklarda Plevral Ampiyemde Video Yardımlı Torakoskopik Dekortikasyonun Sonuçları
- Efficacy of Cefoperazone-Sulbactam as Empirical Monotherapy Therapy for Febrile Neutropenia in Children with Solid Tumors and Lymphomas
  Lenfoma ve Solid Tümörlü Çocuklarda Febril Nötropenide Sefaperazon-Sulbaktam Monoterapisinin Etkinliği
- Laparoscopic Pediatric Inguinal Hernia Repair with Percutaneous Internal Ring Suturing with Finer Needle and Suture; A 5-Year Experience of A Single Surgeon
  Perkütan İnternal Ring Süturizasyonu Tekniği ile Daha İnce İğne ve Sütur Kullanılarak, Laparoskopik Pediatrik İnguinal Herni Onarımı; Tek Cerrah, 5 Yıllık Deneyim
- Children with Special Educational Needs and Parental Burnout During the Pandemic Lockdown Period
  COVİD-19 Pandemisinde Özel Gereksinimli Çocuklar ve Ebeveyn Tükenmişliği
- COVID-19 Patients Who Admitted To Pediatric Emergency Department
  Çocuk Acil Servise Başvuran COVİD-19 Hastalar
- Musculoskeletal Involvement in Pediatric Behçet's Disease: A Single Center Experience
  Pediatrik Behçet Hastalığında Kas İskelet Sistemi Tutulumu: Tek Merkez Deneyimi
- Perspectives of School-Aged Overweight/Obese Children and Their Parents on "Healthy Nutrition Period": A Qualitative Study
  Okul Çağındaki Fazla Kilolu/Obez Çocukların ve Ebeveynlerinin "Sağlıklı Beslenme Sürecine Yönelik" Bakış Açıları: Nitel Bir Çalışma

Case Reports / *Olgu Sunumları*

- A Rare Case Report: Pediatric Aural Myiasis Composed of Multiple Live Larvae
  Nadir Bir Olgu Sunumu: Çok Sayıda Canlı Larvadan Oluşan Pediatrik Aural Miyazis
- Prosthetic Treatment of Pediatric Patients with Ectodermal Dysplasia: Two Case Reports
  Ektodermal Displazili Çocuk Hastaların Protetik Tedavisi: İki Olgu Raporu

Review / *Derleme*

- Ophthalmological Findings in Metabolic Diseases
  Metabolik Hastalıklarda Göz Bulguları

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- **Accidental Home Injuries in Children in The Second Wave Of COVID-19: A Single Center Experience**
  Elif BENDERLİOĞLU, Halise AKÇA, Funda KURT, Ayla AKÇA ÇAĞLAR, Leman AKÇAN YILDIZ, Miray TÜMER, Emrah ŞENEL
- **Frequency of Low Immunglobuline level in Pre-School Recurrent Wheezing**
  Merve YOLDAŞ ÇELİK, İlknur KÜLHAŞ ÇELİK, Tayfur GİNİŞ, Betül BÜYÜKTİRYAKİ, Müge TOYRAN, Emine DİBEK MISIRLIOĞLU, Can Naci KOCABAŞ, Ersoy CİVELEK
- **The Clinical and Molecular Cytogenetic Analyses of Six Patients with Pelizaeus-Merzbacher Disease From Four Families**
  Nejmiye AKKUŞ, Pelin ÖZYAVUZ ÇUBUK
- **Outcomes of Video-Assisted Thoracoscopic Decortication in Pleural Empyema in Children**
  Ufuk ATEŞ, Ergun ERGÜN, Anar QURBANOV, Pari KHALILOVA, Sümeyye SÖZDUYAR, Ergin ÇİFTCİ, Halil ÖZDEMİR, Gül ARGA, Hatice Kübra KONCA, Emrah GÜN, Tanıl KENDİRLİ, Meltem BİNGOL KOLOĞLU, Aydın YAĞMURLU, Murat ÇAKMAK, Gülnur GÖLLÜ
- **Efficacy of Cefoperazone-Sulbactam as Empirical Monotherapy Therapy for Febrile Neutropenia in Children with Solid Tumors and Lymphomas**
  İnci ERGÜRHAN İLHAN, Selma ÇAKMAKCI, Meriç KAYMAK CİHAN, Turan BAYHAN, Neriman SARI
- **Laparoscopic Pediatric Inguinal Hernia Repair with Percutaneous Internal Ring Suturing with Finer Needle and Suture; A 5-Year Experience of A Single Surgeon**
  Aybegüm KALYONCU AYÇENK
- **Children with Special Educational Needs and Parental Burnout During the Pandemic Lockdown Period**
  İrem Damla ÇİMEN, Zeliha YEĞİN, Ahmet Sefa GÜMÜŞSOY, Tuğçe KAPUCU
- **COVID-19 Patients Who Admitted To Pediatric Emergency Department**
  İlknur FİDANCI, Medine Ayşin TAŞAR, Burcu Ceylan CURA YAYLA, Kübra AYKAÇ, Bahar AKINTUĞ, Mustafa BERKAY KILIÇ, Gökçe DİLEK İŞCAN
- **Musculoskeletal Involvement in Pediatric Behçet's Disease: A Single Center Experience**
  Serkan COŞKUN, Zahide EKİCİ TEKİN, Elif ÇELİKEL, Vildan GÜNGÖRER, Nilüfer TEKGÖZ, Müge SEZER, Cüneyt KARAGÖL, Melike Mehveş KAPLAN, Nimet ÖNER, Merve Cansu POLAT, Banu ÇELİKEL ACAR
- **Perspectives of School-Aged Overweight/Obese Children and Their Parents on "Healthy Nutrition Period": A Qualitative Study**
  Yasemin ERGÜL, Nursel DAL, Kezban SAHİN

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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.

INSTRUCTIONS FOR AUTHORS

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

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

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

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

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

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

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

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

Each individual listed as an author should fulfill the authorship criteria recommended by the International Committee of Medical Journal Editors (ICMJE - www.icmje.org). The ICMJE recommends that authorship should be based on the following 4 criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

2. Drafting the work or revising it critically for important intellectual content; AND

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

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

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

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

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

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

The Editorial Board of the journal handles all of the appeal and complaint cases within the scope of COPE guidelines. In such cases, authors should get in direct contact with the editorial office to regard their appeals and complaints. When needed, an ombudsperson may be assigned to resolve cases that cannot be resolved internally. The Editor in Chief is the final authority in the decision-making process for all of the appeals and complaints.

When submitting a manuscript to the Turkish Journal of Pediatric Disease, authors should accept to assign the copyright of their manuscript to the Turkish Journal of Pediatric Disease. If authors rejected for publication, the copyright of the manuscript will be assigned back to the authors. The Turkish Journal of Pediatric Disease requires each submission to be accompanied by a Copyright Transfer and Acknowledgement of Authorship Form (available for download at https://dergipark.org.tr/en/pub/tchd). When using previously published content including figures, tables, or any other material in both of the

print and electronic formats, authors must obtain permission from the copyright holder. Legal, financial and criminal liabilities in this regard belong to the author(s).

Statistical analysis to support the conclusions are usually necessary. Statistical analyses must be conducted in accordance with the international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information about the statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified certainly.

Statements or opinions expressed in the manuscripts published in the Turkish Journal of Pediatric Disease reflect the views of the author(s) and not the opinions of the editors, the editorial board, or the publisher; the editors, the editorial board, and the publisher disclaim any responsibility or liability for such materials. The final responsibility in regard to the published content rests with the authors.

MANUSCRIPT PREPARATION

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

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

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at

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

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

Authors are required to submit the following:

Copyright Transfer and Acknowledgement of Authorship Form and

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

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

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

Preparation of the Manuscript Title page:

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

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

Important Notice: The title page should be submitted separately.

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

MANUSCRIPT TYPES

Original Articles:

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

Title: maximum of 20 words

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

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

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

References: up to 40

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

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

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

Review Articles:

Word count: up to 5000

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

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

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

References: up to 80

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

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

Case Reports:

Word count: up to 2000

Abstract: up to 200

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

Figures and tables: total 5

References: up to 15

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

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

Letters to the Editor:

Word count: up to 1500

Figures and tables: total 3

References: up to 15

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

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

Study Protocols:

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

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

Tables

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

Figures and Figure Legends

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

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

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

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

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

REFERENCES

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

If the reference is a journal;

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

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

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

If the reference is a journal supplement;

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

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

If the reference is a book;

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

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

If the reference is a book chapter;

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

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

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

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

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

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

If the reference is an online journal:

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

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

If the reference is a website:

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

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

If the reference is a thesis:

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

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

REVISIONS

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

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

CHANGE OF AUTHORSHIP AND WITHDRAWAL REQUEST

Change of Authoship

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)

Please note, if you are adding or removing author/authors, a new copyright transfer form signed by all authors should also be sent to the editorial office after the Editorial Board approves the change of the authorship.

Withdrawal Policy

Turkish Journal of Pediatric Disease is committed to provide high quality articles and uphold the publication ethics to advance the intellectual agenda of science. We expect our authors to comply mbestly with the practice in publication ethics as well as in the quality of their articles.

Withdrawal of a manuscript will be permitted only for the most compelling and unavoidable reasons. For the withdrawal of a manuscript, authors need to submit an "Article withdrawal Form", signed by all of the authors mentioning the reason for withdrawaling to the Editorial Office. The form is available at the web page of the journal. Authors must not assume that their manuscript has been withdrawn until they have received appropriate notification to this effect from the editorial office.

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

YAZARLAR İÇİN BİLGİ

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

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

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

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

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

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

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

Tüm başvurular intihal araştırlması 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

Editöre mektup daha önce yayınlanmış bir makalenin önemli bölümlerini, gözden kaçan yönlerini veya eksik bölümlerini tartışır. Dergi kapsamında okurların dikkatini çekebilecek konularda, özellikle eğitici vakalarda yer alan yazılarda editöre mektup şeklinde de gönderilebilir. Okuyucular ayrıca yayınlanan yazılar hakkındaki yorumlarını editöre mektup şeklinde sunabilirler. Bir özet ve Anahtar Kelimeler dahil edilmemelidir. Tablo, şekil, görüntü içerebilir. Metin alt başlıkları içermemelidir. Yorum yapılan makaleye bu yazının içinde uygun şekilde atıfta bulunulmalıdır.

Editöre mektuplar; İngilizce başlık. Türkiye'de bulunan bir merkez tarafından gönderilmişse editör mektubu için Türkçe bir başlık da gerekmektedir.

Çalışma Metodları:

Türkiye Çocuk Hastalıkları Dergisi araştırmanın şeffaflığını artırmak ve devam etmekte olan araştırmalar hakkında ilgili kişileri bilgilendirmek için çalışma metodları yayınlamaktadır. Çalışma metodlarının yayın kararı editör tarafından verilmektedir. Pilot çalışmaların veya fizibilite çalışmalarının metodları genellikle yayınlanmamaktadır.

Çalışma metodları yazıları, çalışmanın hipotezi, gerekçesi ve metodolojisi hakkında ayrıntılı bir açıklama sunan SPIRIT yönergelerine uymalıdır. Tüm çalışmalar için etik kurul onayı alınmış olmalıdır. Klinik araştırmalar için tüm protokoller, araştırma kayıt numarasını ve kayıt tarihi verilmelidir.

Tablolar

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

Şekiller ve şekil alt yazıları

Şekiller, grafikler ve fotoğraflar, gönderim sistemi aracılığıyla ayrı dosyalar (TIFF veya JPEG formatında) olarak gönderilmelidir. Dosyalar bir Word belgesine veya ana metne yerleştirilmemelidir. Şekil alt birimleri olduğunda, alt birimler tek bir görüntü oluşturacak şekilde birleştirilmemeli, her alt birim, başvuru sistemi aracılığıyla ayrı ayrı yüklenmelidir. Resimlerin üzerine etiketleme (örneğin a,d,c,d gibi) yapılmamalıdır. Şekil altyazılarını desteklemek için görüntülerde kalın ve ince oklar, ok uçları, yıldızlar, yıldız işaretleri ve benzeri işaretler kullanılabilir. Görüntülerde bir bireyi veya kurumu gösterebilecek her türlü bilgi kör edilmelidir. Gönderilen her bir şeklin çözünürlüğü en az 300 DPI olmalıdır. Değerlendirme sürecinde gecikmeleri önlemek için, gönderilen tüm şekiller net ve büyük boyutlu olmalıdır (en küçük boyutlar: 100 × 100 mm). Şekil açıklamaları ana metnin sonunda metindeki sıraya göre ayrı ayrı listelenmelidir.

Makalede kullanılan tüm kısaltmalar ve akronimler, hem özet hem de ana metinde ilk kullanımda tanımlanmalıdır. Kısaltma, tanımın ardından parantez içinde verilmelidir.

Ana metinde bir ilaç, ürün, donanım veya yazılım programından bahsedildiğinde, ürünün adı, ürünün üreticisi ve şehri ve şirketin ülkesini (ABD'de ise eyalet dahil) içeren ürün bilgileri, parantez içinde aşağıdaki biçimde sağlanmalıdır: The skin prick tests were performed using a multi-prick test device (Quantitest, Panatrex Inc, Placentia, California, USA)

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

Yayınlara atıf yapılırken, en son ve en güncel yayınlar tercih edilmelidir. Yazarlar on yıldan eski referansları kullanmaktan kaçınmalıdır. Yazılarda 10 yıldan eski tarihli referans sayısının toplam referans sayısının %20'sini geçmemesine dikkat edilmelidir. Elektronik olarak yayınlanmış ancak cilt ve sayfa numarası verilmemiş yazılar atfedilirken DOI numarası verilmelidir. Yazarlar kaynakların doğruluğundan sorumludur. Referans numaraları metindeki

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,

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

CONTENTS / İÇİNDEKİLER

Original Articles / Özgün Araştırmalar

433 Accidental Home Injuries in Children in The Second Wave Of COVID-19: A Single Center Experience
COVİD-19 Enfeksiyonunun İkinci Dalgasında Çocuklarda Ev Kazaları: Tek Merkez Deneyimi
Elif BENDERLİOĞLU, Halise AKÇA, Funda KURT, Ayla AKÇA ÇAĞLAR, Leman AKÇAN YILDIZ,Miray TÜMER, Emrah ŞENEL

439 Frequency of Low Immunglobuline level in Pre-School Recurrent Wheezing
Okul Öncesi Tekrarlayan Vizing ile İzlenen Hastalarda İmmünglobulin Düşüklüğü Sıklığı
Merve YOLDAŞ ÇELİK, İlknur KÜLHAŞ ÇELİK, Tayfur GİNİŞ, Betül BÜYÜKTİRYAKİ, Müge TOYRAN, Emine DİBEK MISIRLIOĞLU, Can Naci KOCABAŞ, Ersoy CİVELEK

445 The Clinical and Molecular Cytogenetic Analyses of Six Patients with Pelizaeus-Merzbacher Disease From Four Families
Dört Aileden Pelizaeus-Merzbacher Sendromlu Altı Hastanın Klinik ve Moleküler Sitogenetik Analizleri
Nejmiye AKKUŞ, Pelin ÖZYAVUZ ÇUBUK

451 Outcomes of Video-Assisted Thoracoscopic Decortication in Pleural Empyema in Children
Çocuklarda Plevral Ampiyemde Video Yardımlı Torakoskopikn Dekortikasyonun Sonuçları
Ufuk ATEŞ, Ergun ERGÜN, Anar QURBANOV, Pari KHALILOVA, Sümeyye SÖZDUYAR, Ergin ÇİFTCİ, Halil ÖZDEMİR, Gül ARGA, Hatice Kübra KONCA, Emrah GÜN, Tanıl KENDİRLİ, Meltem BİNGOL KOLOĞLU, Aydın YAĞMURLU, Murat ÇAKMAK, Gülnur GÖLLÜ

455 Efficacy of Cefoperazone-Sulbactam as Empirical Monotherapy Therapy for Febrile Neutropenia in Children with Solid Tumors and Lymphomas
Lenfoma ve Solid Tümörlü Çocuklarda Febril Nötropenide Sefaperazon-Sulbaktam Monoterapisinin Etkinliği
İnci ERGÜRHAN İLHAN, Selma ÇAKMAKCI, Meriç KAYMAK CİHAN, Turan BAYHAN, Neriman SARI

461 Laparoscopic Pediatric Inguinal Hernia Repair with Percutaneous Internal Ring Suturing with Finer Needle and Suture; A 5-Year Experience of A Single Surgeon
Madalyonun Diğer Yüzü: Perkütan İnternal Ring Süturizasyonu Tekniği ile Daha İnce İğne ve Sütur Kullanılarak, Laparoskopik Pediatrik İnguinal Herni Onarımı; Tek Cerrah, 5 Yıllık Deneyim
Aybegüm KALYONCU AYÇENK

466 Children with Special Educational Needs and Parental Burnout During the Pandemic Lockdown Period
COVİD-19 Pandemisinde Özel Gereksinimli Çocuklar ve Ebeveyn Tükenmişliği
İrem Damla ÇİMEN, Zeliha YEĞİN, Ahmet Sefa GÜMÜŞSOY, Tuğçe KAPUCU

476 COVID-19 Patients Who Admitted to Pediatric Emergency Department
Çocuk Acil Servise Başvuran COVİD-19 Hastalar
İlknur FİDANCI, Medine Ayşin TAŞAR, Burcu Ceylan CURA YAYLA, Kübra AYKAÇ, Bahar AKINTUĞ, Mustafa BERKAY KILIÇ, Gökçe DİLEK İŞCAN

483 Musculoskeletal Involvement in Pediatric Behçet's Disease: A Single Center Experience
Pediatrik Behçet Hastalığında Kas İskelet Sistemi Tutulumu: Tek Merkez Deneyimi
Serkan COŞKUN, Zahide EKİCİ TEKİN, Elif ÇELİKEL, Vildan GÜNGÖRER, Nilüfer TEKGÖZ, Müge SEZER, Cüneyt KARAGÖL, Melike Mehveş KAPLAN, Nimet ÖNER, Merve Cansu POLAT, Banu ÇELİKEL ACAR

488 Perspectives of School-Aged Overweight/Obese Children and Their Parents on "Healthy Nutrition Period": A Qualitative Study
Okul Çağındaki Fazla Kilolu/Obez Çocukların ve Ebeveynlerinin "Sağlıklı Beslenme Sürecine Yönelik" Bakış Açıları: Nitel Bir Çalışma
Yasemin ERGÜL, Nursel DAL, Kezban SAHİN

Case Reports / *Olgu Sunumları*

498 A Rare Case Report: Pediatric Aural Myiasis Composed of Multiple Live Larvae
Nadir Bir Olgu Sunumu: Çok Sayıda Canlı Larvadan Oluşan Pediatrik Aural Miyazis
Gamze ÖZTÜRK YILMAZ, Gökhan YILMAZ

501 Prosthetic Treatment of Pediatric Patients with Ectodermal Dysplasia: Two Case Reports
Ektodermal Displazili Çocuk Hastaların Protetik Tedavisi: İki Olgu Raporu
Arif BOLACA, Melih İlhan DEMİRCİLER, Aylin GÜLTEKİN KURU

Review *Derleme*

506 Ophthalmological Findings in Metabolic Diseases
Metabolik Hastalıklarda Göz Bulguları
Oya KIREKER KÖYLÜ, Çiğdem Seher KASAPKARA

Accidental Home Injuries in Children in The Second Wave Of COVID-19: A Single Center Experience

COVİD-19 Enfeksiyonunun İkinci Dalgasında Çocuklarda Ev Kazaları: Tek Merkez Deneyimi

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ABSTRACT

Objective: The COVID-19 pandemic has affected the whole world in terms of health, social life, and economics. In this study, the frequency of pediatric home accidents in the second wave of the pandemic, where social isolation continues, was investigated.

Material and Methods: This is a single center, retrospective study. We evaluated cases of patients under the age of 18 who were admitted to the hospital due to a home accident between November 1, 2020 and January 31, 2021 (the second wave of the pandemic). Results were compared with the patients who were admitted to the same emergency department within the same period of the previous year. Researchers examined home accidents in three groups: crash-fall-incision (1), intoxication-foreign body ingestion (2), and burns (3). The patients were divided into four age groups: 0-1 year, 2-5 years, 6-11 years, and 12-17 years.

Results: The study was completed with 607 cases pre-Covid and 683 cases post-Covid. The median age was 44.4 month (17-57) from 2019-2020 and 49.1 month (18-64) from 2020-2021 (p=0.154). The outpatient and sequela-free discharges were more frequent in both periods (p=0.046). In the second wave of the pandemic, there was an increase in burns and fall related admissions compared to before the pandemic (p<0.001). All types of home accidents were frequently detected at the ages of five years and younger.

Conclusion: In this study, analyzing the second wave of the pandemic compared to pre-pandemic times, Researchers noted a decrease in the number of emergency admissions and an increase in admissions related to home accidents.

Key Words: Children, COVID-19, Home Accident

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ÖZ

Amaç: COVİD-19 pandemisi tüm dünyada sağlık, sosyal hayat ve ekonomiyi etkilemiştir. Çalışmamızda pandeminin ikinci dalgasında, sosyal izolasyon devam ederken çocukluk dönemi ev kazalarının sıklığının araştırılmıştır.

Gereç ve Yöntemler: Çalışmamız tek merkezli ve retrospektif bir çalışmadır. 1 Kasım 2020-31 Ocak 2021 tarihleri arasında (pandeminin ikinci dalgası) ev kazası nedeniyle hastaneye başvuran 18 yaş altı hastalar değerlendirilmiştir. Sonuçlar bir önceki yılın aynı döneminde, ev kazası nedeniyle hastanemize başvuran hastalar ile karşılaştırıldı. Ev kazaları, çarpma-düşme-kesi, intoksikasyon-yabancı cisim alımı ve yanık olmak üzere 3 grupta incelendi. Hastalar 0-1 yaş, 2-5 yaş, 6-11 yaş ve 12-17 yaş olmak üzere dört yaş grubuna ayrıldı.

Bulgular: Çalışma Covid öncesi 607 olgu ve Covid-19 sonrası 683 olguyla tamamlandı. Ortanca yaş 2019-20 yıllarında 44.4 (17-57) ay, 2020-21 yıllarında 49.1 (18-64) aydı (p=0.154). Her iki dönemde de ayaktan hasta ve sekelsiz taburculuk daha sıktı (p=0.046). Pandeminin ikinci dalgasında pandemi öncesine göre yanık ve düşmelere bağlı başvurularda artış saptandı (p<0.001). Tüm kazalar 5 yaş ve altında daha sık görüldü.

Sonuç: Çalışmamızda pandemi öncesine göre pandeminin ikinci dalgasında; acil başvuru sayısında azalma gözlenirken, ev kazası nedeniyle başvuranlarda artış gözlendi.

Anahtar Sözcükler: Çocuklar, COVİD-19, Ev Kazaları

INTRODUCTION

The COVID-19 pandemic started at the beginning of 2020 and quickly affected the entire world. The pandemic has had short-term and long-term effects on both health care systems and social circles globally. An impact of the first wave of COVID-19 on health services was a decrease in emergency department (ED) visits worldwide (1-3). This may be due to restrictions, stay-at-home orders, and fear of getting infected at the hospital. Another important feature of this period was the closure of social areas, such as schools and daycares, and restrictions on leaving the house. As was to be expected, studies have demonstrated a decrease in the number of ED visits due to sports-related injuries, traffic accidents and communicable infections (1,2). Other studies have shown an increase in home accidents in the first wave of the pandemic (4-6). After the first wave of the pandemic ended, long-term and initially indetectable effects began to be reported. What happened to the children who had stay home longer than typical with parents who worked remotely or with other caregivers such as their grandparents? There is not enough data on how such children were affected during the second wave.

The aim of this study is to determine the frequency of home accidents in children during the second wave of the COVID-19 pandemic.

MATERIAL and METHODS

This is a retrospective, single-center study. It was approved by the medical ethics committee. From November 1, 2020 to January 31, 2021, patients under the age of 18 who were admitted to this hospital with ICD (International Classification of Diseases) diagnostic codes were included in the study. Researchers compared findings with the cases recorded over same period of the previous year.

Although the first known case of COVID-19 was recorded in December of 2019, the first case in Türkiye was reported on March 11th, 2020. Schools in Türkiye were closed on March 16th, 2020, and they remained closed throughout spring and summer. Schools temporarily opened at the end of September but closed again in November. Children remained at home until February 15th, 2021. Because Turkish schools were closed between November of 2020 and January of 2021, Researchers evaluated hospital admissions in this period to observe to effects of the second wave of the pandemic. Researchers designated the period of the second wave of COVID-19 as Group 2, and the same period of the previous year as Group 1.

Using accident-related ICD codes, (S00-T98, V01-X59, W00-W10, W17-19), Researchers identified 1.910 patients from 2019 to 2020 and 1.597 patients from 2020 to 2021 from November first to January 31st. Accidents outside of the home and intentional events were exclusion criteria. 162 admissions due to outdoor accidents, 116 traffic accident admissions, and 21 assault admissions were excluded from the study.

1.918 cases were removed due to incomplete file information (there was not enough evidence that the trauma occurred in the home). The study was completed with 607 cases in Group 1 and 683 cases in Group 2.

Home accidents were analyzed in three subgroups. Crash-fall-incision, intoxication-foreign body ingestion, and burns. Researchers divided children into four age groups: aged 0-1 year, 2-5 years, 6-11 years and 12–17 years.

SPSS Statistics 20 (IBM Corp, Armonk, New York) was used for statistical analysis. The Chi Square test was used to compare categorical variables between the pre-COVID-19 period and the COVID-19 period. A non-parametric test was used to compare the mean of two independent variables that were not normally distributed. The Kolmogorov-Smirnov test was used to evaluate normal distribution. p <0.050 was considered statistically significant.

RESULTS

Although Researchers designed the study around hospital admissions, they also looked at the number of Emergency

Table I: Characteristics of pediatric home accident from Nov 1- Jan 31 stratified by Group 1 and Group 2

Characteristics	Group 1 (n=607)	Group 2 (n=683)	p
Gender			
Male*	338 (55.7)	373 (54.6)	0.699†
Female*	269 (44.3)	310 (45.4)	
Median age, month (IQR)	31.0 (17-57)	34.0 (18-64)	0.154§
Accident subgroups*			
Crash/fall/incision	149 (38)	243 (62)	<0.001†
Intoxication/Foreign bodies	308 (52.6)	278 (47.4)	
Burns	150 (48.1)	162 (51.9)	
Follow-up*			
Outpatient	449 (48.5)	477 (51.5)	0.046†
Inpatient	68 (38.4)	109 (61.6)	
Intensive care unit	90 (48.1)	97 (51.9)	
Prognosis*			
With sequelae	30 (51.7)	28 (48.3)	0.466†
Without sequelae	577 (46.8)	655 (53.2)	

** n(%), †Chi-squared test, §Mann Whitney U test,* ***IQR:*** *Interquartile range*

Table II: The frequency of home accidents in the pre covid and during the covid period according to age groups

Accident subgroups Age groups	Crash/fall/ incision (n=392)	Intoxication/ Foreign bodies (n=586)	Burns (n=312)	Total (n=1290)	p
1-1 years*					
Group 1	57[a] (36.5)	87[b] (52.1)	74[a] (56.5)	218 (48)	0.001
Group 2	99[a] (63.5)	80[b] (47.9)	57[a, b] (43.5)	236 (52)	
2-5 years*					
Group 1	60[a] (35.7)	165[b] (55.2)	57[a] (45.2)	282 (47.6)	<0.001
Group 2	108[a] (64.3)	134[a] (44.8)	69[a] (54.8)	311 (52.4)	
6-11 years*					
Group 1	21[a] (48.8)	42[a] (47.7)	13[a] (38.2)	76 (46.1)	0.586
Group 2	22[a] (51.2)	46[b] (52.3)	21[a, b] (61.8)	89 (53.9)	
12-17 years*					
Group 1	11[a] (44)	14[a] (43.8)	6[a] (28.6)	31 (39.7)	0.473
Group 2	14[a] (56)	18[a] (56.2)	15[a] (71.4)	47 (60.3)	

** n(%), [a, b]: Each subscript letter denotes a subset of accident groups whose column proportions do not differ significantly from each other at the 0.05 level.*

Department admissions. Group 2 saw a 12% increase in November compared to Group 1, while there was a 62% decrease in December and a 50% decrease in January, respectively.

The number of pediatric patients admitted to this hospital with home accident-related ICD codes between November 1st and January 31st decreased in Group 2 compared to the Group 1. A statistically significant increase was found in Group 1 when home accident rates were examined according to the number of admissions. There was no significant difference between Groups 1 and 2 according to gender, age, prognosis, and follow-up. The median age was 44.4 month (17-57) in Group 1 and 49.1 month (18-64) in Group 2 (p=0.154) (Table I).

In this study, while there was an increase in burn and fall related admissions in Group 1, there was a decrease in intoxication and foreign body ingestion cases (Table I). All types of home accidents were frequently detected at the ages of five years and younger. While there was a significant difference between the home accident subgroups in the first five years of age, there was no difference in the ages of six years and older (Table II).

Most crash and fall injuries were caused by falling from furniture and beds. There were 16 cases of falling from great heights (windows and balconies), and 69% of them were in Group 2 (Table III). The mean age in cases of falling from great heights was 119±79 months. Half of the cases were under the age of five, but eight cases were over the age of 11. The children over the age of 11 had fallen while cleaning windows or running away from home. Older children drank corrosive substances stored in reused old water bottles, mistaking them for water. 88% of intoxications and 83% of foreign body aspirations occurred in children five years or younger. Bronchoscopy was performed in 53 cases, and esophagoscopy and clamp procedures were performed in 13 cases. No foreign body was found in 36% of those who were procedures. Two of the 15 magnet ingestion cases developed intestinal perforation cases and were discharged with sequelae.

Intensive care unit (ICU) stays (102 cases, 54.5%) and discharges with sequelae (42 cases, 72.4%) were significantly higher in the burn group (p<0.001). However, there is no significant difference between Group 1 and 2.

Table III: Some characteristics of home accidents subgroups

	Group 1 n (%)	Group 2 n (%)	Total
Crash/fall/incision injuries	149	243	392
Falling from furniture	36 (32)	76 (68)	112
Falling from beds	30 (40.5)	44 (59.5)	74
Falling from height	5 (31)	11 (69)	16
Incision	30 (62.5)	18 (37.5)	48
Others*	48 (33.8)	94 (66.2)	142
Intoxication/foreign body ingestion	308	278	586
Intoxication			
Medication	34 (56.6)	26 (43.4)	60
Corrosive substance intake	34 (56.6)	26 (43.4)	60
Carbon monoxide poisoning	30 (49.2)	31 (50.8)	61
Foreign body ingestion**			
Coins	24 (55.8)	19 (44.2)	43
Nuts	25 (49)	26 (51)	51
Toy parts	9 (37.5)	18 (62.5)	27
Button batteries	21 (77.7)	6 (22.2)	27
Magnets	6 (40)	9 (60)	15
Others*	125 (51.6)	117 (48.4)	242
Burns	150	162	312
Tea/coffee/boiling water	51 (49.5)	52 (50.5)	103
Contact with stove or heater	25 (45.5)	30 (54.5)	55
Others†	74 (48)	80 (52)	154

**Few, nonspecific, or unknown causes that cannot be grouped, †Those that are categorized into groups of foreign bodies are those that are aspirated through breathing. Eye, ear, and nasal incontinence are in the others*

DISCUSSION

The first wave of COVID-19 had serious health consequences including high ICU admi

e fact that people were still afraid of being infected with COVID-19 and avoided attending hospitals as much as possible.

In this study, fall injuries increased the most sharply of all home accidents post-pandemic. As in the literature, most of the fall injuries in this study were low-energy traumas that did not require hospitalization and were non-sequelae; moreover, most fall injuries were caused by falling from home furniture. Although the exact incidence of falls from great heights in children is not known in Türkiye, in a Turkish study it was demonstrated that the most common two causes of injury in the zero to four-year-old age group were burns and falls, and the most common cause of injury in the five to nine-year-old age group was falls (12). In a pediatric ICU study conducted in this hospital, 106 cases of falls from great heights were reported in one year (13). Falling from windows and balconies is a problem that has been largely solved by preventative measures in developed countries (14). A study from France pointed out that during the COVID-19 pandemic, there was a nearly 30% increase in home accidents and a 3.2-fold increased risk of falling from window (15). The Researchers note that although the study was carried out in winter period, 16 cases of falls from great heights have been recorded in the study.

In this study, burns are another group of home accidents that have increased significantly during the pandemic. Previous studies demonstrated that while there was a decrease in the number of burn-related injuries during the pandemic, the cases that did occur were more severe (16). In this study, unlike reported articles, there was an increase in total burn admissions during the pandemic, but there was no change in severe burn cases. This can be explained by the fact that the hospital observed is an important reference burn center in Türkiye; moreover, serious burn cases continued to be referred to this hospital both before and during the pandemic.

The rate of sequelae at discharge was also found to be higher in cases with high degree burns at the time of hospital admission. Surprisingly, only one in 16 patients who fell from great height were discharged with sequelae (usually those who fall from the 1st and 2nd floor). Intoxication, foreign body aspiration, and corrosive substance intake are known to be high risk in terms of morbidity and mortality (8). In this study, the most common sequelae after burns were due to battery ingestion, foreign body aspiration, and corrosive substance intake. Many foreign body ingestions involve batteries. These cases can have long-term complications such as perforation and increased possibility of sequelae. Previously, a significant increase in accidental battery ingestion was detected in the literature (17, 18). This increase continued during and even after the pandemic period, and various studies reported a significant number of accidental battery ingestions (19-21).

During the COVID-19 lockdown, one of the issues was the potential social and economic stress for parents and the reduced protective social support for children. This has raised concerns about possible increases in child neglect cases (22).

The studies evaluating childhood maltreatment cases have conflicting results. While some studies report an increase in childhood maltreatment cases during the pandemic, others demonstrate the opposite (23-26). It is conceivable that the increased number of child home accidents may be attributed to the arbitrarily increased time spent at home during pandemic. This can explain the increased rates of child maltreatment. However, the lack of protective social support may coincide with less frequent reporting of maltreatment cases. So, actual maltreatment cases might not change but may go undetected (27).

Strengths and limitations

The long-term impact of social isolation and economic stress on children, which continued after the first wave of the pandemic, has not been studied in detail. The Researchers hold that this report will reveal the importance of this issue. This is an important strength of this study.

Retrospective and single-centered design are the most important limitations of this study. The other limitation is that incomplete file information was commonly detected among cases with accident-related ICD codes, so these cases may be underreported.

There is a much greater likelihood of accidental injuries at home than detected, which has increased significantly during the pandemic period. Similarly, outpatient admissions may also be excluded. This should be taken into consideration when evaluating the study results.

CONCLUSION

In this study, Researchers found that in the 2nd wave of the COVID-19 pandemic, while social isolation continued, hospital admissions due to home accidents in children were higher than in the previous year. While a statistically significant increase in home accidents was found only in fall and burn injuries, a decrease in intoxication was detected. There is a significant difference in the subgroups of fall and burn injuries before and during the pandemic, especially at the ages of five and under.

In times of difficult health conditions, such as pandemics, the damage to vulnerable groups may be greater than expected.

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Frequency of Low Immunglobuline level in Pre-School Recurrent Wheezing

Okul Öncesi Tekrarlayan Vizing ile İzlenen Hastalarda İmmünglobulin Düşüklüğü Sıklığı

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ABSTRACT

Objective: Immunoglobulin lowering may be associated with recurrent wheezing symptoms and clinic by increasing the tendency to viral respiratory tract infections. This study aimed to investigate the frequency of immunoglobulinemia in preschoolers with wheezing.

Material and Methods: The study was conducted between 01.01.2013 - 01.01.2016 between T.C. University of Health Sciences, Ankara Child Health and Diseases Hematology Oncology Training, and Research Hospital, The Pediatric Allergy and Immunology Clinic included patients who had been followed up and treated for at least one year with recurrent wheezing attacks within 72 months. The patients' immunoglobulin (G, A, M) values were retrospectively analyzed. Immunoglobulin levels were determined to be normal and low according to age limits.

Results: The study included 585 patients (65.6% male, 34.4% female) under the age of 6 years with a mean age of 26.9 months. The mean follow-up period of the patients is 2.2 years. In 33.7% of these patients, at least one immunoglobulin was low. None of these patients had any signs or symptoms of immunodeficiency. Immunoglobulin A was low in 21% of the patients, immünglobulin G in 18%, and immünglobulin M in 7.5% of all patients.

Conclusion: Hypogammaglobulinemia was found in approximately 1/3 of the patients. There were no signs of immunodeficiency in these patients. Whether this is a special group in preschooler recurrent wheezing and hypogammaglobulinemia combination should be etiologically investigated.

Key Words: Immunoglobulin A, Immunoglobulin G, Immunoglobulin M, Low immunoglobulin, Pre-school recurrent wheezing

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Contribution of the Authors / Yazarların katkısı*: *YOLDAŞ ÇELİK M: Organizing, supervising the course of progress and taking responsibility for the research/study, Taking responsibility for patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility for the writing of the whole or important parts of the study. ***KÜLHAŞ ÇELİK İ:*** Taking responsibility for patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, and the logical interpretation and conclusion of the results. ***GİNİŞ T:*** Taking responsibility for patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility for the logical interpretation, and conclusion of the results. ***BÜYÜKTİRYAKİ B:*** Taking responsibility for patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, and the logical interpretation and conclusion of the results. ***TOYRAN M:*** Taking responsibility for patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility for logical interpretation, and conclusion of the results. ***DİBEK MISIRLIOĞLU E:*** Constructing the hypothesis or idea of research and article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress, and taking responsibility for the research/study. ***KOCABAŞ CN:*** Constructing the hypothesis or idea of research and article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress, and taking responsibility for the research/study. ***CİVELEK E:*** Constructing the hypothesis or idea of research and article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking responsibility for the research/study, Reviewing the paper before submission scientifically besides spelling and grammar.

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ÖZ

Amaç: İmmünglobulin düşüklüğü viral solunum yolu enfeksiyonlarına eğilimi arttırarak tekrarlayan vizing semptomları ve kliniği ile ilişki olabilir. Bu çalışmada okul öncesi vizingli hastalarda immünglobulin düşüklüğü sıklığını araştırmak amaçlandı.

Gereç ve Yöntemler: Çalışmaya 01.01.2013 - 01.01.2016 tarihleri arasında T.C. Sağlık Bilimleri Üniversitesi Ankara Çocuk Sağlığı ve Hastalıkları Hematoloji Onkoloji Eğitim ve Araştırma Hastanesi Çocuk Allerji ve İmmünoloji Kliniği'nde 72 ay altında tekrarlayan vizing ataklarıyla en az bir yıldır takip ve tedavi edilen hastalar dahil edildi. Hastaların immünglobulin (G,A,M) değerleri geriye dönük olarak incelendi. İmmünglobulin düzeyleri yaş sınırlarına göre normal ve düşük olarak belirlendi.

Bulgular: Çalışmada ortalama başvuru yaşı 26.9 ay olan 6 yaş altı 585 (%65.6 erkek, %34.4 kız) hasta dahil edilmiştir. Hastaların ortalama takip süresi 2.2 yıldır. Bu hastaların %33.7 sinde en az bir immünglobulinde düşüklük saptanmıştır. Bu hastaların hiçbirinde immün yetmezlik düşündürecek semptom ve bulgular saptanmamıştır. Tüm hastaların %21'inde immünglobulin A, %18'inde immünglobulin G, %7.5'inde immünglobulin M değerlerinde düşüklük olduğu saptanmıştır.

Sonuç: Hastaların yaklaşık 1/3'ünde hipogamaglobulinemi saptandı. Bu hastalarda immün yetmezlik belirtileri yoktu. Okul öncesi tekrarlayan hışıltı ve hipogamaglobulinemi kombinasyonu saptanan hastaların özel bir grup olup olmadığı konusunda araştırmalar yapılmalıdır.

Anahtar Sözcükler: İmmunglobulin A, İmmunglobulin G, İmmunglobulin M, Düşük immunglobulin, Okul öncesi tekrarlayan vizing

INTRODUCTION

Wheezing is a common respiratory symptom in childhood. Almost half of the children report at least one wheezing episode in the first six years (1). Since airway narrowing and inflammation cannot be evaluated clearly in this age group; the diagnosis is according to physical examination and symptoms. These children may be incorrectly diagnosed with pneumonia and poor treatment. Children who experience preschool wheezing have an increased risk of asthma (2). Therefore, recognizing recurrent wheezing is very important. In a study conducted in Türkiye, according to the The International Study of Asthma and Allergies in Childhood (ISAAC) phase 2 protocol, the general prevalence of wheezing was 15.8%, and the widespread majority of bronchial hyperreactivity was 24.2% (3).

Transient hypogammaglobulinemia of infancy (THI) is a temporary immunodeficiency in which immunoglobulin G levels are below 2 standard deviations for age. Immunoglobulin M and immunoglobulin A deficiency may also accompany (4). THI is one of the most common primary immune disorders in childhood and usually resolves by six years of age (5). Although its incidence is unknown, it is considered more common than estimated since routine immunoglobulin levels are not checked in healthy children. It causes an increase in frequency, especially in upper and lower respiratory tract infections (6). Studies show low immunoglobulin levels increase susceptibility to respiratory virus infections, exacerbate asthma, and cause chronic obstructive respiratory diseases (7-9). In a study by Karaman et al. (10), immunoglobulin G4 levels were significantly lower in recurrent preschool wheezing. Coexistence can be observed between allergic diseases and immune deficiencies (11-14).

In patients followed up with recurrent wheezing, low immunoglobulin may be associated with recurrent wheezing symptoms by increasing the tendency to viral respiratory tract infections. Our study aimed to investigate the frequency of low immunoglobulin in patients with preschool wheezing.

MATERIALS and METHODS

The study was conducted between 01.01.2013 - 01.01.2016 between T.C. University of Health Sciences, Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital, Pediatric Allergy and Immunology Clinic. This study was approved by the Clinical Research Ethics Committee of Ankara Pediatrics Hematology Oncology Training and Research Hospital (14.06.20217/2017-084). Inclusion criteria of the patients were determined as followed-up in the clinic with recurrent wheezing for at least one year and under the age of 72 months. Patients who presented to the clinic with wheezing at least three times a year were considered recurrent wheezing. The criteria for the exclusion of cases were other causes that might lead to hypogammaglobulinemia (systemic disease, cellular immune deficiency, malignity, genetic syndromes). Laboratories such as lymphocyte subgroup analysis, vaccine responses, complement level measurement, and nitroblue tetrazolium test were performed on suspected patients. Patients thought to have a specific immunodeficiency were excluded from the study. Electronic health records and files of patients were evaluated retrospectively in terms of concomitant low immunoglobulin levels.

The patients' immunoglobulin (G, A, M) values were retrospectively analyzed. Immunoglobulin levels were determined to be normal and low according to age limits. All data about the patients were scanned in the patient follow-up files and the database in the information operating system. Immunoglobulin (IgG, IgA, IgM, IgE) measurement was performed nephelometrically with a device called Immunochemistry System-IMMAGE 800. Immunoglobulin measurements of the patients, which were made once at any time, were compared with the normal immunoglobulin values of Turkish children for age below -2 SD value (15) was considered as hypogammaglobulinemia.

All results were evaluated with the Statistical Package for Social Sciences 18.0 (SPSS Inc., Chicago, IL, 2009) program. Discrete variables were given as numbers and percentages, normally distributed continuous variables as mean ± standard

deviation, and non-normally distributed continuous variables as median (interquartile range). The Chi-square test was used to compare discrete variables.

RESULT

There were 585 patients (201 females (%34.4) and 384 males (%65.6) included in the study. All patients were diagnosed with wheezing under the age of 72 months. The mean age of initiation was 26.9 months. The current mean age of the patients was 4.2 years (min: 61 days, max: 72 months). The mean follow-up period of the patients was 2.2 years. Immunoglobulin G, Immunoglobulin M, and Immunoglobulin A levels were measured in all patients.

At least one immunoglobulin isotype was low in 33.7% of all patients. The prevalence values of low immunoglobulin levels were 22.7% for one immunoglobulin, 7.5% for two immunoglobulins, and 3.4% for three immunoglobulins. Immunoglobulin deficiency for isotypes was detected in 21.9% of Immunoglobulin A, 18.6% of immunoglobulin G, and 7.5% of immunoglobulin M. In female patients, the low immunoglobulin ratio was 28.4% at IgA, 16.4% at IgG, and 6.5% at IgM. The low immunoglobulin ratio in male patients was 18.5% at IgA, 19.8% at IgG, and 8.1% at IgM. Low immunoglobulin A frequency was significantly higher in the female gender (p<0.050) (Table I).

For patients between 61 days and five months, low immunoglobulin levels were detected in all girls and 75% of boys. For patients between 9-12 months, low immunoglobulin levels were detected in 47.6% of girls, in 75% of boys. For patients between 12-24 months, immunoglobulin deficiency was detected in 50.7% of girls, in 52.4% of boys (Figure 1).

Low immunoglobulin A was detected in all girls and 75% of boys between 61 days and five months, in 44% of girls and 30% of boys between 12-24 months, in 27% of girls and 16% of boys between 37-48 months (Figure 2). Low immunoglobulin M was evaluated in 15% of boys between 61 days and 5 months, 13% of girls, and 23.3% between 12-24 months (Figure 3). The results of low immunoglobulin G levels were between 9-12 months old patients in 28.6% of girls, in 14.8% of boys, between 12-24 months in 20.3% of girls, in 32% of boys, and between 49-72 months in 23.1% of girls, in 30% of boys (Figure 4).

Table I: Frequency of immunoglobulin A, M, G deficiency in female and male patients.

	Female n (%)	Male n (%)	Total n (%)	p
Low immunoglobulin A	57 (28.4)	71 (18.5)	128 (21.9)	=0.006
Low immunoglobulin G	33 (16.4)	76 (19.8)	109 (18.6)	>0.050
Low immunoglobulin M	13 (6.5)	31 (8.1)	44 (7.5)	>0.050

Table II: Frequency of any immunoglobulin deficiency in patients younger than four years old and over four years old

	Under 4 years old n (%)	Over 4 years old n (%)	p
Low in one Immunoglobulin	125 (22.2)	8 (34.8)	>0.050
Low in Two Immunoglobulins	43 (7.7)	1 (4.3)	>0.050
Low in Three Immunoglobulins	20 (3.6)	0 (0)	>0.050

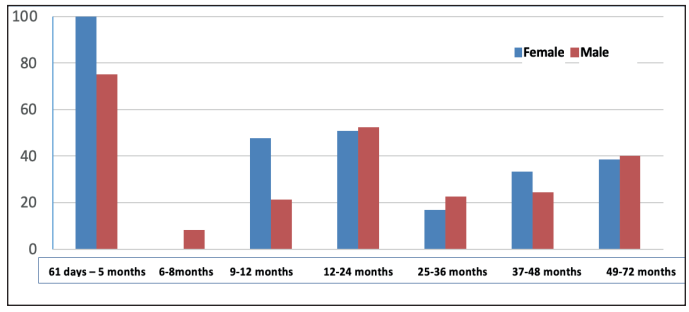

Figure 1: Frequency of patients with low levels of any Immunoglobulin by gender and age in different age groups.

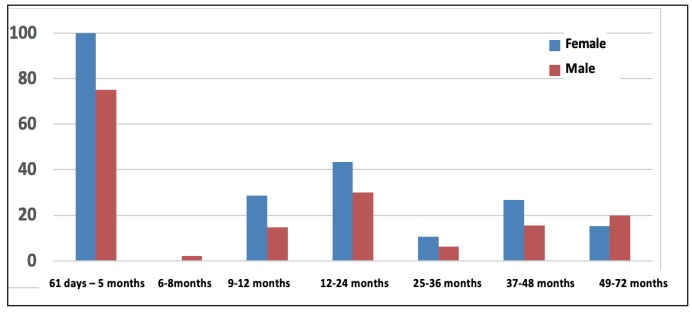

Figure 2: Frequency of patients with low immunoglobulin A according to gender and age in different age groups.

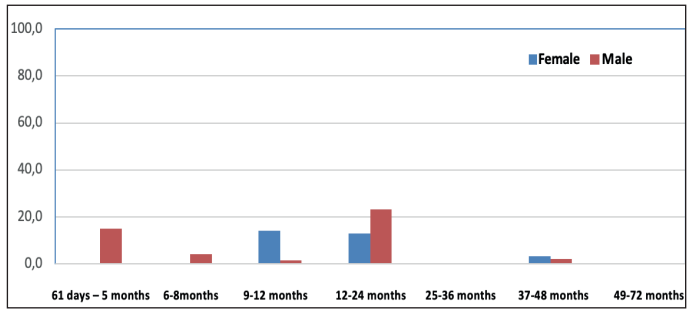

Figure 3: Frequency of patients with low immunoglobulin M according to gender and age in different age groups.

In patients under four years of age, the frequency of low levels of any immunoglobulin was 22.2%, 7.7% of two immunoglobulins, and 3.6% of three immunoglobulins. In patients over four years of age, the frequency of any immunoglobulin was 34.8%, and the frequency of low levels of two immunoglobulins was 4.3%. No patient had low levels of three immunoglobulins in patients over four years of age (Table II).

Among the 585 patients, there were 562 patients under four years old, and 23 were over four years old. The immunoglobulin

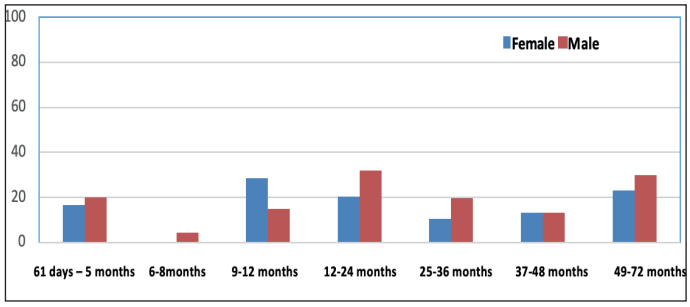

Figure 4: Frequency of patients with low immunoglobulin G levels by gender and age in different age groups.

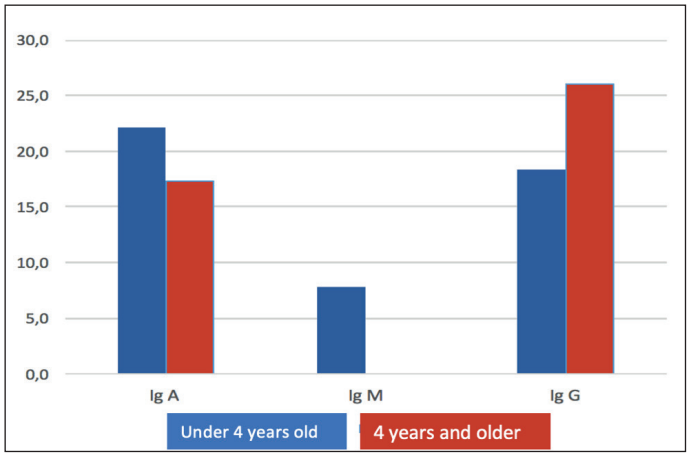

Figure 5: Frequency of low immunoglobulin A, M, and G values in patients younger than four years old and over four years old

A values of the patients were compared, and it was found that low immunoglobulin A was 22.1% in patients under four years and 17.4% in patients over four years. The immunoglobulin G values were compared. Low immunoglobulin G levels in patients under four years old were 18.3%, and low immunoglobulin G levels in patients over four years old were 26.1%. Immunoglobulin M values were compared; low immunoglobulin M levels were 7.8% in patients under four years. Immunoglobulin M levels were normal in patients over four years (Figure 5).

DISCUSSION

Our study found a decrease in at least one immunoglobulin isotype in 33.7% of the patients. Symptoms and signs of immune deficiency diseases were not detected during the evaluation of the patients, but the process related to the patients in the later stages is unknown. It is thought that low immunoglobulin levels in a group of patients with recurrent wheezing may cause recurrent viral infections or severe viral infections, leading to a preschool wheezing clinic. In addition, many studies indicate that there may be a relationship between immune deficiencies and allergic diseases (12,13,16,17).

Many factors, such as personal and environmental factors, play a role in the development of asthma, and the male gender is one of the risk factors (18). Low immunoglobulin A was found more frequently in females when the frequency of low immunoglobulin levels was evaluated according to the genders. Since all of these patients were under 72 months of age, they were not evaluated for selective or partial immunoglobulin A deficiency. No significant difference was found between both genders regarding immunoglobulin M and G levels.

Kaufman et al. (19) evaluated the relation with atopy by measuring the immunoglobulin level in 641 adult cases with recurrent allergic disease symptoms. They found immunoglobulin levels low in 6.7% of the cases (19). In our study, low immunoglobulin levels were more common. This result may be due to the temporary delay in immunoglobulin production because the patients we followed were younger than six. In addition, some of the patients we followed may have had transient infantile hypogammaglobulinemia. This difference may also be due to ethnic, genetic, and geographic disparities and differences between normal immunoglobulin values (20).

Immunoglobulin A:

The most important function of immunoglobulin A in the body is to form the first line of defense against pathogens by preventing the attachment of bacteria and toxins to epithelial cells. High levels of secretory immunoglobulin A antibodies can avoid the absorption of allergens by preventing the adhesion and penetration of antigens (21). Immunoglobulin A, the most abundant immunoglobulin in the mucosa, acts as an active barrier to inhaled and ingested antigens. Barrier changes and epithelial disorders are also prominent features of allergic asthma (22, 23). It is reported that immunoglobulin A secreted in breast milk reduces the risk of asthm (24, 25).

Our study found low immunoglobulin A levels in 21% of patients with recurrent wheezing. Our findings suggest that there may be a relationship between low immunoglobulin A levels and recurrent wheezing. In the saliva, secretory immunoglobulin A is protective against the development of recurrent wheezing in children (26, 27). Another study reported that high fecal immunoglobulin A levels in the first six months of life might reduce the risk of immunoglobulin E related disease development (28). It has been shown in various studies that infants with higher nasal immunoglobulin A levels have fewer respiratory tract infections and a lower incidence of wheezing during viral infection (29). In a study conducted in Iceland, babies with low immunoglobulin A levels had more asthma and otitis media than those with normal levels. A significant correlation was also found between the severity of allergic symptoms and low immunoglobulin A levels (30).

Selective immunoglobulin A deficiency is one of the immunodeficiencies most commonly associated with allergy and atopy. In a study conducted on patients diagnosed with selective immunoglobulin A deficiency, there was a correlation with allergic findings in 83.7%.

Immunoglobulin M:

Immunoglobulin M is the first immunoglobulin isotype synthesized in the neonatal period. Immunoglobulin M is an important antibody in most external secretions, particularly in saliva and respiratory epithelial fluid, and plays a role in the pathogenesis of some autoimmune diseases like rheumatoid arthritis. However, there needs to be more information about the role of immunoglobulin M in the pathogenesis of asthma (31). It has been reported that individuals with immunoglobulin M deficiency are more susceptible to opportunistic respiratory tract infections than healthy individuals (32). In addition to immunoglobulin A, secretory immunoglobulin M may be important for pulmonary mucosal barrier homeostasis (31). In our study, immunoglobulin M was low in 7.5% of all patients. In patients older than 48 months, low immunoglobulin M was not detected.

Immunoglobulin G:

Immunoglobulin G, the major immunoglobulin of the body, constitutes 75-80% of serum immunoglobulins (33). It is known that there is a transplacental transmission of immunoglobulin G (28). Based on this information, low immunoglobulin G levels were detected in patients between 61 days and five months in our study (female 16.7%, male 20%) had a higher percentage than expected.

In a study aiming to investigate humoral immunity in children with asthma, immunoglobulin G, M, A, and E levels were normal in cases with severe asthma, but immunoglobulin G (especially immunoglobulin G3) and immunoglobulin A subgroup deficiencies were found (16). In a study to determine the relationship between serum immunoglobulins and recurrent wheezing in patients with recurrent wheezing, serum immunoglobulin G subclasses were measured. Immunoglobulin G3 was significantly deficient in patients aged 2-6 years compared to the control group (34). In another study, immunoglobulin G3 levels were low in 39.6% of three years old patients with recurrent wheezing (35). It has been reported that low IgG4 levels may cause recurrent wheezing in infants (36,37). These studies suggest that wheezing in childhood may be associated with immunoglobulin G subclass deficiency. In our research, immunoglobulin G subclasses were not examined in patients, but new studies on this subject are needed in light of the significant results in previous studies. We found that 18% of all patients had low immunoglobulin G levels. These findings showed that low immunoglobulin levels in patients with recurrent wheezing might predispose them to wheezing attacks due to delayed maturation of the immune system.

In conclusion, our study found low immunoglobulin A in 21% of all patients. Our study has led us to think that the immunoglobulin A level improves in advancing ages, and the wheezing disappears. Further research is needed to determine whether this is a special group of patients with preschool wheezing. Future studies on immunoglobulin A may develop new therapeutic strategies to develop protective immunity against pathogens and help induce immune tolerance to allergens. In addition, the findings of this study support the idea that in case of delayed production of immunoglobulin G, the immune response may be affected, and a predisposition to recurrent wheezing attacks may occur.

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The Clinical and Molecular Cytogenetic Analyses of Six Patients with Pelizaeus-Merzbacher Disease From Four Families

Dört Aileden Pelizaeus-Merzbacher Sendromlu Altı Hastanın Klinik ve Moleküler Sitogenetik Analizleri

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ABSTRACT

Objective: Pelizaeus-Merzbacher Disease is a rare X-linked recessive leukodystrophy caused by a mutation in the proteolipid protein (PLP) gene on chromosome Xq22. PMD is an early-onset neurological disorder characterized by nystagmus, spastic quadriplegia, ataxia, and developmental delay. Genetic analysis has identified Xq22 microduplications (60-70%), point mutations (10–25%), and deletions (5-10%) within the coding region of the PLP genes in Pelizaeus-Merzbacher Disease. This study evaluated six patients with *PLP1* deletion and duplication in four Turkish families.

Material and Methods: To detect the duplication and deletion of *PLP1*, chromosomal microarray analysis, and multiplex ligation-related probe amplification assays were performed.

Results: In these four families, two brothers had a hemizygous deletion in the *PLP1* gene, their carrier mother had a deletion in the *PLP1* gene, and another two unrelated boys and one girl had duplication of the *PLP1*. Also, we identified the rare case of two brother patients who were found to have a hemizygous deletion in the *PLP1* gene. Their carrier mother had unexplained dementia.

Conclusion: Genotype-phenotype correlations of the *PLP1* mutation in these families were identified in this study while trying to elucidate the genetic etiology of six individuals from four different families.

Key Words: Dysmyelinating Disorders,Pelizaeus-Merzbacher Disease, *PLP1* Gene

ÖZ

Amaç: Pelizaeus-Merzbacher Hastalığı, Xq22 kromozomu üzerindeki proteolipid protein (PLP) genindeki bir mutasyonun neden olduğu X'e bağlı resesif nadir görülen bir lökodistrofidir. PMD, nistagmus, spastik kuadripleji, ataksi ve gelişimsel gecikme ile karakterize erken başlangıçlı bir nörolojik bozukluktur. Genetik analiz, Pelizaeus-Merzbacher Hastalığında PLP genlerinin kodlama bölgesinde Xq22 mikroduplikasyonlarını (%60-70), nokta mutasyonlarını (%10-25) ve delesyonları (%5-10) tanımlamıştır. Bu çalışma, dört Türk ailede *PLP1* delesyonu ve duplikasyonu olan altı hastayı değerlendirdi.

Gereç ve Yöntemler: *PLP1*'in duplikasyonu ve delesyonunu saptamak için kromozomal mikroarray analizi ve multipleks ligasyona bağlı prob amplifikasyon deneyleri yapıldı.

Bulgular: Bu dört ailede, iki erkek kardeşte *PLP1* geninde hemizigot delesyonu, taşıyıcı annelerinde *PLP1* geninde delesyon ve akraba olmayan diğer iki erkek ve bir kızda *PLP1* duplikasyonu vardı. Ayrıca, *PLP1* geninde hemizigot delesyona sahip olduğu tespit edilen iki erkek kardeş hastanın nadir vakasını belirledik. Taşıyıcı annelerinde açıklanamayan bunama vardı.

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

Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Kocaeli Derince Training and Research Hospital, Clinical Research Ethics Committee (Document Number: 2020-121/10.09.2020).

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

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Sonuç: Bu çalışmada, dört farklı aileden altı bireyin genetik etiyolojisi aydınlatılmaya çalışılırken, bu ailelerdeki *PLP1* mutasyonunun genotip-fenotip korelasyonları belirlendi.

Anahtar Sözcükler: Dismiyelinizan Hastalıklar, Pelizaeus-Merzbacher Hastalığı, *PLP1* Geni

INTRODUCTION

Pelizaeus-Merzbacher's disease (PMD, MIM 312080) is a rare disease due to X-linked recessive features and mutations in the *PLP1* gene on the Xq22 chromosome. It causes dysmyelination by affecting the Central Nervous System (CNS) (1). Identified as the chronic form of pediatric leukoencephalopathy, PMD is a failure of myelin metabolism and axonal myelination in oligodendrocytes (2). Several studies have reported point mutation, duplications, insertions, and deletions in the genetic material of patients with PMD. Approximately 60-70% of PMD duplication involving *PLP1* has been reported as the most common mutations in this disease (3). Harmful mutations are rare in this disease, and point mutations like splicing, missense, and nonsense have been detected in only 10-25% of patients. *PLP1* gene duplication is the most common reason for the impaired myelin construction of the CNS by producing a structural protein (4-6). *PLP1* is formed of seven exons encoding a major myelin protein in the CNS myelin. *PLP1* gene encodes two proteins *PLP1* and its isoform DM20. Both proteins are much more expressed by oligodendrocytes (2,4).

Delayed motor functions, with muscular hypotonia and nystagmus, are disorders often seen in PMD patients. Cognitive defects are determined in patients with PMD. Speech-related language development is affected, and most patients may receive language training if they have delays or significant language problems (7,8). Magnetic resonance imaging (MRI) of patients with PMD reveals a diffuse pattern of the CNS, including cerebral hemispheres, cerebellum, and brainstem(9). In this study, we performed chromosomal microarray analysis (CMA) and multiplex ligation-related probe amplification (MLPA) to examine a cohort of 6 patients with PMD and elucidate the relationship between their genotypes and phenotypes.

Clinical and genetic features of patients for the definitive diagnosis of this rare hereditary PMD disease that can contribute to genetic counseling and prenatal diagnosis in Türkiye were analyzed. We further delineate and expand the PLP-related genotype-phenotype correlations and phenotypic spectrum.

MATERIAL and METHODS

No pathological finding was determined in karyotype for all patients included in the study. Blood samples were obtained from the patients and parents, and genomic DNA was isolated from peripheral blood using the salting-out method.

PLP1 gene MLPA or chromosomal microarray analysis was performed. Furthermore, mothers were examined for genetic carriers of the *PLP1* gene.

Affymetryc Cytoscan Optima (312K) array was performed on patients 1, 4, and 6.

Multiplex Ligation-dependent Probe Amplification(MLPA) using the Pelizaeus Merzbacher Disease region of chromosome X confirmed the deletions and duplications within the *PLP1* gene for all patients.

The study was approved by Kocaeli Derince Training and Research Hospital, Clinical Research Ethics Committee (Document Number: 2020-121/10.09.2020).

MLPA analysis

The SALSA MLPA Probemix P022 *PLP1* kit (MRC Holland, Amsterdam, The Netherlands) was used to detect deletions or duplications in the *PLP1* gene and Xq22 region. MLPA was performed according to the manufacturer's recommendations. The SALSA MLPA Probemix P022-B2 *PLP1* contains 37 MLPA probes, seven for the *PLP1* gene, 20 for the Xq22.2 region, and ten reference probes. Complete probe sequences and the identity of the genes detected by the reference probes are available online (www.mlpa.com). MLPA data were analyzed with the Coffalyser software.

Chromosomal Microarray

All microarray procedures were performed using CytoScan Optima Array Kit (Thermo Fisher Scientific, MA, United States). Microarray data were analyzed with Chromosome Analysis Suite (ChAS) 4.3 from Affymetrix, using GRCh37/hg19 libraries.

Interpretation of copy number variants (CNVs)

Variants were classified as variants of unknown significance according to the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen) recommendation. CNVs were compared to variants reported in the Database of Genomic Variants (DGV, http://projects.tcag.ca/variation), Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources (DECIPHER, https://decipher.sanger.ac.uk), ClinVar and the in-house database at the Department of Medical Genetics, Haseki Education and Research Hospital.

RESULTS

Diagnosis of PMD was determined in 6 patients from 4 families. All individuals had nonconsanguineous parents.

PLP1 gene duplications were identified in 3 patients (patients 4,5 and 6), and *PLP1* gene deletions were observed in 3 patients (family 1).

In the first family, two affected siblings with *PLP1* hemizygous deletion, and their mother had a deletion of the *PLP1* gene of exons 2 through 8 (Figure 1). Patient 1, a two years old boy with

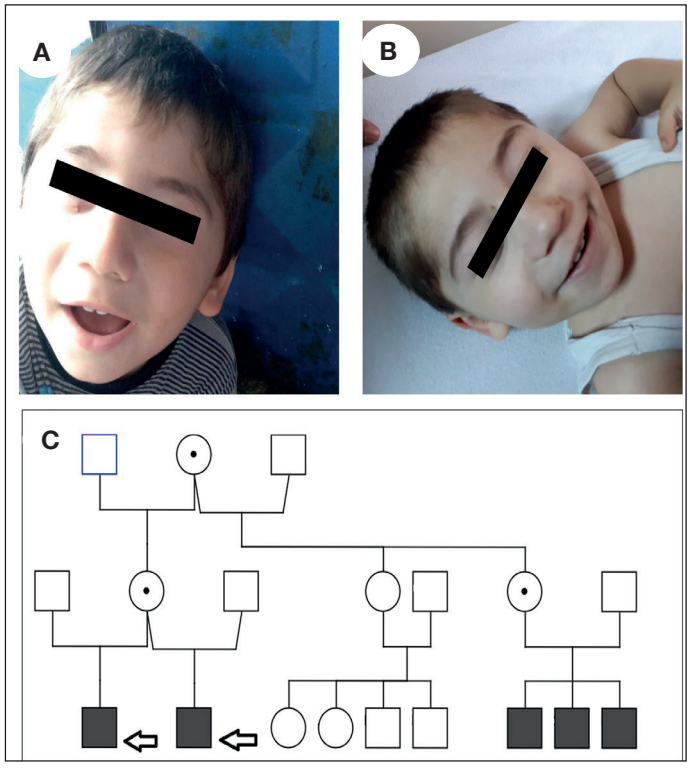

Figure 1: Photographs of patients and pedigree of the first family **a.** Photograph of the patient **b.** Photograph of the patient **c.** Pedigree of the first family.

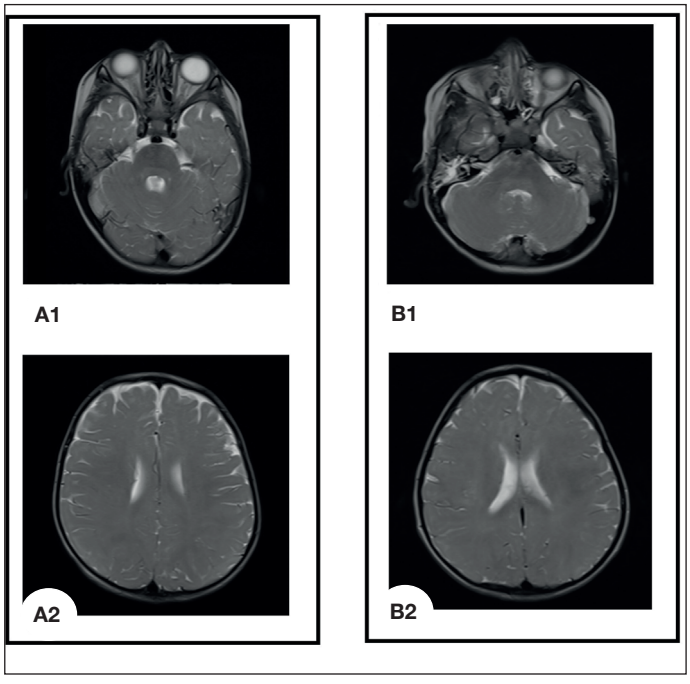

Figure 2: a.1 and b.1) Hyperintense, consistent with hypomyelination in the dorsal brain stem in axial T2W sequence

a.2 and b.2) Hyperintensity consistent with diffuse hypomyelination in the white matter in the centrum semiovale plane in the axial T2W image

hypotonia, developmental delay, and nystagmus, was referred for evaluation. The index patient was the first child of the mother. He was born at term by cesarean section, and his birth weight was 3400 gr. Height and occipitofrontal circumference

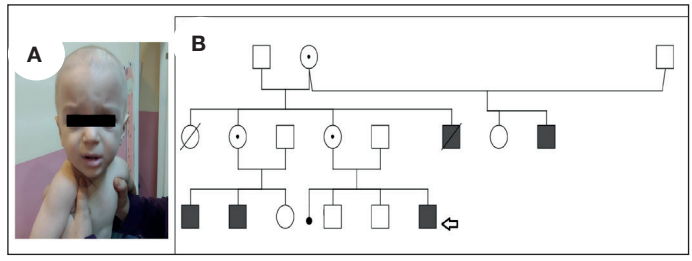

Figure 3: Photograph of the patient and pedigree of the second family **a)** Photograph of the patient **b)** Pedigree of the second family.

(OFC) was not recorded. Child-related measurements were as follows: weight was 10 kg (<3 percentile), and length was 80 cm (<3 percentile). He was unable to walk or talk and lacks head control.

Patient 2, the big brother of our index patient, was a four-year old boy with a severe developmental delay. He was unable to sit, walk or talk. His weight was 12 kg (10 percentile), his length is 85 cm (<3 percentile), and his OFC is 46 cm(<3 percentile) (Figure 1).

Consequently, they showed severe psychomotor developmental delay and hypotonia.

Patient 3 is the mother of patients 1 and 2. The mother, who was 30 years old, had mild intellectual disability. Brain MRI could not be carried out. Physical examination was normal, and no nystagmus (Figure 2).

In the second family, patient 4 demonstrated a duplication of the *PLP1* gene of exons 2 through 8. The mother of patient 4 had carriers of *PLP1* duplication and had a resting tremor (Figure 3). Patient 4, a one-year-old boy, was evaluated for nystagmus, vomiting, and severe developmental delay. He was born as the third child of nonconsanguineous parents at the 38th gestational week at a birth weight of 3200 gr. Immediately after birth, because of Meconium Aspiration Syndrome (MAS), he was referred to the neonatal intensive care unit. Birth height and OFC were not recorded. At the time of examination, his weight was 6700 gr (<3p), his body length was 72 cm (3-10p), and OFC was 46.5 cm (25-50p). The patient had hypotonia, and at 8 months of age, he couldn't manage head control. Brain MRI findings were normal.

In the third family, duplication of the *PLP1* gene was detected by MLPA analysis of patient 5. He weighted 8.5 kg at 25 months of age (<3p) and was 80 cm (<3p) in height, and head circumference was not recorded. Physical examination revealed spastic quadriplegia, bilateral nystagmus, and cachectic findings, and the patient was unable to talk, walk or even hold his neck. Hypotonia and severe developmental delay were observed. Brain MRI could not be carried out. The patient's older brother had *PLP1* duplication. Additionally, his mother was heterozygous for the same duplication and showed no PMD symptoms.

The patient's uncle and older brother were reported to have the same clinical findings. However, we could not carry out their examination and neuroimaging (Figure 4).

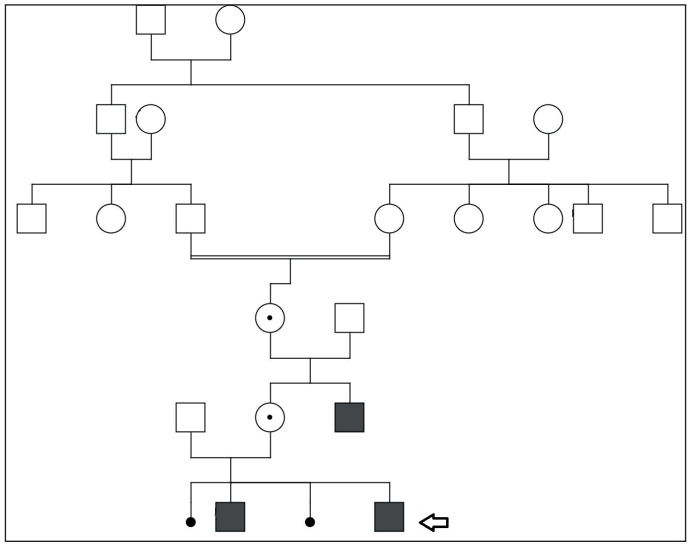

Figure 4: Pedigree of the third family.

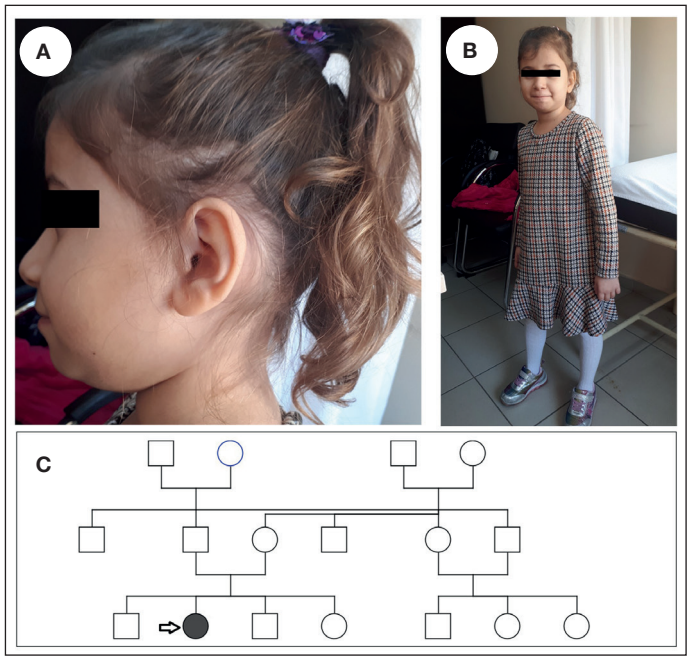

Figure 5: Photograph of the patient and pedigree of the fourth family **a and b)** Photograph of the patient **c)** Pedigree of the fourth family.

In the fourth family, patient 6 showed duplication of the *PLP1* gene of exons 2 through 8. Her mother was negative for the PLP duplication by MLPA analyses, suggesting that the duplication occurred as a de novo event (Figure 5). However, all other patients' mothers were carriers (Table I).

We detected *PLP1* gene deletions in half of the patients. The other half of the patients had *PLP1* gene duplication. Additionally, while 83% of the patients had a maternal inheritance, one patient had de novo duplication.

The most common finding determined in all patients was intellectual disability or global developmental retardation and developmental delay. While male patients had severe mental motor retardation and developmental delay, female patients had mild intellectual disability or developmental delay (Table II).

The female patients mentioned in the article had learning difficulties and comprehension difficulties. Patient 6 has had fine motor development disorders and did not learn to read and write. Along with these findings, patient 3 had dementia findings. However, in other male patients, hypotonia and severe developmental delay were observed.

DISCUSSION

We here reported two brothers with a hemizygous deletion in the *PLP1* gene, their carrier mother with a deletion in the *PLP1* gene, and another two boys and one girl with a duplication of the *PLP1* from four families in total. The clinical symptoms of the four male patients in this study included a lack of stable head control and severe mental motor retardation, and the other two female patients had mild mental retardation. Male patients of the *PLP1* with deletions and duplications had more severe mental motor retardation than female patients. Consistent with the literature, we did not find any significant difference in clinical signs between *PLP1* with deletions and duplications of the male patients.

An uncommon X-linked recessive central nervous system disease with neonatal neurological deficits, including hypomyelination features, is called PMD (MIM 312080). Significant pendular nystagmus, tremors, spasticity, and generalized hypotonia, which develop into a motor developmental delay in early infancy, are the clinical manifestations of this syndrome (10). Developmental and psychomotor delay, ataxia, microcephaly, hearing disorders, the rotary motion of the head, dysmyelination of the CNS, and spasticity are the common features in patients with PMD (11,12). We described six patients with PMD from four different families. The male patients of *PLP1* deletion were severe intellectual disability or global developmental delays and lacked head control. These patients had severe developmental delay, generalized hypotonia, spasticity, bilateral nystagmus, dysarthria, dysphagia, spastic quadriplegia, and were cachectic.

Mutations in the *PLP1* (proteolipid protein 1) gene encoding the isoform DM20, which is attached to the proteolipid protein and oligodendrocytes, the two major myelin proteins in the CNS, are the main cause of the PMD disease that belongs to the series of HLDs (hypomyelination leukodystrophy) (13).

The process of abnormal CNS myelination occurs due to point mutations and proliferation in the *PLP1* gene, causing Pelizaeus-Merzbacher's disease (PMD; MIM 312080). It can progress to spastic paraplegia (SPG2; MIM 312920) which is a type of X-linked HLD. *PLP1* deletions are much less common than duplications. Consistent with the literature, a complete genotype-phenotype correlation cannot be established in our patients either.

Table I: Genomic finding in six patients with Pelizaeus Merzbacher Disease.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
MLPA	*PLP1* exon2-8 hemizygous deletion	*PLP1* exon2-8 hemizygous deletion	*PLP1* exon2-8 heterozygous deletion	*PLP1* exon2-8 hemizygous duplication	*PLP1* exon2-8 hemizygous duplication	*PLP1* exon2-8 duplication
Microarray analysis	arr[hg19] Xq22.2(102995019-103162012)x0	NA	NA	arr[hg19] Xq22.2(102643610-103305273) x2	NA	arr[hg19] Xq22.1q23(100,213,231-109,412,333)x3
Deletion/ duplication	167 kb deletion	NA	NA	662 kb duplication	NA	9,199 kb duplication
Origin	Maternal	Maternal	Maternal	Maternal	Maternal	De novo

Table II: Clinical findings in six patients with Pelizaeus Merzbacher Disease.

Family Patient	Family 1			Family 2	Family 3	Family 4
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age at examination/ Gender	2y/M	4y/M	30y/F	1y/M	2y/M	11y/F
Consanguinity	-	-	-	-	-	-
Psychomotor development						
Develepmontel delay	Severe develepmontel delay	Severe develepmontel delay	NA	+	Severe develepmontel delay	Mild mental retardation
Mental motor retardation	Severe mental motor retardation	Severe mental motor retardation	Mild mental retardation	Severe mental motor retardation	Severe mental motor retardation	Mild mental retardation
Head control, Sitting and Walking	-	-	+	-	-	+
Growth retardation	+	+	-	-	+	+
Hypotonia/ Bedridden	+	+	-	+	+	-
Seizures	-	-	-	-	-	-
Nystagmus	+	+	-	+	+	-
Other symptoms	Spastic quadriplegia, and cachectic	Spastic quadriplegia, and cachectic	Dementia	Meconium Aspiration Syndrome (MAS)	Spastic quadriplegia, and cachectic	Frequent falls
MRI findings	Diffuse hypomyelination	Diffuse hypomyelination	NA	Normal	NA	At one year of age, thin corpus callosum. 10 years were normal
Clinical findings in the mother	Dementia	Dementia	Dementia	-	-	-

The *PLP1*-null syndrome is a relatively mild neurology syndrome that is also graduated as a mild form of PMD, caused by other *PLP1* null mutations and complete deletion of *PLP1* (4,11,15-17).

HLDs, which are PLP-related disorders, can affect males, while the phenotypes may cause diseases ranging from mild hereditary spastic paraplegia to severe forms of type 2 PMD (SPG2) (15). *PLP1* missense mutations constituting the most severe form of PMD (connatal form) are *PLP1*-related disorders, and the most common types of PMD duplications are SPG2 and classical PMD (1,14).

Considering the affected siblings, it was apparent that the absence of hyperreflexia and subtle eye-movement abnormalities of the surrogate carrier mother indicates a familial form of PMD. However, progressive leukodystrophy with dementia may develop in the later life of carrier females with point mutation or deletion that may cause late-onset spastic paraplegia phenotype of variable severity. The mother of our patients 1 and 2 had unexplained dementia, and she was the carrier of *PLP1* deletion. Patient 6 had *PLP1* duplication. She exhibited a delay in all motor developmental milestones and had a history of frequent falls and an awkward gait. She had been going to primary school with personal assistance help. There was no nystagmus and no history of seizures. However, their short and long-term memory was impaired.

Sixty to seventy percent of PMD patients have complete replication of the *PLP1* gene on Xq22. PLP duplications prevent regular myelination resulting in an increased dose of *PLP1*. An increased dose of *PLP1* is related to the classic form of the disease, but patients may have phenotypes ranging from severe connatal to mild PMD. The disease is usually asymptomatic even if *PLP1* duplication exists in carrier females (18). Similarly, the mother of patient 5 had *PLP1* duplication and was asymptomatic. On the other hand, patient 3's carrier mother who had a deletion in the *PLP1* had unexplained dementia. In this case, genetic tests play an important role in the diagnosis of the disease. Also, patient 6 had duplication in the *PLP1* with mild mental motor retardation, developmental delay, and frequent fall.

CMA is the first-line test for individuals with developmental delays (19-21). Microarray analysis, the increased detection rate of chromosomal imbalances in the human genome, has allowed the diagnosis of syndromic phenotypes with previously unknown etiologies. CMA detects microdeletion and microduplication syndrome in this group with a diagnostic yield (22). Microarray-based screening analysis results of patients with undiagnosed neurologic disease revealed the potential use of this method in providing a diagnosis for these patients.

CONCLUSION

Although PMD is a neurological disorder, it has no specific pathognomonic clinical features. In these cases, the importance of genetic evaluation to achieve a final diagnosis is emphasized since there are no specific clinical findings. Diagnosis and recognition of these neurological diseases are essential for appropriate genetic counseling and disease prognosis. Further research is needed to explain the pathophysiological mechanism of PMD. In this way, treatment methods can be developed.

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Outcomes of Video-Assisted Thoracoscopic Decortication in Pleural Empyema in Children

Çocuklarda Plevral Ampiyemde Video Yardımlı Torakoskopik Dekortikasyonun Sonuçları

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ABSTRACT

Objective: The aim of this study is to determine efficacy, safety, and feasibility of video-assisted thoracoscopic surgery (VATS) in childhood empyema with two port technique.

Material and Methods: 34 patients under 17 years of age were included to the study. Demographic and clinical data of the patients were recorded retrospectively

Results: 34 patients under 17 years of age were included in the study. The first time the complaints started was 12 days. VATS was performed on mean 12 (2-46) days after the complaints of the patients started. The empyemas were in right hemithorax in 21 children and left in 11. Two patients underwent bilateral decortication Mean of chest tube removal time was 9.70 (2-26) days. While the postoperative stay was 23.50 (4-120) days, the total hospital stay was 32.50 (7-142) days. Emphysema developed in 7 patients in the following period. Chest tube revision was performed in a patient. Emphysema spontaneously regressed at follow-up in 6 patients. Two children died from non-thoracoscopy reasons after respiratory arrest and liver transplantation.

Conclusion: VATS is a feasible method with good results pleural empyema in children. The results are satisfactory in the early or late period of disease.

Key Words: Child, Empyema, Surgery, Thoracoscopic, VATS

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Contribution of the Authors / Yazarların katkısı*: *ATEŞ U: 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 the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***ERGÜN E:*** Constructing the hypothesis or idea of research and/or article, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, , Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study.***QURBANOV A:*** Planning methodology to reach the Conclusions, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Reviewing the article before submission scientifically besides spelling and grammar. ***KHALILOVA P:*** Planning methodology to reach the Conclusions, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***SÖZDUYAR S:*** Constructing the hypothesis or idea of research and/or article, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study. ***ÇİFTCİ E:*** Constructing the hypothesis or idea of research and/or article, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Reviewing the article before submission scientifically besides spelling and grammar. ***ÖZDEMİR H:*** 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, Reviewing the article before submission scientifically besides spelling and grammar. ***ARGA G:*** 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. ***KONCA HK:*** Constructing the hypothesis or idea of research and/or article, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in the writing of the whole or important parts of the study. ***GÜN E:*** Constructing the hypothesis or idea of research and/or article, Taking responsibility in logical interpretation and conclusion of the results, Reviewing the article before submission scientifically besides spelling and grammar. 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ÖZ

Amaç: Bu çalışmanın amacı, çocukluk çağı ampiyeminde iki port tekniği ile video yardımlı torakoskopik cerrahinin (VATS) etkinlik, güvenlik ve uygulanabilirliğini belirlemektir.

Gereç ve Yöntemler: Çalışmaya 17 yaş altı 34 hasta dahil edildi. Hastaların demografik ve klinik verileri geriye dönük olarak kaydedildi.

Bulgular: Çalışmaya 17 yaş altı 34 hasta dahil edildi. Şikayetlerin ilk başladığı gün 12 gündü. Hastaların şikayetleri başladıktan ortalama 12 (2-46) gün sonra VATS uygulandı. Ampiyem 21 çocukta sağ hemitoraksta, 11 çocukta sol taraftaydı. İki hastaya bilateral dekortikasyon uygulandı. Drenaj için takılan göğüs tüpünün çıkarılma süresi ortalama 9.70 (2-26) gündü. Ameliyat sonrası kalış süresi 23.50 (4-120) gün iken, toplam hastanede kalış süresi 32.50 (7-142) gündü. Takipler sırasında 7 hastada amfizem gelişti. Bir hastaya göğüs tüpü revizyonu yapıldı. 6 hastada spontan geriledi. İki çocuk solunum arresti ve karaciğer nakli sonrası torakoskopi dışı nedenlerden exitus oldu.

Sonuç: VATS, çocuklarda plevral ampiyemde sonuçları iyi olan, uygulanabilir bir yöntemdir. Sonuçlar hastalığın erken veya geç döneminde tatmin edicidir.

Anahtar Sözcükler: Çocuk, Ampiyem, Cerrahi, Torakoskopik, VATS

INTRODUCTION

Pleural empyema is defined as purulent fluid accumulation in the pleural cavity. Common conditions associated with this disease include pneumonic processes in patients with pulmonary and malignant diseases, heart disease, diabetes mellitus, drug and alcohol abuse, neurological disorders, post-thoracotomy problems, and immunological disorders (1). Nowadays, thoracic empyema occurs in 1 of 150 children hospitalized with pneumonia (1).

Treatment methods include parenteral antibiotics, intrapleural fibrinolytic injections (streptokinase), video assisted thoracoscopic surgery (VATS) and open thoracotomy.

Empyema is characterized by three stages (1). Treatment varies by stage. Stage 1: exudative stage, parapneumonic effusion developing in the first 24-72 hours. Treatment with intravenous antibiotics and simple thoracentesis is preferred. Stage 2: fibrinopurulent stage lasts 7-10 days. The third stage, or organized stage, occurs 2-4 weeks after the first symptom. Thickening of the visceral and parietal pleura is characterized by cavities composed of fibrins extending into the lung parenchyma. In the 2nd and 3rd stages, additional thoracoscopy or thoracotomy is preferred.

Early parenteral antibiotic therapy may be sufficient for some cases and intervention may not be needed (2 for those who fail to respond, an open thoracotomy and formal decortication. Since the 1990s two new treatment modalities have been described; fibrinolysis (promoting pleural drainage and circulation). But it is controversial whether perform VATS or fibrinolytic injection in resistant cases (2 for those who fail to respond, an open thoracotomy and formal decortication. Since the 1990s two new treatment modalities have been described; fibrinolysis (promoting pleural drainage and circulation). In authors center VATS is the method of choice since it was recommended as the gold Standard approach by American Association of Thoracic Surgeons in 2017 (shenguideline).

Most cases respond to antibiotic therapy and intercostals drainage in earlier stages; however, in majority of cases surgical management is required due to delayed presentations, multiresistant strains, delayed diagnosis, poor compliance with medication at early stages of the disease. A meta-analysis performed regarding management of paediatric empyema thoracis has shown that primary operative therapy is associated with lesser mortality, decreased hospital stay, shorter duration of antibiotic therapy and less chances of reintervention (3,4) decortication is usually preferred to ensure functional lung re-expansion. However, there could be patients exhibiting incomplete postoperative lung expansion and inadequate drainage despite decortication. Therefore, we evaluated factors affecting postoperative lung expansion in patients undergoing decortication. Methods A total of 221 patients with pyogenic empyema who underwent video-assisted thoracoscopic surgery (VATS).

In this study, it was aimed to present the results of VATS procedures in children who admitted to the clinic with empyema at different stages.

MATERIAL and METHODS

This study was approved by Ankara University Human Research Ethics Committee (Approval no: İ6-369-20).

34 patients under 17 years of age were included to the study. Age, gender, weight, time between onset of symptoms and hospital apply, stage of disease accompanying diseases, hospital stays and perioperative complications are analyzed retrospectively. The patients were classified according to the results of computed tomography and clinical complaints. It was investigated whether interventional procedures such as chest tube insertion and thoracentesis were performed before VATS. Reoperation and mortality were also taken into consideration.

General anesthesia was performed in all cases. The patient was positioned in lateral decubitis while appropriate side up. One camera port and one access port were used. For this, usually the 4th, 5th or 6th intercostal spaces; anterior, middle and posterior axillary lines were preferred. Decortication and aspiration were performed with generally blunt dissections and fibrins were excised. A chest tube was inserted (Figure 1).

Patients were extubated in the operating room and controlled with postoperative chest radiographs in early postoperative period. Early mobilization was recommended. Intravenous antibiotics were continued. Tube removal was planned when

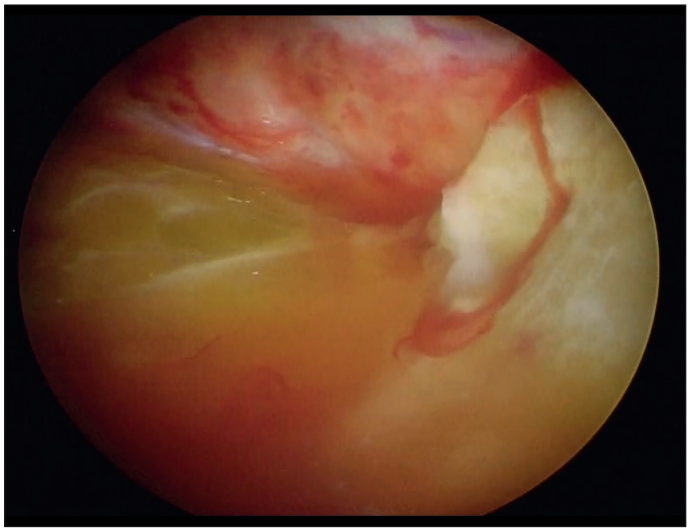

Figure 1: Intraoperative image

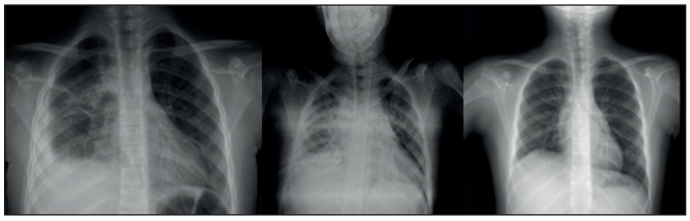

Figure 2: Preoperative, postoperative first and last X-ray images

there was no air leak and/or incoming fluid (Figure 2).

The patients were discharged after the decision taken after the children were evaluated by surgery, infectious diseases and pulmonology departments and recommended a visit with a chest X-ray at postoperative first week.

Results were expressed at mean values 6 SEM. Student's t test for paired data was used for quantitative variables and either x2 or Fisher's test for qualitative variables. Statistical significance was determined at p less than 0.050.

RESULTS

34 patients under 17 years of age were included in the study. Ten of them were women and 24 were men. Their average age was 67.38 (8-210) months, and their average body weight was 25 (8-90) kg. When the staging was examined, it was observed that six patients were stage 2 and 28 patients were stage 3. Left-sided empyema was found in 11 children, while 21 children had right-sided empyema. Bilateral empyema was observed in 2 patients. In these patients, bilateral decortication was performed in the same session. Two children underwent contralateral VATS after 2.5 months of the first operation. The first time the complaints started was 12 days. Additional disease was observed in ten patients (glaucoma, ADEM, inguinal hernia, AML, pineal dysgerminoma, immunodeficiency, PFIC 2, Down syndrome, polyneuropathy, splenectomy). VATS was performed on mean 12 (2-46) days after the complaints of the patients started. Chest tube was placed in 11 patients before VATS in emergency situations in other centers. Mean of chest tube removal time was 9.70 (2-26) days. While the postoperative stay was 23.50 (4-120) days, the total hospital stay was 32.50 (7-142) days. The intraoperative pleural culture of nine patients were tested positive for *Streptococcus pneumoniae* (n=6), *Acinetobacter baumanii* (n=1), *Bacillus spp* (n=1), *Pseudomonas aeruginosa* (n=1). Emphysema developed in 7 patients in the following period. Chest tube revision was performed in a patient. Emphysema regressed at follow-up in 6 patients. Two children died from non-thoracoscopy reasons after respiratory arrest and liver transplantation. There were no complications related to surgery in the postoperative period. The first patient died 3 months later, the second patient 1 year later. Detailed data are shown in Table I.

Table I: Patient details classified by stage

Stage	Stage 2	Stage 3
Patients (n)	6	28
Age (month)	116	57
Weight (kg)	35	22.8
Sex (F/M)	1/6	9/19
Side (R/L/Bilateral)	4/2/0	17/9/2
Thoracentesis/chest tube before VATS (days)	6/9	2/2
Chest tube removal after VATS (days)	5.5	10.6
Comorbidite	2	8
Hospital stay (days)	24.6	34.1
Complications	0	7
Exitus	1	1

DISCUSSION

As a result of VATS performed on 34 patients with stage 2 and stage 3 empyema, a cure rate of 94% was observed.

Over time, VATS has become more common treatment for children with pleural empyema (4). Although it was more preferred in stage 3 patients before, it has now began to performed in lower stages more and more (6,7). Besides the less invasive nature of VATS, the shorter hospital stay and fewer postoperative complications are among the reasons for preference rather than thoracotomy (1,6–10).

In terms of surgical technique and convenience, VATS is safe and effective in the treatment of complicated parapneumonic effusion and pleural empyema (8). VATS has been shown to be a feasible option if there is sufficient surgical equipment and experience (8).

One of the other commonly used treatment options is fibrinolytic therapy. Although the invasiveness of fibrinolytic therapy is low, there are sources showing that the results do not differ significantly, and that VATS is a safer option (9). There

are also studies supporting the opposite (10). However, it has been reported that fibrinolytic therapy will be of limited value in patients with multiloculated parapneumonic effusion or empyema, and that fibrinolytic agents have side effects such as anaphylaxis, bleeding, and pulmonary edema (11). In our study, these complications were not observed in patients who underwent VATS as expected.

Leily Mohajerzadeh et al. (1) showed that based on a comparison of the advantages and disadvantages of thoracotomy and VATS for the treatment of empyema, it seems that the less invasive VATS technique is suitable for the management of pediatric patients with empyema, since it was associated with a shorter hospital stay, a lower rate of postoperative complications, and less bleeding during the operation. It is very important to pay attention to maintain psychological balance when working with pediatric patients. As Rodriguez et al. (12) presented, thoracoscopic surgery creates less psychological and physical trauma in children compared to thoracotomy. The cosmetic aspect of the surgery also gives better results. Avoiding thoracotomy allows the child to be nearly scar free with only two or at most three five millimeters port scars (12,13). This cosmetic success may also prevent the physicological damage to the growing child.

Although VATS was performed mostly in advanced stage of empyema patients in the past, recent studies have proved that VATS may be even more beneficial in the early stage of the disease (7,8,12). Velauitham et al. (7) demonstrated in a 24-patient study that early primary VATS therapy as a first-line intervention for pediatric empyema can be safely implemented with lower morbidity, lower intervention rate, improved outcome, and shorter hospitalization. The fact that none of the 6 patients with stage 2 in our study developed complications in the postoperative period supports this finding.

Retrospective collection of data and relatively small number of cases were among few limitations of the study. Also lack of a control group which includes children that undergo fibrinolytic therapy is another one. It was aimed to minimize this limitation by comparing our data to the literature on fibrinolytic therapy.

CONCLUSION

In conclusion, VATS seems to be a feasible method with good results in children with pleural empyema. Randomized prospective studies with larger amount of patients on treatment options and also timing of the intervention may be beneficial for further comments.

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Efficacy of Cefoperazone-Sulbactam as Empirical Monotherapy Therapy for Febrile Neutropenia in Children with Solid Tumors and Lymphomas

Lenfoma ve Solid Tümörlü Çocuklarda Febril Nötropenide Sefaperazon-Sulbaktam Monoterapisinin Etkinliği

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ABSTRACT

Objective: Monotherapy with a beta lactam or a cephalosporin has become the standard of care for the treatment of febrile neutropenia (FEN). We aimed to evaluate the efficacy of cefoperazone/sulbactam (CS) as empirical monotherapy for febrile neutropenia in children with solid tumors and lymphomas.

Material and Methods: Children with FEN received cefaperazone-sulbactam (80 mg/kg/day, every 8 hours). Treatment responses (a) successful, complete resolution of all signs and symptoms of infection at 72 hours and after 7 days of CS treatment; (b) success with modification, change of therapy for viral, parasitic or fungal infection or addition of glycopeptides; (c) failure was defined as the emergence of a new or resistant infection, treatment-resistant bacteremia, the need to switch to carbapenems.

Results: Our study included 157 patients and 350 febrile neutropenia episodes. The most common diagnoses were osteosarcoma (35%), Ewing sarcoma (30%), non-hodgkin lymphoma (13%) and rhabdomyosarcoma (9%), respectively. The origin of fever could not be determined in 223 (64%) of FEN episodes, 79 (22%) had microbiologically documented infection (MDI), and 48 (14%) had clinically documented infection (CDI). The success rate was 65% (229), the success rate with modification was 9% (31) and the failure rate was 26% (90). SC monotherapy was successful in 33% of attacks with MDI and in 60% of attacks with CDI. However, SC monotherapy was successful in 82% of febrile episodes of unknown origin.

Conclusion: Cefoperazone/sulbactam is effective and safe in febrile neutropenic children with solid tumors and lymphomas for monotherapy.

Key Words: Cancer, Cefoperazone, Child, Febrile neutropenia, Sulbactam

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ÖZ

Amaç: Febril nötropeninin tedavisinde beta laktam veya bir sefalosporin ile monoterapi, standart haline gelmiştir. Bu çalışmada solid tümörlü ve lenfomalı çocuklarda febril nötropeninin ampirik tedavisi olarak sefoperazon/sulbaktamın (SS) etkinliğini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Febril nötropenik çocuk hastalara sefaperazon-sulbaktam (80 mg / kg / gün, 8 saatte bir) başlandı. Tedavi yanıtları (a) başarılı, 72. saatte ve 7 günlük SS tedavisinden sonra enfeksiyonun tüm belirti ve semptomlarının tamamen düzelmesi; (b) modifikasyon ile başarılı, viral, parazitik veya mantar enfeksiyonu için tedavi değişikliği veya glikopeptid ilavesi; (c) başarısızlık, yeni veya dirençli bir enfeksiyonun ortaya çıkması, tedaviye dirençli bakteriyemi, karbapenemlere geçme veya aynı spektrumda bir antibiyotik ekleme ihtiyacı olarak tanımlandı.

Bulgular: Yüz elli yedi hastaya ait 350 febril nötropeni atağı (K: 73, E: 84, ortanca yaş: 11.8 yıl (0.6-18)) kaydedildi. En sık tanılar sırasıyla osteosarkom (%35), Ewing sarkomu (%30), non-hodgkin lenfoma (%13) ve rabdomyosarkomdu (%9). Ortanca mutlak nötrofil sayısı 60/mm^3 (0-800) ve nötropeni süresi 7 gün (3-60)'dı. Ortanca tedavi süresi 7 gündü (3-30). FEN ataklarının 223'ünde (%64) ateşin kaynağı tespit edilemedi, 79'unda (%22) mikrobiyolojik dokümante enfeksiyon (MDE) vardı ve 48'inde (%14) klinik dokümante enfeksiyon mevcuttu (KDE). Başarı oranı %65 (229), modifikasyon ile başarı oranı % 9 (31) ve başarısızlık oranı %26 (90)'dı. Sefoperazon/sulbaktam monoterapisi MDE olan atakların %33'ünde, KDE olan atakların %60'ında başarılı oldu. Ancak SS monoterapisi nedeni bilinmeyen ateşli atakların %82'sinde başarılı oldu.

Sonuç: Sefoperazon/sulbaktam, solid tümör ve lenfomalı çocuklarda nötropenik ateşin tedavisinde monoterapi olarak etkili ve güvenlidir.

Anahtar Sözcükler: Kanser, Sefoperazon, Çocuk, Febril nötropeni, Sulbaktam

INTRODUCTION

Fever is a common sign of an infection in neutropenic patients in pediatric oncology. If left without treatment, destructive complications of bacterial sepsis may occur. Therefore, febrile neutropenia (FEN) should be treated as a medical emergency (1).

An optimal initial antibiotic treatment should have a wide spectrum including but not restricted to Pseudomonas, be bactericidal, have low potential of side effects and the treatment options should be based on the microbiological data of the centers (1,2).

In earlier years, combination therapies in FEN were accepted as standard treatment method because of their antimicrobial synergy to gram-negative bacteria and decreased resistance. Mostly preferred combination regimen was wide-spectrum β-lactam antibiotic and amikacin (3-5). However, after the development of 3rd and 4th generation cephalosporins such as ceftazidime, cefepime and carbapenems, monotherapy has proven to be safe to use in FEN (3,6). Antibiotic monotherapy has attractive aspects such as easy administration, low cost, reduced toxicity especially due to aminoglycosides (1). Another option for empirical treatment of infections in FEN is β-lactam/β-lactamase inhibitor combinations. They have a broad spectrum including both gram-negative and gram-positive bacteria and also prevent resistance to β-lactam alone (7). Sulbactam is a molecule given in combination with β-lactam antibiotics to eliminate the effects of β-lactamase. By the addition of sulbactam to cefoperazone, a third- generation cephalosporin with a restricted effect on gram-negative bacteria, it broadens its spectrum of action (8,9). In this retrospective study, we aimed to assess the efficacy of cefoperazone-sulbactam (CS) as empirical monotherapy for FEN in pediatric cancer patients with solid tumors.

MATERIALS and METHODS

We reviewed the medical records of pediatric cancer patients that experienced episodes of febrile neutropenia between October 2004 and August 2016. Children with neutropenic fever (age ≤ 18years) hospitalized at Ankara Oncology Hospital for lymphomas and solid tumors were included in the study. Informed written consent was obtained from all patients. Fever was defined as either a single axillary temperature of ≥ 38°C or sustained temperature over 1 hr. of ≥ 37.5°C. Neutropenia was defined as an absolute neutrophil count (ANC)≤ 500 cells/mm^3 or an ANC with expected fall to ≤500 cells/mm^3 within 48 hr (2).

Informed consent was obtained from all enrolled patients and study was approved by the ethics committee at Ankara City Hospital and carried out by the Declaration of Helsinki principles and all applicable regulations (E2-21-604).

Evaluation before treatment

After a detailed medical history and complete physical examination, at least two venous blood cultures (both peripheral vein and central venous catheter (CVC) if present), urine culture and culture from any suspected local sites were obtained. Blood samples were collected for complete blood count, liver and kidney function tests, and urine analysis was also done. A chest X-ray was performed for patients whom presented with respiratory symptoms. The remission status, white blood cell count, the absolute neutrophil count (ANC), duration of neutropenia, number of febrile days, granulocyte-colony stimulating factor use were recorded.

Classification of febrile neutropenia episodes

The FEN episodes were divided into three groups as clinically documented infection (CDI), microbiologically documented infection (MDI) or fever of unknown origin (FUO). Clinically documented infection was described when there was a focus of infection on physical examination without a pathogen documented. Microbiologically documented infection was described as the documentation of a microorganism. Fever of

unknown origin was described when there was no clinical or microbiologic sign of infection in a FEN episode.

Antibacterial treatment

Empirical CS 80 mg/kg/day was promptly initiated to all patients in three divided doses. All patients were hospitalized. Patients were monitored daily until being afebrile and ANC ≥500 cells/mm^3. If fever persisted >38.0°C at 72 hours of treatment with no documented microorganism or the patient deteriorated, treatment was switched to carbapenems and glycopeptides were added. If a resistant bacterium was detected and the patient had no clinical improvement, antibiotherapy was planned according to antibiogram results. If fever persisted on the 5-7th day of the FEN episode, liposomal amphotericin-B at 3 mg/kg/dose was added. Treatment continued if fever disappeared or the patient clinically improved despite fever, no infectious agent was detected and neutropenia started to recover. If the patients improved clinically, treatment was discontinued after 5 days without fever, even if they were still neutropenic.

Evaluation of the Treatment

Treatment responses were defined as (a) successful treatment, complete resolution of all signs and symptoms of infection at 72 h and after 7 days of treatment with CS; (b) successful with modification, the need for treatment change for a viral, parasitic or fungal infection, or addition of glycopeptide; or (c) failure, emergence of a new infection, a resistant microorganism, therapy resistant bacteremia, the need to switch to carbapenems or add an antibiotic with the same spectrum.

Statistical analysis

Data were analyzed with IBM SPSS V23. Compliance with normal distribution was examined by Kolmogorov-Smirnov test. Mann-Whitney U test was used to compare quantitative variables that were not normally distributed according to groups. Analysis results are median for quantitative data. Categorical data were presented as frequency and percentage, with deviation and median (minimum - maximum). p-values of < 0.050 were defined as significant.

RESULTS

Patient Characteristics

From October 2004 to August 2016, a total of 350 FEN episodes were recorded in 157 (73 female, 84 male) pediatric cancer patients. The median age was 11.8 years (0.6-18). Median absolute neutrophil count and duration of neutropenia were 60/mm^3 (0–800) and 7 days (3–60). The median time of antibiotherapy was 7 days (3-30). Underlying diagnoses were osteosarcoma (35%), Ewing's sarcoma (30%), non-hodgkin lymphoma (NHL) (14%) rhabdomyosarcoma (9%) and other (12%) (Table I).

Characteristics of febrile episodes

Of the 350 episodes, 113 (32%) were during induction therapy, 114 33%) were during partial remission, 87 (25%) were during the treatment for relapsed disease, and the remaining 36 (10%) were during remission treatment. Prophylactic antibiotics were not administered to any patient.

Table I: Characteristics of Patients and Febrile Neutropenia Episodes

Total number of episodes Total number of patients	Cefoperazone-sulbactam (n:350) (n:157)
Age (years)	
Range	0.6-18
Median	11.8
Sex*	
Male	73 (54)
Female	84 (46)
Primary disease*	
Osteosarcoma	55 (35)
Ewing's Sarcoma	47 (30)
NHL	22 (14)
RMS	14 (9)
Other	19 (12)
Neutrophil [count cells/mm^3*	
Range	0-800
<100	164 (47)
100-500	102 (29)
>500	8 (2)
Unknown	76 (22)
WBC(×10^9/L)†	450 (0-2600)
Remission status*	
In remission	36 (10)
Not in remission	314 (90)
Grade 3-4 mucositis	41 (12)
GCSF use	289 (82)
Central venous catheter	
Yes	164 (47)
No	186 (53)

** n (%), †median (min.–max.)*

The origin of fever could not be detected in 223 (64%) episodes (FUO), microbiologically documented infection was present in 79 (22%) episodes (MDI), and infection was clinically documented (CDI) in 48 (14%). As shown in Table II, the two most common sites of infection were gastrointestinal tract infection [48% (n = 23)] and respiratory tract infection including pneumonia [45% (n= 22)].

In 60% of the 79 MDI episodes a single gram-positive bacterium, in % 36 of episodes a single gram-negative bacterium and in 4% fungi were isolated (Table II). Polymicrobial organisms were not documented.

Treatment Responses

Table III presents the outcome of empirical CS regimen. Modifications were needed in 121 (35%) of the 350 episodes. The overall success rate was 74%, of which 65% were successful without modification and 9% were successful with modification. The most commonly used agents for modification were carbapenems and glycopeptides. The use of aminoglycosides alone or in combination was 2.5%. No death

Table II: Documentation of infections in febrile neutropenia episodes

	n=350
Clinically documented	48 (14%)
URTI	7
LRTI	15
Skin/soft tissue infection	3
Gastrointestinal infection	23
Anal abcess	16
Neutropenic enterocolitis	3
Other abdominal infections	4
Microbiologically documented	79 (22%)
Gram positive	47 (60%)
S. epidermidis	25
MRSA	13
Streptococcus pneumoniae	1
Kocuria kristinae	3
Enterococcus spp	5
Gram negative	29 (36%)
Escherichia coli	13
Klebsiella spp	6
Proteus spp	4
Salmonella spp	1
Pseudomonas spp	2
Serratia	1
Enterobacter spp	2
Fungus	3 (4%)
Candida spp	3
Fever of unknown origin	223 (64%)

URTI: *Upper respiratory tract infections,* ***LRTI:*** *Lower respiratory tract infections,* ***MRSA:*** *Methicillin resistant Staphyloccocus aureus*

Table III: Outcome of treatments of febrile neutropenic episodes

Total number of episodes	Cefoperazone-sulbactam (n=350)
Duration of neutropenia	3-60 (median 7 days)
Duration of fever	1-40 (median 2 days)
Duration of antibiotic treatment	3-30 (median 7 days)
The results of treatment	
Successful	229 (65%)
Successful with modification	30 (9%)
Unsuccessful	91 (26%)
Adverse events	None
Modifications	121 (35%)
Carbapenem+Glycopeptides	48
Carbapenem+Glycopeptides+Antifungals	22
Glycopeptides	28
Carbapenem	13
Amikacin	7
Amikacin + Antifungals	2
Glycopeptides + Antifungals	1
Death	None

occurred during the FEN episodes. The only factor affecting treatment success was the presence of microbiologically documented infection (p <0.050). The success rate was 33% in MDI and 60% in CDI episodes. In FUO, the success rate was the highest with 82% of 223 episodes. A total of 41 (12%) grades 3-4 mucositis were observed in all 350 FEN episodes. One patient had severe gastrointestinal bleeding not treatment-related but due to disease involvement. No other adverse effects were observed.

DISCUSSION

In current pediatric guidelines, monotherapy with an antipseudomonal β-lactam, a fourth- generation cephalosporin or carbapenem is highly recommended due to its efficacy, safety, and fewer side effects in high-risk febrile neutropenia as the initial treatment (10). In a recent systematic review, monotherapy in FEN has been shown to be at least as effective and safe as aminoglycoside-containing combination regimens (11). Several clinical studies have explored the efficacy and safety of CS in FEN both in adults and pediatrics. Most of these studies compared the CS with other agents such as piperacillin/tazobactam or carbapenems and CS was found to be as effective as the others (9,12-16). A recent meta-analysis showed that the clinical efficacy and tolerability of CS in the treatment of febrile neutropenia is as high as the drugs compared to it (17). Cefoperazone-sulbactam is one of the essential drugs to be used empirically according to Turkish febrile neutropenia guidelines (18). Cefoperazone-sulbactam has been used as monotherapy for febrile neutropenia for a long time in our center. Our results show that CS can be used safely without the need for a combination in febrile neutropenia. The overall success rate in our study (74%) was comparable to the success rate in literature that vary between %53-88.

FUO rates in our study (64%) were similar to other studies reported to range from 44% to 80% (9,14-16,19). The group in which CS was most effective was FUO with overall success rate 84%. Clinically documented infection rate in our study was 14%, which was a relatively low rate. Very variable CDI rates such as 12.5%, 26%, 32% and 59% have been reported in the literature, and this may be due to the fact that complications such as severe mucositis were considered in the CDI category in some studies (6,9,14,20). In contrast to the literature, where respiratory tract infections are the most common, gastrointestinal tract infections, especially anal abscess were the leading among in CDI group in our study (21,22). This can be related to social economic situations in Türkiye and recurrent episodes with the same clinical findings in some patients.

In the last 3 decades, a worldwide change from gram negatives to gram positives has been observed in infectious agents isolated in febrile neutropenia (23). Studies in our country have also shown that gram positive bacteria are predominantly isolated in FEN (6,14,24). This is because of frequent use of central venous catheters and more intensive chemotherapy in childhood cancers (25). Central venous catheters are routinely

used in our center, and in 164 out of 350 episodes, patients had catheters. Moreover, 64 of the 79 MDI episodes occurred in patients with catheters and 84% of these were catheter-related bloodstream infections. These data in our study highlight the importance of catheter care. The MDI rate in our study was 22%, similar to the rates in the literature (15.5-24%). The group in which CS was least effective and required the most modification was MDI (success rate %33). Considering the resistance patterns of the isolated microorganisms, it is seen that 60% of patients in MDI group had gram positive growth and they are mostly resistant to methicillin or penicillin. In this case, even if other antipseudomonal agents were used instead of CS in empirical monotherapy, failure could be seen in the MDI group. For this reason, failure cannot be attributed to CS alone.

Consistent with the IDSA 2010, the most common bacterial species isolated in our study are gram-positives, and 53% of them were coagulase-negative staphylococci (2).

In our study, 65% of the patients had primary bone sarcoma and only %14 had non-Hodgkin's lymphoma but interestingly the modification was required most frequently in patients with non-Hodgkin's lymphoma (26 of 42 episodes). The probable reason for this was that 45% of patients with NHL had severe mucositis during FEN episodes. Although patients with osteosarcoma received methotrexate at high doses of 12 gr/m^2, the reason for the relatively low incidence of mucositis may be the intensive oral care prophylaxis we apply. The modification rate was significantly higher in patients with neutropenia lasting more than 10 days (28% vs 74%, $p < 0.001$) and in patients with severe mucositis (30% vs 65%, $p<0.001$). The overall modification rate (35%) is similar to the literature, with no deaths during episodes.

To our knowledge, this is the study with the largest number of FEN episodes in which CS was used as monotherapy in children. Our results show that, cefoperazone/sulbactam is both effective and safe as empirical therapy in febrile neutropenic children with solid tumors and lymphomas. Therefore, CS may be preferred for monotherapy in FEN in a developing country due to its negligible side effect profile, low cost compared to its counterparts, and successful overcoming of most episodes.

This study has some limitations. First, since this is not a randomized controlled trial, we compared the results with the literature. This study reflects the results of a single center. It would be valuable if we had the opportunity to do cost effective analysis. This may be possible with larger multicenter studies.

In conclusion, CS is effective and safe in febrile neutropenic children with solid tumors and lymphomas for empirical monotherapy. No severe toxicity was observed.

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Laparoscopic Pediatric Inguinal Hernia Repair with Percutaneous Internal Ring Suturing with Finer Needle and Suture; A 5-Year Experience of A Single Surgeon

Perkütan İnternal Ring Süturizasyonu Tekniği ile Daha İnce İğne ve Sütur Kullanılarak, Laparoskopik Pediatrik İnguinal Herni Onarımı; Tek Cerrah, 5 Yıllık Deneyim

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ABSTRACT

Objective: Percutaneous internal ring suturing (PIRS) method is an effective minimally invasive laparoscopic method that was preferred for indirect hernia repair in children. The aim of this study is to report the evaluation of surgical results in our PIRS series modified with finer needle and suture with the diagnosis of indirect inguinal hernia, communicating hydrocele and incarcerated inguinal hernia.

Material and Methods: This was a retrospective study that included children aged 3 months to 12 years who under went PIRS technique dueto inguinal hernia between 2017 and 2022. Per-operative findings, surgical time, follow-upfindings, complications, and recurrence data were evaluated.

Results: One hundred patients underwent a total of 129 PIRS procedures. Right side were diagnosed in 63 (63%) of the patients (1 communicating hydrocele and 1 recurrent inguinal hernia). One communicating hydrocele and one recurrent inguinal hernia were present on the left side of 32 (32%) patients. Five patients were diagnosed bilaterally (one incarcerated hernia). 24 patients (29%) with no symptoms were found to have contralateral hernias: 11 on the right (45%) and 13 on the left (55%) side. The average duration of surgery for unilateral PIRS was 13.5 minutes and bilateral PIRS was 24.3 minutes. Average follow-up duration was nine months. There were complications in nine patients (9%). Recurrence was observed in 3 (3%) of 100 patients.

Conclusion: PIRS is a simple and safe alternative to open hernia repair in terms of surgical outcomes for the management of inguinal hernia in children.

Key Words: Children, Complication, Inguinal hernia, Laparoscopic, Percutaneous, Recurrence

ÖZ

Amaç: Çocuklarda indirektinguinalherni onarımında perkütaninternal ring süturizasyonu (PİRS) minimal invaziv, kolay uygulanan ve güvenli bir laparoskopik cerrahi tedavi yöntemidir. Bu çalışmada indirektinguinalherni, kominikanhidrosel ve inkarsereinguinalherni tanılarıyla daha ince iğne ve sütur kullanılarak modifiye edilmiş PİRS tekniği ile opere edilen hastaların cerrahi sonuçlarının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Bu çalışmada 2017-2023 yılları arasında, 3-12 yaş aralığında, PİRS tekniği ile opere edilen hastaların dosyaları retrospektif yöntemle taranmıştır. Hastaların yaşı, cinsiyeti, kilosu, inguinalherni/kominikanhidrosel/inkarsereherni tanı ve taraf bulgusu, hastalık öyküsü, cerrahi bulgusu, cerrahi süresi, komplikasyon ve rekürrens bilgisi çalışmaya dahil edilmiştir.

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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 the Ordu University Clinical Research Ethics Committee (protocol No.2023/104-14.04.2023).

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

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Bulgular: 100 hastaya 129 PİRS prosedürü uygulanmıştır. Preoperatif değerlendirmede 63 hastada (%63) sağ taraf bulgusu saptanmıştır (1 kominikanhidrosel, 1 rekürreninguinalherni). 32 hastada (%32) sol taraf bulgusu saptanmıştır (1 kominikan hidrosel,1 rekürreninguinalherni). 5 hastada bilateral taraf bulgusu mevcuttur (1 inkarsereherni). 24 hastanın (%29) asemptomatikkontralateralhernisi saptanmıştır. Bu hastaların 11'i (%45) sağ tarafta, 13'ü sol taraftaydı (%55). Tek taraflı PİRS onarımı ortalama cerrahi süresi 13.5 dakika, bilateral PİRS onarımı ise 24.13 dakika sürmüştür. Tüm hastaların ortalama takip süresi 9 aydır. Hastaların 9'unda komplikasyon gözlenmiştir (%9). 3 hastada rekürrens saptanmıştır (%3).

Sonuç: İndirektinguinalherni tedavisinde cerrahi sonuçlar değerlendirildiğinde PİRS yöntemi, açık herni onarımına bir alternatif olarak kolay uygulanan, güvenli ve minimal invaziv bir tedavidir.

Anahtar Sözcükler: Çocuk, Komplikasyon, İnguinal herni, Laparoskopik, Perkütan, Rekürrens

INTRODUCTION

Congenital indirect inguinal hernia is the most prevalent disease in children, affecting 1–5% of the population (1). Boys are diagnosed with indirect inguinal hernia more frequently than girls and 60% of cases occur on the right side 10% are diagnosed as bilateral hernias. In newborns, the risk is significantly increasing to 5% of full-term and %30 of preterm infants (2, 3). High ligation of the hernia duct at the level of the internal ring is the only therapy for indirect inguinal hernia. (4). Although open herniorrhaphy continues to be the dominant treatment for inguinal hernia, laparoscopic repair has gained widespread acceptance. In 1997, El-Gohary et al. (5) reported for the first time the laparoscopic repair of inguinal hernias in female patients. Since then, laparoscopic procedures are typically performed via two or three incisions and require internal ring suturing. In 2006, Patkowski D. described the PIRS procedure, which is performed via a single umbilical optic port and an external skin puncture (6).

Since numerous laparoscopic techniques have been reported, pediatric surgeons have begun to debate the limitations of the open technique, which include the need for wide inguinal tissue dissection, the inability to detect contralateral metachronous hernias, and the inability to differentiate between direct and indirect inguinal hernias. The risk of complications with an open technique ranges from 1% to 3.5%, and the risk of testicular atrophy is 1% (7, 8). All dissections performed on the cord during surgery result in impaired testicular vascularization and volume loss (9). Especially infants, who have anatomical challenges such as the fragility of the hernia sac and the susceptibility of the spermatic cord to open technique dissection, require more technical surgical skills (10). Conversely, minimally invasive surgical techniques are developing swiftly throughout the world. Extraperitoneal laparoscopic repair of inguinal hernias has a low recurrence rate, minimal scarring, detection and repair of contralateral metachronous hernias, and less pain than open surgery (5). Children undergoing laparoscopic and open inguinal hernia repair have comparable operative durations, complication rates, and recurrence rates for unilateral hernias. Laparoscopic bilateral hernia repair has been demonstrated to be faster (11). This study aims to report the surgical outcomes of our modified PIRS series, which utilizes a finer needle and suture.

PATIENTS and METHODS

This is a retrospective analysis of a single center involving patients who were diagnosed with inguinal hernia and communicating hydrocele between 2017 and 2023 and repaired with the PIRS technique. The demographic characteristics, side of inguinal/incarcerated hernia/communicating hydrocele at the time of diagnosis, medical history, per-operative findings, operation, surgical time, follow-up findings, complications, and recurrence rates of patients were recorded. A single surgeon performed all the procedures. This study was approved by the Ordu University Clinical Research Ethics Committee (protocol No.2023/104-14.04.2023).

Patients Demographics

The study included a total of 100 patients. Of these patients, 48 girls and 52 boys, mean age 40 months (2–144 months), 95 patients were operated on with the diagnosis of inguinal hernia, two patients with communicating hydrocele, two patients with recurrent inguinal hernia (the first operation was performed as an open herniorrhaphy at another center), and one patient with the diagnosis of incarcerated hernia. During the preoperative examination of these patients, 63 were marked on the right side, 32 on the left, and five were marked on both sides.

Operation Technique

All procedures were performed under general anesthesia with local anesthesia administered to the umbilical and inguinal incision sites. The patients received a single dose of prophylactic antibiotics. In a supine position, a 5-mm trocar was inserted into the abdomen using the open Hasson technique. Allprocedures were utilized with an insufflation pressure of 8 mmHg. A 5mm telescope with a 30-degreeviewing angle was utilized. After exploring the internal ring areas on both sides, testicular vessels, cord or ovary, and adjacent tissues, a 2mm stab incision was made to the hernia-related area. During repair, a 20G angiocath needle and a 3/0 non-absorbable monofilament suture were used (Figure 1). Due to the use of a thinner needle, loops, and sutures were created by leaping at least twice from the peritoneum along the canal wall. In males, while suturing the canal using the standard PIRS technique, special care was taken to avoid the cord and vascular elements. To prevent postoperative hydrocele, external pressure was applied to the inguinal canal while the suture was secured in

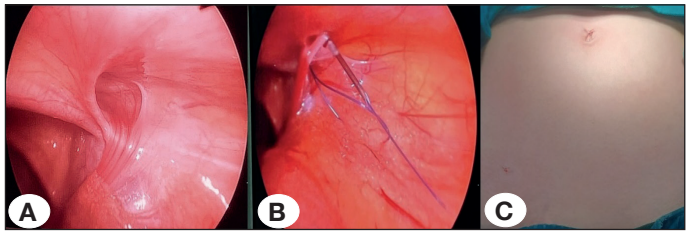

Figure 1: A) Patent processus vajinalis, **B)** İnternal ring suturing with 20 G angiocath and 3/0 non-absorbablesuture, **C)** Postoperative view.

the extracorporeal region. Using the same technique, a second suture was placed in patients who were deemed to have an open area after the procedure. When a metachronous hernia was discovered during the primary side repair, the contralateral side was also repaired. The patients were fed two hours after surgery and discharged on the same day. Following discharge, patients were evaluated in the outpatient clinic one week, one month, and six months later.

RESULTS

One hundred patients underwent a total of 129 PIRS procedures. 48 of these patients were female (48%), 52 were male (52%), their average age was 40 months (2–144 months), and their average weight was 15kg (Table I). The right side was the diagnosis for 63 (63%) of the patients who presented to the outpatient clinic (1 communicating hydrocele and 1 recurrent inguinal hernia). One communicating hydrocele and one recurrent inguinal hernia were present on the left side of 32 (32%) patients. Five patients (5%) had bilateral side diagnoses. 24 patients (29%) with no symptoms were discovered to have contralateral hernias preoperatively: 11 on the right (45%) and 13 on the left (55%) side. All were repaired inthe same session.

15 of 100 patients were infants, or younger than one year-old (15 percent). With the diagnosis of metachronous hernia, bilateral PIRS was performed on six of the nine patients who underwent surgery for unilateral hernia. One of these patients was a one-year-old who underwent surgery for a left incarcerated hernia. During the operation, it was discovered that the ovary caused incarceration; consequently, an additional conduit was inserted and the ovary was reduced. There were no complications during the metachronous hernia repair procedure. A 6-month-old infant was diagnosed with bilateral inguinal hernia owing to a left-sided ovary and underwent surgery for the condition. One additional functional port was added, and the operation was concluded.

Six patients did not achieve effective closure following the primary hernia side suture; therefore, the second suture was performed using the same technique, and the procedure was successful. On the side with two sutures, only one of these six patients experienced a recurrence.

Table I: Patient characteristics of variables, complication and recurrence total rate.

Age, median, month	40
Weight, median (kg)	15 kg
Gender*	
Female	48 (48)
Male	52 (52)
Side*	
Right	63 (63)
Left	32 (32)
Bilateral	5 (5)
Contralateral Hernia*	24 (29)
Right	11 (45)
Left	13 (55)
Complication Total*	9 (9)
First 50 patient	6 (12)
Last 50 patient	3 (6)
Recurrence Total*	3 (3)
First 50 patient	2 (4)
Last 50 patient	1 (2)

***** *n(%)*

The average duration of surgery for unilateral PIRS was 13.5 minutes and bilateral PIRS was 24.3 minutes. No patient underwent an open operation. The average length of hospitalization for patients is nine hours.

Complications were observed in 9 patients (9%).İliac hematoma developed during the procedure in 3 patients. The hematoma was controlled by external pressure. No recurrence was observed in the follow-up of two of these patients. Complications such as pain, wound infection, ileus were not observed in any of the patients Six patients complained of suture palpation at the inguinal incision site in the first month of follow-up. This complaint was resolved during the sixth month of patient follow-up.Recurrence was observed in 3 of 100 patients (3%). The first of these patients was a 30-month-old female patient, and recurrence was observed in the 6th month.Considering the operation note of this patient, it was observed that 2 sutures were placed on the left side where recurrence was observed. Open herniorraphy was performed to this patient.During the operation, both sutures were seen under the skin as a loop independent of the processus vaginalis. The second patient, a 36-month-old girl, presented with recurrent right inguinal hernia in the second month.In this patient, PIRS operation was performed for the second time. In the second operation, a smaller canal opening was observed compared to the first. No suture was observed. No recurrence was observed in the follow-up. The third patient was 3.5 months old, diagnosed with bilateral inguinal hernia with a history of prematurity.In this patient, recurrence was observed on the 9th postoperative day on the right side with a wider opening. Open herniorraphy was performed to this patient.

When comparing the complication and recurrence rates between the first 50 patients and the last 50 patients, the complication rate in the first 50 patients is 12% (n:6) and the

recurrence rate is 4% (n:2), whereas in the second 50 patients, these rates decrease to 6% (n:3) and 2% (n:1), respectively.

DISCUSSION

El-Gohary, Misra D, and Schier F. first performed laparoscopic inguinal hernia repair on children (5,12,13). However, in these three repair procedures, three apertures were utilized. In 2006, Patkowski et al. (6) developed the PIRS technique and published their first series. This technique utilizes a single telescope aperture. The most significant advantages of the PIRS method are its simplicity, its minimal material requirements, and its brief operation time.

Because of its low recurrence and complication rates, open herniotomy (OH) has been the standard treatment for pediatric inguinal hernias. However, there are numerous advantages to laparoscopic repair over OH repair. Advantages of laparoscopic repair include minimal invasiveness, scar advantage, less discomfort and pain medication, shorter operation time, faster postoperative recovery, and the ability to see contralateral hernias.

In Patkowski's series, a 2.0 non-absorbable monofilament suture is utilized with an 18-gauge needle in the PIRS technique. In this study, the PIRS technique was performed with a finer needle and suture (6). The rate of complications in Patkowski's series was 6.6%, while ours was 9%. In Patkowksi's series, the recurrence rate was 2.1%, whereas in our series, it was 3%. In the second 50 patients, the complication rate decreases to 6% when the learning curve is evaluated. In light of these findings, it is recommended that thinner needles and sutures be used in the PIRS technique for the peritoneal jumping in order to reduce invasiveness and increase manipulation ability.

Laparoscopy has a number of significant advantages, one of which is the shorter duration of the operation. In this study, the mean operation time for unilateral hernia repair was determined to be 13.5 minutes, while that for bilateral repair was 24.3 minutes. Also demonstrated by Francesco Morini's meta-analysis is the assumption that bilateral repair has a significant operative time advantage (14).

According to several reviews, the incidence of metachronous contralateral hernia ranges from 7 to 10%, with a higher incidence among younger patients and those with a left-sided initial hernia. Kokorowski et al. (15) reported that 30% of patients had contralateral hernias and that 7.3% of patients had clinically significant metachronous inguinal hernias. In this study, 29% of patients had contralateral hernias, all of which were surgically repaired. Studies revealed that 55% of these patients had a left-sided preoperative diagnosis. Children with a primary left-sided hernia have an increased risk of developing a right-sided metachronous hernia, as supported by this study. There was no difference in the female male ratio.

In the literature, it has been observed that laparoscopic PIRS has a significantly lower complication rate than open repair. Significantly higher rates of wound infection, bladder injury or perforation, postoperative hydrocele, iatrogenic cryptorchidism, and testicular atrophy were observed following OH (16). In our study, nine patients (9%) experienced complications. Three patients developed a Liac hematoma during the procedure. None of them were observed to have a recurrence. Complications such as pain, wound infection, ileus were not observed in any of the patients. Six patients complained of suture palpation at the inguinal incision site in the first month of follow-up. This complaint was resolved during the sixth month of patient follow-up.

However, it is debate over the preference of surgeons, due to the high recurrence rates in laparoscopic repair compared to the OH seen in various publications.The first of these publications is the Patkowski series in 2006, 140 PİRS performed and the recurrence rate is 2.9% (6). Wolak et al. (17) reported the 67 patient with PİRS technique, recurrence rate as 1.15% .Thomas et al. (18) reported 250 patient PİRS series, the recurrence rate was 1.4%. Wolak PK et al. (19) published in 2022, the recurrence rate was 4.4%. Neverthless, Francesco Moriniet al. (14) evaluated 8 randomized controlled trials about open versus laparoscopic hernia repair and found no difference in complication and recurrence rates in 2021.

We believe that the difference between these rates may be due to the influence of the laparoscopy technique's learning curve. In our study, the complication rate in the first 50 patients was 12% and the recurrence rate was 4%, whereas in the second 50 patients, these rates decreased to 6% and 2%, respectively.

CONCLUSIONS

PIRS method is an effective technique for pediatric inguinal hernia repair. It is a method that is easy for the surgeon and has good results for the patient. The procedure has a short learningcurve.As a result of this study, we suggest that laparoscopy is a good alternative to open surgery for inguinal hernia repair, especially after the learning curve process.

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Children with Special Educational Needs and Parental Burnout During the Pandemic Lockdown Period

COVİD-19 Pandemisinde Özel Gereksinimli Çocuklar ve Ebeveyn Tükenmişliği

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ABSTRACT

Objective: This study aimed to investigate whether children with special needs and their parents had problems with special education needs during the lockdown, and to examine the relationship between the special education process and the parent-child relationship, the level of burnout of parents.

Material and Methods: Our study included 283 parents with children registered to a special education and rehabilitation centers in Kocaeli province of Türkiye between March 2021- June 2021. Sociodemographic data form, Maslach Burnout Inventory and Parent-Child Relationship Scale were given to parents.

Results: Burnout of the parents with children with autism spectrum disorder is at a higher level. The development of the children with parents who had high burnout scores regressed. The progress in the development of children whose mothers were employed, whose parents did not work from home, whose family's monthly income was 4501 TL and above, and who received special education for 0-24 months until the restriction period of the pandemic was reported as better by the parents. Parents with children aged 11-below have more positive relationship with their children.

Conclusion: Our study demonstrated that the closure of special education may play a role in increased burnout and negatively affected children and parents. Monitoring the development process of children and the mood of parents during pandemics or other situations that lead to the closure of special education centres will be important to identify the problem areas and prepare support programmes.

Key Words: Burn-out, Child, Special education, People with disabilities, Parent-child relationship

ÖZ

Amaç: COVİD-19 enfeksiyonu yaşamın her alanını etkilemiştir. Bununla birlikte toplumun bazı kesimleri pandemi ve sonuçlarından daha fazla etkilenmiştir. Özel Gereksinimli Çocuklara (ÖGÇ) sahip aileler de şüphesiz pandemiden daha fazla etkilenen gruplar içerisinde yer almıştır. Çalışmamızda; ÖGÇ'lerin ve ebeveynlerinin pandemide özel eğitim merkezlerinin kapanma döneminde özel eğitim gereksinimleri ile ilgili sorun yaşayıp yaşamadıklarını saptamak, özel eğitime ara verilme sürecinin ebeveyn-çocuk ilişkisi, ebeveynlerin tükenmişlik düzeyi ve ÖGÇ'nin gelişim süreci ile ilişkisini incelemek amaçlanmıştır.

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Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. For this study, the approval was collected from the Republic of Türkiye Ministry of Education, Kocaeli Provincial Directorate of National Education and Kocaeli University Medical Faculty Clinic Studies Ethical Board on 05/02/2021 with GOKAEK-2021/3.15 decree.

Contribution of the Authors / Yazarların katkısı*: *ÇİMEN İD: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***YEĞİN Z:*** 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. ***GÜMÜŞSOY AS:*** 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. ***KAPUCU T:*** 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: Çalışmamıza Mart 2021-Haziran 2021 tarihleri arasında Kocaeli ilinde özel eğitim ve rehabilitasyon merkezlerine kayıtlı, 0-18 yaş arası çocuğu olan ebeveynler alınmıştır. Ebeveynlere; sosyodemografik veri formu, Maslach Tükenmişlik Ölçeği ve Ebeveyn Çocuk İlişkisi Ölçeği verilmiştir.

Bulgular: Çalışma sonucunda; çocukların özel eğitim aldığı tanı ve ebeveyn tükenmişliği arasında ilişki olduğu, tükenmişliğin OSB tanılı çocuğu olan ailelerde daha yüksek olduğu gözlenmiştir. Tükenmişlik puanı yüksek olan ailelerin çocuklarının gelişimde pandemi döneminde gerileme olması dikkat çekmiştir. Annesi çalışan, ebeveyni evden çalışmayan, ailenin aylık geliri 4501 TL ve üstü olan, özel eğitime gitmiş olduğu toplam süre 0-24 ay arası olan grupta çocukların gelişiminde ilerlemenin daha fazla olduğu saptanmıştır. 11 yaş ve altı çocuğu olan ebeveynlerin çocuklarıyla anlamlı oranda daha fazla olumlu ilişkisinin olduğu gözlenmiştir.

Sonuç: COVİD-19 pandemisinde özel eğitim merkezlerinin kapanması, sosyal desteğin azalması, çocukları ile sürekli bir arada olmaları gibi nedenler ile ebeveynlere binen yükün artması ÖGÇ olan ailelerin tükenmişlik düzeyini artmasında rol oynamış olabilir. Pandemi döneminde ÖGÇ'lerin gelişim sürecini ve ailelerin ruhsal durumunu takip etmek, sorun alanlarını tespit etmek ve uygun destek programlarının hazırlanmasında önemli olacaktır.

Anahtar Sözcükler: Tükenmişlik, Çocuk, Özel gereksinim, Özel eğitim, Ebeveyn-çocuk ilişkisi

INTRODUCTION

COVID-19 infection was first detected in December 2019 in Wuhan and declared a pandemic on 11 March 2020. While the children with typical development and their parents were significantly affected by the pandemic and lockdown, children with special needs (CSN) and their families experienced a more problematic process. CSN are defined as children who show different developmental properties than their peers with typical development in one or multiple physical or mental development areas due to any reason (1). In Türkiye, CSN receive special education in schools under the Ministry of Education and Special Education and Rehabilitation Centers. In addition to these education applications, the home education needs of the children are met by their parents. With the "Regulation on Special Education Services" issued by the Ministry of National Education, special education activities to be carried out within the ministry started to be carried out in line with the relevant regulation. According to the revised and re-published Special Education Services Regulation, "special education" is defined as education carried out in an environment suitable for the disabilities and characteristics of these children with specially trained personnel and developed education programs for the education of children in need of special education (2). The regulations provided by the Ministry of Family, Labor and Social Services and the Ministry of Health to assess the CSN state that the children with intellectual disability, hearing disability, visual disability, motor skill disability, language and speech disorders, specific learning disability (SLD) and autism spectrum disorder (ASD) have support requirement (3).

The spread of the COVID-19 infection around the world, have led the countries to take various precautions in social, economic, health and education fields. Türkiye implemented various precautions like restricted entrance and exit to various cities and declared a curfew. In addition to these precautions, education activities were suspended and schools started distance education as of 16 March 2020. During the pandemic-related lockdown period, the special education centers in Türkiye were closed, therefore, CSN were deprived of education support. Later, the Ministry of Education declared to provide distance education via a mobile application for CSN. The families of the CSN experienced intense stress regarding the developmental process of their children and searched for certain solutions to support the intellectual and motor development of their children. This education support was challenging for CSN and their families who might experience problems with using the distance education applications and the parents experienced various problems such as a sense of failure in terms of necessary motivation and preparation process for all the children around the world to actively participate in the education process (4,5). The United Nations Report identified three major problems for the education of CSN during the pandemic. The report stated that the families experienced problems accessing the materials during the pandemic, the importance of family education was insufficient and there were learning gaps (6).

Roskam et al. (7) defined parental burnout as a severe state of exhaustion experienced by a person in the parental role. Factors that may pose a risk for parental burnout include; having an ill child, neuroticism and lack of emotion and stress management skills, low self-esteem and high need for control, parents not receiving sufficient emotional support from their spouses or social environment, lack of competence in child rearing, mother's involvement in work life, conflict between the roles of parent and working woman, being a parent at a young age, having a child of a younger age, low socio-economic status, low status level and a high number of children living in the same household (7-12).

A CSN in the family leads to psychological stress among the entire family (13). The parents might experience problems due to personal care needs, nutrition, health, social disharmony and dependence on their children (14). The families experienced more stress due to families becoming educators when the schools were closed during the pandemic, changing parenthood roles in the house and parents continuously staying at home (15,16). The literature shows that the parents with CSN have higher burnout levels than the parents without CSN before the pandemic and it is thought that this burnout level might be increased due to the pandemic and lockdown and the parent-child relationship might be affected (9,17,18). Based on this, our study aims to determine whether CSN and their parents had

problems with special education needs during the lockdown when special education practices were stopped during the pandemic, and to examine the relationship between the special education process and the parent-child relationship, the level of burnout of parents, and the development process of CSN. In addition, it was aimed to determine the sociodemographic characteristics that may negatively affect the developmental level of child with special needs and to intervene early. The results of the study will be useful in understanding the effects of the closure of special education centers due to epidemics or other reasons on the development processes of CSN and their families. In addition, it is thought that it will contribute to the literature on what can be done to support both the development of children and the psychological processes of families in case of similar situations.

MATERIALS and METHODS

The study forms were completed by parents with children aged 0-18 years enrolled in special education centers in Kocaeli between March and June 2021, when the restrictions were applied. A total of 283 parents' data were included in the study. The forms were sent to the special education center directors registered on the list provided by the Ministry of Education via Google surveys, consent was collected from the parents and the data was sent to an email address without identity information. Forms were collected without identity information. All parents were given an informed consent form, which explained the study in detail, and their consent to participate in the study was obtained. The forms of parents who accepted to participate in the study and completed the forms without any missing parts were included in this study. The parents are given a sociodemographic data form, Maslach Burnout Inventory and Parent-Child Relationship Scale. For this study, the approval was collected from the Republic of Türkiye Ministry of Education, Kocaeli Provincial Directorate of National Education and Kocaeli University Medical Faculty Clinic Studies Ethical Board on 05/02/2021 with GOKAEK-2021/3.15 decree. The study was planned as a cross-sectional study.

Instruments

Sociodemographic data form (SDF): The form created by the researchers asked questions about the child's age-gender, parents' age-education level, diagnosis for special education, how long the child is receiving special education, how long was the child away from special education, whether children's level of development has progressed during the pandemic according to the assessment of families, the applications parents follow instead of special education, whether there is online special education support and the pandemic period.

Maslach Burnout Inventory (MBI): The scale developed by Maslach and Jackson consists of three subscales and 22 items which are emotional exhaustion, personal accomplishment and depersonalization (19). The subscale scores are calculated separately for each subscale with "never; zero, always; six". High scores in the emotional exhaustion and depersonalization subscales and low scores in the personal accomplishment subscale are considered burnout. The scale was adapted to Turkish by Ergin (20).

Parent-Child Relationship Scale (PCRS): The scale developed by Hetherington and Clingempeel consists of 15 items and is scored based on a five-point likert-type scale (One=Never; five=Extreme) (21). This scale has two subscales which are the positive parent-child relationship and the negative parent-child relationship. The increased scores from the subscales mean the increased quality of the relationship. The Turkish adaptation of the scale was completed by Aytaç et al. (22).

Statistical Analysis

IBM SPSS 20.0 (IBM Corp., Armonk, NY, USA) package program was selected for the statistical analysis. Normal distribution was evaluated with the Kolmogorov-Smirnov test. The numerical variables with normal distribution were given as mean±standart deviation, numerical variables with non-normal distribution were given as median (25.-75. percentile) and categoric variables were given as frequency (percentage). The variance between the two groups was identified with Mann Whitney U test for numerical variables with non-normal distribution. The between-group variance when the number of groups was two or more were identified with the Kruskal Wallis test for numerical variables with non-normal distribution. The relationships between categoric variables were identified with Pearson Chi-Square and Fisher Exact tests. $p<0.050$ statistical significance was accepted to be sufficient for the two-way hypothesis test.

RESULT

A total of 283 forms were completed by the parents of the CSN with 110 (38.90%) female and 173 (61.1%) male were included in this study. The age mean of the group was found 8.38±3.69, the age mean of the mothers' was found 35.72±5.49 and the age mean of the fathers' was found 39.44±5.94. More than half of the mothers (52.30%) graduated from elementary school and the majority of the mothers (82%) didn't work. The majority of the fathers (44.90%) graduated from elementary school and 95.8% of the fathers worked. Among the children with special needs, 59 (20.80%) had ASD, 50 (17.7%) had a language-speech disorder, 40 (14.10%) had intellectual disabilities, 40 (14.10%) had SLD, 94 (33.20%) had other disorders to be registered to the special education center. Table I shows the sociodemographic data, pandemic and special education process characteristics of the group.

When the relationship between the sociodemographic characteristics of the participants and their scores on the

Table I: Sociodemographic, pandemic and special education process characteristics.

Groups	n (%)
Health status of parents	
Both alive	281 (99.3)
Mother or father dead	2(0.7)
Mother and father dead	0 (0)
Marriage status of parents	
They are together	236 (83.4)
They broke up/divorced	30 (10.6)
2nd marriage of mother and/or father	16 (5.6)
Mother's education	
None	12 (4.2)
Primary / Secondary School	148 (52.3)
High school	72 (25.4)
University	51 (18)
Father's education	
None	1 (0.4)
Primary / Secondary School	127 (44.9)
High school	100 (35.3)
University	55 (19.4)
Mother's job	
Not working	232 (82)
Working	51 (18)
Father's job	
Not working	12 (4.2)
Working	271 (95.8)
Consanguineous marriage	
No	237 (83.7)
Yes	46 (16.3)
Number of siblings	
0	50 (17.7)
1	123 (43.5)
2 or more	110 (38.8)
Total income	
2250 TL and below	44 (15.5)
2251 TL-4500 TL	163 (57.6)
4501 TL and above	76 (26.9)
Parents working from home during the pandemic	
No	223 (78.8)
Yes	60 (21.2)
Caregiver change in the pandemic	
No	262 (92.6)
Yes	21 (7.4)
Inability of parents to continue their work in the pandemic	
No	214 (75.6)
Yes	69 (24.4)
Frequency of talking about the pandemic at home	
Never/Rare	194 (68.6)
Often/Very often	89 (31.4)
Familiar person diagnosed with COVID-19	
No	77 (27.2)
Yes	206 (72.8)
Familiar person with hospitalization due to COVID-19	
No	194 (68.6)
Yes	89 (31.4)
Familiar person who died due to COVID-19	
No	215 (76)
Yes	68 (24)
Sibling with special education	
No	254 (89.8)
Yes	29 (10.2)
The time the child can not receive special education in the pandemic	
Less than 6 months	213 (75.3)
6 months and more	70 (24.7)
Other education applications instead of special education in the pandemic	
No	233 (82.3)
Yes	50 (17.7)
Online special education application	
No	252 (89)
Yes	31 (11)
How the child's development continued in the pandemic	
Regressed	84 (29.7)
Remained stable	131 (46.3)
Advanced	68 (24)

MBI was examined, it was found that the depersonalization dimension score was significantly higher in parents with children aged 11 years and younger. The relationship between Maslach burnout scale and participants' special education diagnoses was evaluated. A significant relationship was found between special education diagnosis and emotional exhaustion subscale and depersonalization subscale. However, there was no significant relationship between personal accomplishment and total scores. The difference in the emotional exhaustion subscale was due to the difference between language-speech disorder and autism spectrum disorder groups. Table II shows the sociodemographic characteristic comparison for MBI.

Looking at the relationship between the development of CSN and the scales during the pandemic period; it was found that parents with high scores in emotional burnout and depersonalization dimensions had more regression in the development of their children. Progress in the development of the child during the pandemic period was found to be higher in the group whose mother was employed, who did not have a parent working from home office, whose family's monthly income was 4501 TL and above, and whose duration of special education was 0-24 months. The regression was significantly higher in the group with a period of 6 months or more when the child did not receive special education. A significant difference was found between the groups with and without other practices instead of special education during the pandemic and the developmental status of CSN during the pandemic. Table III shows the comparison of different factors for a child's development during the pandemic.

Regarding the parent-child relationship, it was observed that parents with children aged 11 and under had significantly more

Table II: Sociodemographic comparison of MBI

Features	Maslach Burnout Inventory							
	Personal accomplishment		Emotional exhaustion		Depersonalization		Total score	
	Median (25-75 p)	p	Median (25-75 p)	p	Median (25-75 p)	p	Median (25-75 p)	p
Age								
11 and below	29.50 (22.00-34.00)	0.541*	14.00 (11.00-18.00)	0.455*	6.00 (5.00-9.00)	0.006*,‡	6.00 (5.00-9.00)	0.758*
Between 12-18	29.00 (22.50-36.00)		14.00 (10.00-17.00)		5.00 (5.00-6.50)		5.00 (5.00-6.50)	
Gender								
Female	19.50 (11.00-27.00)	0.365*	13.50 (10.00-18.00)	0.859*	6.00 (5.00-8.00)	0.886*	40.50 (33.00-50.25)	0.838*
Male	18.00 (10.00-27.00)		14.00 (11.00-18.00)		6.00 (5.00-8.00)		40.00 (34.00-50.00)	
Diagnosis of the child with special education								
Autism spectrum disorder	31.00 (28.00-34.00)	0.472†	16.00 (12.00-21.00)	>0.05†,‡	7.00 (5.00-11.00)	0.012†,‡	43.00 (35.00-51.00)	0.341†
Intellectual disability	29.00 (16.25-35.75)		13.00 (10.25-15.00)		5.00 (5.00-7.00)		40.50 (38.00-46.00)	
Language- speech disorder	25.00 (18.75-34.00)		13.00 (10.00-15.25)		5.00 (5.00-8.00)		42.00 (39.75-46.00)	
Specific learning disability	28.50 (24.00-34.75)		13.00 (10.25-16.00)		5.00 (5.00-7.00)		40.00 (36.00-45.00)	
Other	30.00 (23.00-35.00)		15.00 (11.00-19.25)		6.00 (5.00-9.00)		42.00 (37.00-45.00)	
Total income								
2250 TL and below	27.00 (14.25-34.75)	0.114†	12.00 (10.00-15.75)	0.012†,‡	5.00 (5.00-7.00)	0.217†	39.00 (34.25-46.75)	0.731†
2251 TL-4500 TL	30.00 (23.00-35.00)		13.00 (11.00-17.00)		6.00 (5.00-9.00)		39.00 (33.00-51.00)	
4501 TL and above	30.00 (24.00-34.00)		16.50 (12.00-20.75)		6.00 (5.00-8.00)		41.00 (35.25-48.75)	
Parents working from home during the pandemic								
No	30.00 (22.00-35.00)	0.283*	14.00 (11.00-18.00)	0.891*	6.00 (5.00-8.00)	0.893*	41.00 (34.00-51.00)	0.332*
Yes	28.50 (19.25-33.75)		13.00 (11.00-18.00)		6.00 (5.00-8.00)		39.00 (35.00-46.00)	
Sibling with special education								
No	29.00 (22.00-34.25)	0.412*	14.00 (11.00-18.00)	0.514*	6.00 (5.00-8.00)	0.348*	40.00 (33.00-50.00)	0.814*
Yes	32.00 (22.50-34.50)		14.00 (10.00-17.50)		5.00 (5.00-8.50)		42.00 (37.50-47.50)	
The time the child can not receive special education in the pandemic								
Less than 6 months	30.00 (23.00-35.00)	0.089*	13.00 (11.00-18.00)	0.322*	6.00 (5.00-8.00)	0.332*	41.00 (34.00-50.00)	0.372*
6 months and more	28.00 (19.75-33.00)		14.00 (11.00-20.00)		6.00 (5.00-9.00)		38.00 (34.00-47.00)	
Other education applications instead of special education in the pandemic								
No	29.00 (21.00-34.50)	0.279*	14.00 (11.00-18.00)	0.726*	6.00 (5.00-8.00)	0.540*	41.00 (34.00-49.50)	0.709*
Yes	31.00 (24.75-34.25)		13.50 (11.00-19.00)		6.00 (5.00-8.00)		38.50 (34.00-55.00)	
Online special education application								
No	29.00 (22.00-35.00)	0.178*	13.50 (11.00-18.00)	0.595*	6.00 (5.00-8.00)	0.782*	40.50 (34.00-50.00)	0.981*
Yes	29.00 (17.00-32.00)		15.00 (11.00-21.00)		6.00 (5.00-9.00)		40.00 (35.00-49.00)	
The development of the child in the period of the pandemic								
Regressed	28.50 (19.00-33.00)	0.179†	14.50 (10.00-19.00)	0.031†,‡	6.00 (5.00-10.00)	0.035†,‡	40.50 (34.25-50.00)	0.242†
Remained stable	31.00 (24.00-35.00)		14.00 (11.00-19.00)		5.00 (5.00-8.00)		42.00 (35.00-51.00)	
Advanced	29.50 (19.25-34.00)		13.00 (10.00-16.00)		5.00 (5.00-7.00)		38.00 (32.00-47.75)	

**Mann Whitney U, †Kruskal Wallis, ‡p<0.050*

positive relationships with their children. Table IV shows the PCRS and sociodemographic and special needs characteristics.

DISCUSSION

A study conducted in Italy during the lockdown due to the pandemic reported that parents with CSN were in the high-risk group for burnout (23). Another study revealed that the strongest predictor for parent burnout was having a child with special needs and children younger than 10 years old (24). A study that investigated the burnout of mothers with CSN during the pandemic found that the emotional exhaustion dimension scores of mothers with CSN between six-nine years old were higher than mothers with CSN between 10-18 years old (25). In another study looking at the level of burnout in parents of children with autism, it was observed that burnout levels of parents with children with autism increased as the age of their children decreased (26). Our study shows that mothers with pre-adolescent children experienced higher levels of burnout. This could suggest that parents of younger children may not

Table III: Comparison of the development of the CSN and sociodemographic characteristics during the pandemic

Features	The development of the child in the period of the pandemic			
	Regressed	Remained stable	Advanced	p
Mother's age*	35.58±5.45	36.44±5.20	34.5±5.93	0.078§
Father's age*	39.69±5.02	39.77±6.62	38.51±5.57	0.279§
Age†				
11 and below	62 (27.9)	98 (44.1)	62 (27.9)	0.013‡,ǁ
Between 12-18	22 (36.1)	33 (54.1)	6 (9.8)	
Mother's education†				
None	5 (41.7)	4 (33.3)	3 (25.0)	
Primary / Secondary School	43 (29.1)	71 (48.0)	34 (23.0)	0.337‡
High school	25 (34.7)	34 (47.2)	13 (18.1)	
University	11 (21.6)	22 (43.1)	18 (35.3)	
Father's education†	1 (1.2)	0 (0.0)	0 (0.0)	
None	40 (47.6)	60 (45.8)	27 (39.7)	0.171‖
Primary/Secondary School High school	32 (38.1)	47 (35.9)	21 (30.9)	
University	11 (13.1)	24 (18.3)	20 (29.4)	
Mother's job†				
Not working	70 (30.2)	113 (48.7)	49 (21.1)	0.044‡,ǁ
Working	14 (27.5)	18 (35.3)	19 (37.3)	
Father's job†				
Not working	2 (2.4)	5 (3.8)	5 (7.4)	0.303‖
Working	82 (97.6)	126 (96.2)	63 (92.6)	
Total income†				
2250 TL and below	15 (17.9)	22 (16.8)	7 (10.3)	0.045†,ǁ
2251 TL-4500 TL	54 (64.2)	75 (57.3)	34 (50.0)	
4501 TL and above	15 (17.9)	34 (26.0)	27 (39.7)	
Parents working from home during the pandemic†				
No	65 (77.4)	111 (84.7)	47 (69.1)	0.035‡,ǁ
Yes	19 (22.6)	20 (15.3)	21 (30.9)	
Sibling with special education†				
No	77 (91.7)	117 (89.3)	60 (88.2)	0.766‡
Yes	7 (8.3)	14 (10.7)	8 (11.8)	
Total length of time the child attended special education†				
0-24 months	22 (27.2)	51 (39.2)	42 (62.7)	0.000‡,ǁ
More than 24 months	59 (72.8)	79 (60.8)	25 (37.3)	
The time the child can not receive special education in the pandemic				
Less than 6 months	53 (63.1)	101 (77.1)	59 (86.8)	0.003†,ǁ
6 months and more	31 (36.9)	30 (22.9)	9 (13.2)	
Other education applications instead of special education in the pandemic†				
No	75 (89.3)	100 (76.3)	58 (85.3)	0.040‡,ǁ
Yes	9 (10.7)	31 (23.7)	10 (14.7)	
Online special education application†				
No	78 (92.9)	112 (85.5)	62 (91.2)	0.196‡
Yes	6 (7.1)	19 (14.5)	6 (8.8)	

**Mean (±SD), †n(%), ‡Pearson Chi-Square, §Kruskal Wallis, ‖Fischer's Exact test, ǁp<0.050*

be able to adapt to the child's developmental problems and may feel less successful due to a lack of knowledge about the child's diagnosis, educational process and progress. Lockdown decreased social support and the necessity to sustain the child's education with the support of the other individuals in the family during the pandemic might cause the parents to emotionally struggle. Additionally, it was reported that the behavioral problems of the CSN might be increased since the special education centers that served CSN were closed due to the pandemic and the ongoing programs were interrupted (27).

The MBI Emotional Exhaustion dimension score was higher in parents with children with ASD than in parents with children with language-speech disorders. Similarly, in a study conducted in Türkiye, the MBI Emotional Exhaustion score was found to be higher in mothers with children diagnosed with ASD or cerebral palsy than in mothers with children with Down Syndrome or

Table IV: Comparison of sociodemographic characteristics and PCRS

Features	The Parent-Child Relationship Scale			
	Positive		Negative	
	Median (25-75 p)	p	Median (25-75 p)	p
Age				
11 and below	42.00 (39.00-45.00)	0.045*,§	40.00 (33.00-45.00)	0.187*
Between 12-18	13.00 (9.00-16.00)		11.00 (8.50-15.00)	
Gender				
Female	41.50 (39.00-45.00)	0.927*	12.00 (9.00-15.25)	0.211*
Male	41.00 (37.50-45.00)		13.00 (10.00-16.00)	
Diagnosis of the child with special education				
Autism spectrum disorder	41.00 (39.00-44.00)	0.533†	12.00 (9.00-15.00)	0.430†
Intellectual disability	40.50 (38.00-46.00)		12.00 (7.25-15.00)	
Language-speech disorder	42.00 (39.75-46.00)		14.00 (10.75-17.00)	
Specific learning disability	40.00 (36.00-45.00)		11.00 (9.00-16.00)	
Other	42.00 (37.00-45.00)		13.00 (9.00-16.00)	
Total income				
2250 TL and below	41.00 (39.00-45.00)	0.841†	12.00 (7.00-17.00)	0.695†
2251 TL-4500 TL	42.00 (38.00-45.00)		13.00 (9.00-16.00)	
4501 TL and above	41.00 (38.00-45.00)		12.00 (10.00-15.00)	
Parents working from home during the pandemic				
No	1.00 (0.00-1.00)	0.860*	1.00 (0.00-1.00)	0.413*
Yes	1.00 (0.00-1.00)		1.00 (0.00-1.00)	
Sibling with special education				
No	41.00 (38.00-45.00)	0.992*	12.50 (9.00-16.00)	0.948*
Yes	41.00 (39.00-45.50)		12.00 (9.00-16.00)	
The time the child can not receive special education in the pandemic				
Less than 6 months	42.00 (39.00-45.00)	0.082*	13.00 (9.00-16.00)	0.592*
6 months and more	40.00 (36.75-44.00)		12.00 (9.00-15.25)	
Other education applications instead of special education in the pandemic				
No	41.00 (38.50-45.00)	0.415*	13.00 (9.00-16.00)	0.482*
Yes	42.00 (37.00-46.25)		12.00 (9.00-15.00)	
Online special education application				
No	41.00 (39.00-45.00)	0.428*	13.00 (9.00-16.00)	0.773*
Yes	41.00 (36.00-44.00)		11.00 (9.00-16.00)	
The development of the child in the period of the pandemic				
Regressed	41.00 (37.00-44.00)	0.540†	13.00 (9.00-17.00)	0.603†
Remained stable	41.00 (38.00-45.00)		13.00 (9.00-16.00)	
Advanced	43.00 (40.00-45.75)		12.00 (9.00-14.75)	

**Mann Whitney U, †Kruskal Wallis, §p<0.05*

other special needs (25). Children with ASD have difficulty adapting to new environments/situations, especially during the pandemic (28). In addition, with the pause in special education programmes, parents became teachers at home, and the fact that parents did not know enough about the situation of children with ASD and did not receive preparatory training did not allow home education to be implemented well enough. The stressful processes experienced by families in the care of children with ASD, the difficulty of parents in adapting to the sudden changes during the virus pandemic, and the increase in inappropriate behaviours due to lack of physical activity due to restrictions may have led to increased burnout. At the same time, high levels of imprinting attitudes and problematic interaction with parents, problems with online communication between the teacher and parent to monitor the development of the children during home education caused online education to be non-optimal (28-33). In a study conducted in Türkiye, it was reported that the frequency of emotional and behavioural problems in the ASD group was higher than in the group with SLD, intellectual disability and speed-language disorder group (34). The sensitivity of children with ASD to changes in routines, the increase in anger outbursts and behavioral problems due to these changes, the problems related to education and the concerns of families about the development of their children, the difficulties experienced in accessing health services, and the lack of social support may have increased the burnout level of parents. The increase in burnout may also have led parents to adopt more intolerant and harsh approaches to their

children. It has also been reported in the literature that stressed parents are more likely to respond to their children's anxious behaviours or demands in aggressive or abusive ways, and that the pandemic has been very challenging for parents and has significantly increased their stress levels (35,36).

In a study examining the burnout levels of parents of CSN aged 6-18 years during the pandemic period, it was found that there was a significant difference between the MBI Personal Achievement dimension score and monthly economic income, and this difference was due to the difference between the highest income level and the lowest income level (25). In another study conducted with mothers with children diagnosed with ASD in Türkiye, no significant difference was found between income level and Emotional Exhaustion or Personal Achievement scores (37). In our study group, it was observed that the emotional exhaustion dimension score increased as the total income of the family increased. These differences in the results may have resulted from differences in study designs such as the economic distribution of the study groups, age groups, and whether the study was conducted during the lockdown period of the pandemic. In our study, 76% of the parents stated that their children's development regressed or remained stable during the pandemic-related lockdown period. It was found that parents with high scores in the MBI Emotional Exhaustion and Depersonalization dimensions had more regression in the development of their children. A study conducted in Kenya reported that during the pandemic restriction period, 53.33% of CSN found distance education insufficient, 90% thought that their education was significantly affected, and the number of students in special education schools decreased by 60% after the lockdown period (38). The level of burnout in parents may have increased as a result of the increased burden on parents with the closure of special education schools. Parents who experience more burnout may also not be able to deal with their children sufficiently. Parents with high levels of mental distress may be more limited and distant in their communication with their children and more insensitive to their children's needs, and this may increase the likelihood of their children developing maladaptive behaviours (23).

Considering the parent-child relationship, it was observed that parents with children aged 11 years and younger had significantly more positive relationships with their children. The fact that the development of pre-adolescent CSN observed in our study progressed more during the pandemic period may also be due to this relationship. Additionally, the restricted social life of the CSN who need individualization and autonomy during the adolescence period and spending more time at home with their parents might have negatively affected the parent-child relationship.

When the literature was reviewed, few studies on parental burnout during the pandemic period were found. The strengths of our study are that it was conducted during the restriction period of the pandemic, all parents of children between the ages of 0-18 were included, and all special needs diagnoses were examined in our study, while a single diagnosis was evaluated in similar studies in the literature. When we look at the limitations of our study; evaluating the developmental levels of CSN based on the observations of the family, the forms are filled out only by the parents, absence of a scale with Turkish validity and reliability that assesses the burnout of parents with children aged 0-18 years. In addition, the absence of a healthy control group in our study prevented us from seeing the differences between the groups with and without children with special needs. Since the study was a cross-sectional study and there was no clear information about pre-pandemic burnout and the relationship of parents with children with special needs, the effects of the pandemic were not evaluated clearly. Completing the forms online is among the limitations in terms of result reliability.

At the beginning of the study, it was thought that the closure of special education services could have a negative impact on the development of children with severe social interaction difficulties, such as ASD, and lead to outcomes that are difficult to reverse. At the same time, it was predicted that with the discontinuation of special educational support, the stress and anxiety levels of families might increase, they might have to make more efforts to overcome this deficiency, and this situation might increase the level of burnout of parents. The results of the study support our hypotheses. It was thought that parents with children in the younger age group would have more relationship problems due to the discontinuation of special educational support, and it was found that families with children in adolescence were more affected by this situation. This situation weakened the view that special educational support is more beneficial for young children and drew attention to the fact that its effect in adolescence should not be ignored.

As a result, parents were forced to work from home, educate their children at home and do the household chores during the lockdown. At the same time, meetings with family and friends were restricted and most social activity centres were temporarily closed due to social distancing (39). In addition, various businesses reduced or closed their services, leading to situations such as financial challenges and unemployment, which have the potential to increase parental burnout (24). The lockdown measures have led to a significant increase in the amount of time parents and children spend together, and staying at home for more than 2 months has led to a reduction in individual spaces at home. Families with school-age children were forced to allocate some of their time together to education, and this led to parents taking on the role of teachers for their children.

These special living conditions may have contributed to increased parental burnout due to increased housework, inability to use external environmental sources due to the risk of infection contagion, and reduced use of internal sources (40). Investigating how the restrictions and absence of special

education affected the mental health of the families and the development of CSN is important for understanding how the schools and society can support these individuals in similar periods when special education is discontinued.

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COVID-19 Patients Who Admitted to Pediatric Emergency Department

Çocuk Acil Servise Başvuran COVİD-19 Hastalar

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ABSTRACT

Objective: This study to evaluate SARS-CoV-2 PCR test-positive patients who were admitted to Pediatric Emergency Department, together with their admission symptoms and clinical, laboratory, and radiological findings.

Material and Methods: The study was conducted on patients admitted to the Pediatric Emergency Department between March 2020 and January 2021.

Results: A total of 1007 patients who tested positive for SARS-CoV-2 PCR were included in the study. Among these patients, 512 (50.8%) were female, 495 (49.2%) were male, and the median age was 171 months (range: 2-226). Disease classification revealed that 106 (10.5%) patients were asymptomatic.The most common symptoms were fever (45.6%), cough (38%), and sore throat (26.7%). In terms of age groups, fever (p<0.001) and vomiting and nausea (p=0.010) were significantly more prevalent in the group aged over 120 months. Chest X-rays were obtained for 73.4% of the patients, with 1.06% showing abnormal findings. The moderate group exhibited a higher incidence of abnormal chest X-ray findings compared to other clinical severity groups (p=0.010). CRP elevation was the most frequently observed laboratory finding, affecting 28.9% of patients, followed by leukopenia in 38.5% and lymphopenia in 25.2%. CRP, procalcitonin and troponin values were higher in the severe group (p=0.019; p=0.003, p=0.013). Inpatient treatment was administered to 10.3% of the patients.

Conclusion: Although coronavirus disease generally presents with asymptomatic or mild symptoms in children, it is important to be aware that rare cases may exhibit a severe course and even result in death. Detecting asymptomatic cases is crucial in terms of transmission control, especially to protect elderly individuals and adults with underlying diseases.

Key Words: Child, COVID-19, Pediatric emergency

ÖZ

Amaç: Bu çalışmada amaç Çocuk Acil Servise başvuran SARS-CoV-2 PCR testi pozitif olan hastaları başvuru semptomları, klinik, labaratuar ve radyolojik bulgularıyla birlikte değerlendirmek.

0000-0002-8640-297X : FİDANCI İ
0000-0003-4367-725X : TAŞAR MA
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Conflict of Interest / *Çıkar Çatışması*: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. Approval for the study was obtained from the Ankara Training and Research Hospital, Clinical Research Ethics Committee (date: June 30, 2021, number: 600/2021).

Contribution of the Authors / Yazarların katkısı*: *FİDANCI İ: 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. ***TAŞAR MA:*** 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. ***CURA YAYLA BC:*** 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. ***AYKAÇ K:*** 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. ***AKINTUĞ B:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***BERKAY KILIÇ M:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***İŞCAN GD:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments.

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Gereç ve Yöntemler: Çalışma üçüncü basamak Çocuk Acil Servise Mart 2020- Ocak 2021 tarihleri arasında başvuran hastalarda yapıldı. Verilerin analizinde SPSS 26 V kullanıldı.

Bulgular: Çalışmaya 1007 SARS-CoV-2 PCR pozitif hasta dahil edildi. Bunlardan 512 (%50.8)'si kız, 495 (%49.2)'i erkek cinsiyetteydi, yaş ortancası 171 ay (min-max:2-226)'di. Hastaların sınıflamasında 106 (%10.5) hasta asemptomatikti. En sık görülen semptom ateş (%45.6), öksürük (%38.3) ve boğaz ağrısıydı (%26.7). Yaş gruplarına göre bakıldığında 120 ay üstü grupta ateş (p<0.001), kusma ve ishal (p=0.010) anlamlı derecede yüksekti. Hastaların %74.3 üne akciğer grafisi çekildi, %1.06'sı anormal olarak değerlendirildi. Bu durum orta ağırlıktaki grupta daha çok görüldü (p=0.010). Sadece 20 (%1.9) hastaya bilgisayarlı tomografi çekildi, bununda 8 (%0.8) tanesi anormal olarak raporlandı. CRP yüksekliği hastaların %28.9'unda, lökopeni %38.5'unda, lenfopeni %25.2'sinde görülen en yaygın görülen laboratuar bulgularıydı. CRP, Prokalsitonin ve Troponin değerleri ağır grupta anlamlı olarak yüksekti (p=0.019; p=0.003, p=0.013). Hastaların %10.3 hastanede yatarak tedavi aldı.

Sonuç: Koronavirüs hastalığı çocuklarda her ne kadar asemptomatik ve hafif semptomlarla seyretse de komorbid hastalığı olan grupta ağır seyredebileceği ve ölümlerin görülebileceği, asemptomatiklerin bulaş açısından tespitinin özellikle yaşlı ve altta yatan hastalığı olan erişkinleri korumak için önemli olduğu unutulmamalıdır.

Anahtar Sözcükler: Çocuk, COVİD-19, Çocuk acil

INTRODUCTION

A new type of coronavirus, known as severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2), initially emerged in China in December 2019 (1). The disease, which is transmitted through droplets and respiratory secretions, can also be spread by asymptomatic individuals (2). On January 30, 2020, the World Health Organization declared the outbreak a pandemic, and on February 12, 2020, it was officially named COVID-19. The first case in Türkiye was reported on March 11, 2020.

The diagnosis of coronavirus disease was first reported in a child in Shenzhen in January 2020 (3). In children, COVID-19 generally follows a mild course, and it has been observed that 50-70% of cases recover asymptomatically (4,5). The most common symptoms in symptomatic pediatric patients are fever and cough, while diarrhea is less commonly reported (6). Based on clinical symptoms, the disease is classified into asymptomatic, mild, moderate, severe, and critical categories (7). Although COVID-19 tends to have a mild clinical course in previously healthy children, it can lead to severe illness and even death in children with underlying chronic conditions, who belong to the high-risk group.

In the study, we aimed to evaluate pediatric patients with COVID-19 who were admitted to the Pediatric Emergency Department (PED) during the first ten months of the pandemic, focusing on their symptoms, as well as their clinical, laboratory, and radiological findings.

MATERIALS and METHODS

The study was conducted on patients aged 0-18 years, who were admitted to the PED of a tertiary university hospital in Ankara, the capital city of Türkiye, between March 2020 and January 2021. Patients who were admitted during the study period and diagnosed with pediatric coronavirus disease were included, while those who refused treatment and left the hospital without permission were excluded. Demographic data, laboratory and radiological findings, and patient follow-ups were retrospectively obtained from computer records.

The clinical severity classification of pediatric coronavirus disease cases was based on the classification proposed by Dong et al. (8): (a) asymptomatic infection, which included cases with positive diagnoses but no clinical or radiological findings; (b) mild disease, which included cases with acute upper respiratory tract infection without clinical and radiological pneumonia; (c) moderate disease, which included cases with symptoms of pneumonia and respiratory tract infection; (d) severe-critical illness, which included cases with progressive respiratory illness, dyspnea, central cyanosis, acute respiratory distress syndrome, or organ dysfunction such as respiratory failure, shock, encephalopathy, myocardial damage, coagulation abnormalities, and acute kidney injury.

The SARS-CoV-2 nucleic acid was detected using reverse transcription polymerase chain reaction (RT-PCR) following the guidelines provided by the World Health Organization (9).

Hemoglobin and leukocyte counts were evaluated separately according to the age of the patients. Hemoglobin and leukocyte counts were evaluated separately based on the patients' age. The following cutoff values were used to determine high levels: CRP > 10 mg/L, procalcitonin > 0.5 ng/mL, LDH > 300 U/L, ALT > 45 U/L, AST > 50 U/L, creatinine > 62 µmol/L, blood urea nitrogen > 7.1 mmol/L, CK > 170 U/L, CK-MB > 25 U/L, and D-dimer > 0.55 mg/L.

The chest X-ray was evaluated by clinicians.

Approval for the study was obtained from the Ankara Training and Research Hospital, Clinical Research Ethics Committee (date: June 30, 2021, number: 600/2021).

Statistical Analyses

Statistical analyses were performed using the SPSS software version 26. The distribution of variables was assessed

through visual methods (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine their normality. Descriptive analyses were presented using frequency tables for ordinal variables, while medians and minimum-maximum values were used for non-normally distributed variables. Non-parametric tests were conducted to compare these variables as well as the ordinal variables. Categorical variables were analyzed using frequency distributions and compared using Chi-squared or Fisher's Exact tests. The Kruskal-Wallis test was employed for multiple comparisons. All tests were two-tailed in all analyses, and p <0.050 was considered significant.

RESULT

Out of the 26.947 patients admitted to the PED between April 2020 and January 2021, 1.007 (3.7%) were tested and confirmed to be positive for SARS-CoV-2 PCR. Among these patients, 512 (50.8%) were female, and 495 (49.2%) were male. The median age of the 1,007 patients was 171 months (min-max: 2-226). When evaluating the clinical severity classification, mild cases accounted for 81% (n=818), and asymptomatic cases accounted for 10.5% (n=106), totaling 91.74% (n=924) of all patients. It was observed that children with mild clinical presentation were older compared to those with other clinical presentations, and this difference was statistically significant (p=0.010) (Table I, Figure 1-3).

Among the patients with coronavirus disease, 901 (89.4%) presented with symptoms, while only 10.5% (n=106) were asymptomatic. Fever was the most common symptom, reported by 45.6% (n=460) of patients. Cough was the second most prevalent symptom, affecting 38.3% (n=383) of cases, followed by sore throat at 26.7% (n=269), and headache at 13% (n=136) (Table II).

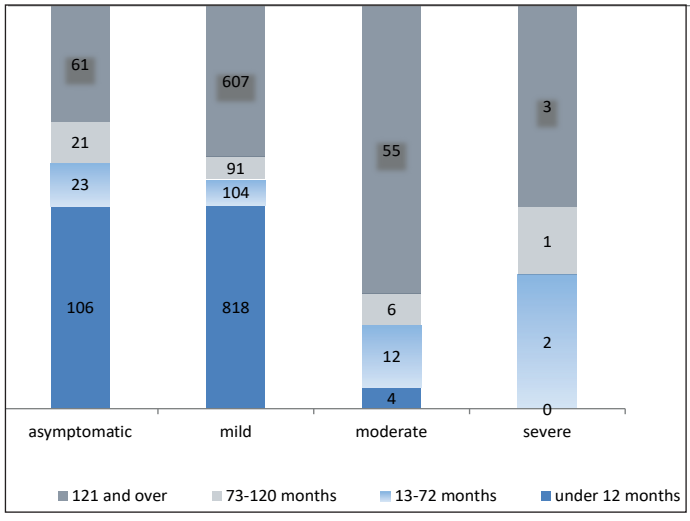

Figure 1: Clinical severity according to age

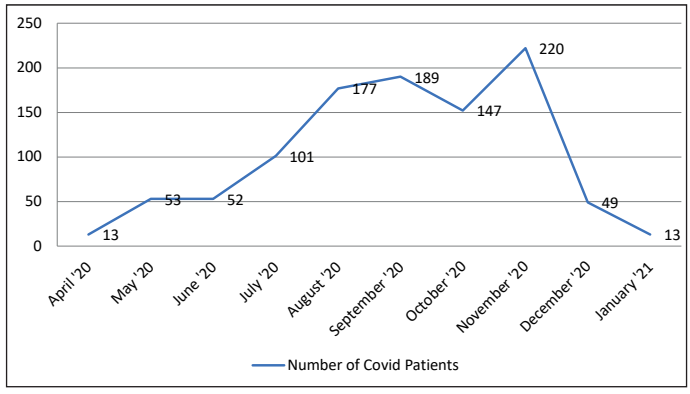

Figure 2: Number of SARS-CoV-2 PCR-positive patients by months

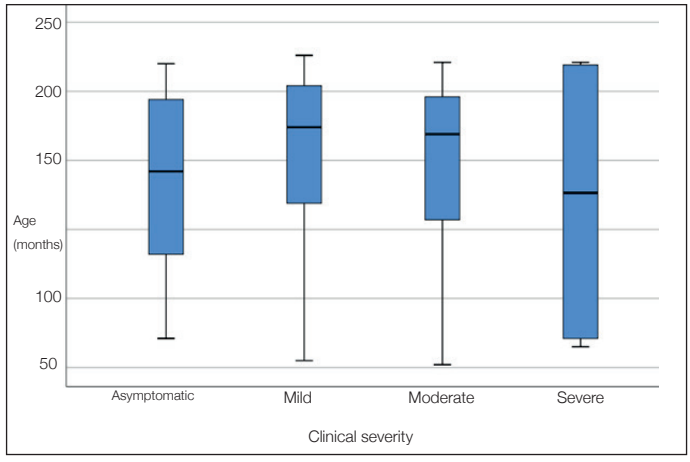

Figure 3: Clinical severity according to age

Patients were divided into four age groups: under 12 months, 13-72 months, 73-120 months, 121 months, and older. Fever (p<0.001), vomiting and/or diarrhea (p=0.010) were substantially more prevalent at the age of 121 months and older (Table II).

Leucopenia was the most common finding in laboratory parameters. It was higher in 38.5 % (n=110) of patients. This was followed by elevated CRP (28.9%), lymphopenia (25.2%), and elevated Procalcitonin levels (5.7%). When CRP, procalcitonin and troponin values were evaluated according to the severity of the disease, CRP, procalcitonin and troponin were found to be significantly higher in the severe group (p=0.019; p=0.003, p=0.013) (Table III).

Chest X-ray was obtained in 74.3% (n=749) of patients, with 80 (10.7%) showing abnormal results. The most common abnormality observed was consolidation, found in 55 (7.3%) patients. This finding was statistically significant in patients with moderate clinical presentation compared to other groups (p<0.001). Among the 20 patients who underwent chest tomography, 8 had abnormal findings, including a ground glass appearance in 6 patients (p=0.006) and pleural effusion in 2 patients (Table IV).

When analyzing symptoms and findings based on gender, it was found that headache was significantly more common in

Table I: Demographic characteristics of the groups

	Total (n=1007)	Asymptomatic (n= 106)	Mild (n=818)	Moderate (n=77)	Severe (n=6)	p
Age (months)*,	171 (2-226)	142 (21-220)	174(5-226)	169(2-221)	121(15-221)	0.010‡
Gender†						
Female	512 (50.8)	50 (47.2)	422 (51.6)	36 (46.8)	4 (66.7)	
Male	495 (49.2)	56 (52.8)	396 (48.4)	41 (53.2)	2 (33.3)	0.597§
Hospitalization†	104 (10.3)	20 (18.9)	60 (7.3)	18 (23.4)	6 (100)	0.002§
Chronic disease (+)†	38 (3.8)	2 (1.9)	29 (3.5)	4 (5.2)	3 (50.0)	0.004§
Hematological/Oncological	3 (7.9)	0	3 (10.3)	0	0	
Neurological	6 (15.8)	1 (50.0)	1 (3.4)	2 (25.0)	2 (66.7)	<0.001§
Asthma	14 (36.8)	0	11 (37.9)	3 (75.0)	0	
Genetic disease	1 (2.6)	0	0	0	1 (16.7)	
Other	14 (36.8)	0	14 (48.3)	0	0	

**(median,min-max), †n (%), ‡Kruskal Wallis, §Chi-Square test*

Table II: Symptoms according to groups

Symptoms n(%)	Total (n=901)	Mild (n=818)	Moderate (n=77)	Severe (n=6)	p
Fever	460 (51)	414 (50.6)	41 (53.2)	5 (83.3)	0.228
Headache	136 (15.1)	127 (15.5)	9 (11.7)	0	0.390
Sore throat	269 (29.8)	256 (31.3)	13 (16.9)	0	0.003
Rhinorrhea	50 (5.5)	47 (5.7)	2 (2.6)	1 (16.7)	0.274
Chest pain	17 (1.9)	14 (1.7)	3 (3.9)	0	0.437
Dyspnea	33 (3.6)	20 (2.4)	12 (15.6)	1 (16.7)	0.001
Cough	383 (42.5)	337 (41.2)	45 (58.4)	1 (16.7)	0.006
Vomiting	78 (8.6)	72 (8.8)	4 (5.2)	2 (33.3)	0.055
Diarrhea	93 (10.3)	84 (10.3)	7 (9.1)	2 (33.3)	0.169
Abdominal pain	40 (4.4)	36 (4.4)	4 (5.2)	0	0.724
Weakness	140 (15.5)	132 (16.1)	7 (9.1)	1 (16.7)	0.221
Myalgia	125 (13.9)	118 (14.4)	7 (9.1)	0	0.266
Rash	2 (0.2)	1 (0.1)	1 (1.3)	0	0.309
Conjunctivitis	4 (0.4)	3 (0.4)	1 (1.3)	0	0.604
Loss of smell and taste	117 (12.9)	106 (13.0)	11 (14.3)	0	0.603
Abnormal Respiratory system examination	25 (2.8)	12 (1.5)	11 (14.3)	2 (33.3)	0.001

males (p=0.028), while contact history was significantly more common in females (p=0.044). No gender difference was observed in other symptoms and findings (p>0.050).

DISCUSSION

Our study is a comprehensive investigation that evaluates the demographic, clinical, and radiological characteristics of 1007 pediatric patients with coronavirus disease who were admitted to the PED. Most of these patients had either asymptomatic or mild presentations. However, it was observed that the disease had a more severe clinical course in patients older than 120 months. In terms of overall admissions, 3.7% of our pediatric patients were diagnosed with coronavirus disease, while this rate varied between 0.2% and 3.0% in other studies (9,10). In our study, the incidence of coronavirus disease was similar in both girls and boys among pediatric patients. Although females were more prevalent in the group with a severe clinical status according to the clinical scoring system, no statistically significant difference in gender was observed (8-10).

The primary manifestations of coronavirus disease in children include fever, nasal congestion, sore throat, and less frequently, gastrointestinal symptoms such as abdominal pain, vomiting, and diarrhea (12,13). Although cough is reported as a common symptom in some studies, fever has consistently been identified as the most prevalent symptom in many studies (5,14,15). In a meta-analysis of 48 pediatric studies on coronavirus disease, fever was found to be the most frequently reported symptom, while gastrointestinal symptoms were less commonly reported. The same meta-analysis highlighted that infants under one year of age who presented with gastrointestinal symptoms had a poor prognosis (16). Gastrointestinal symptoms can

Table III: Laboratory findings according to groups

Laboratory findings n(%)	Total (n=286)	Mild (n=237)	Moderate (n=43)	Severe (n=6)	p*
Leukocytosis	46 (16.1)	36 (15.2)	7 (16.3)	3 (50.0)	0.072
Leucopenia	110 (38.5)	90 (38.0)	17 (39.5)	3 (50.0)	0.830
Neutropenia	23(8.0)	21 (8.9)	2 (4.7)	0	-
Lymphopenia	72 (25.2)	62 (26.2)	9 (20.9)	1 (16.7)	0.670
Thrombocytopenia	8 (2.8)	6 (2.5)	0	2 (33.3)	0.009
Elevated CRP	(n=287) 83 (28.9)	(n=227) 65 (27.4)	(n=44) 13 (29.5)	(n=6) 5 (83.3)	0.019
Elevated procalcitonin	(n=227) 13 (5.7)	(n=186) 9 (4.8)	(n=36) 1 (2.8)	(n=5) 3 (60.0)	0.003
Elevated D-dimer	(n=32) 7 (21.9)	(n=21) 4 (19.0)	(n=6) 2 (33.3)	(n=5) 1 (20.0)	0.768
Elevated troponin	(n=184) 14 (7.6)	(n=145) 8 (5.5)	(n=33) 3 (9.1)	(n=6) 3 (50.0)	0.013

*****Kruskal Wallis Test*

Table IV: Chest X-Ray and CT findings according to groups

	Total (n=749)	Mild (n=666)	Moderate (n=77)	Severe (n=6)	p
Chest X-Ray findings					
Normal	669 (89.3)	655 (98.3)	14 (18.2)	0	
Consolidation	55 (7.3)	5 (0.8)	44 (57.1)	6 (100)	
Hyperaeration	1 (0.1)	0	1 (1.3)	0	
Bronchovascular change	24 (3.2)	6 (0.9)	18 (23.4)	0	
Pleural effusion	2 (0.3)	1 (0.2)	0	1 (16.7)	0.001
	Total (n=16)	**Mild (n=8)**	**Moderate (n=5)**	**Severe (n=3)**	**p**
CT Findings					
Normal	8 (50.0)	7 (87.5)	1 (20.0)	0	0.006
Ground glass	6 (37.5)	1 (12.5)	2 (40.0)	3 (100)	
Subpleural consolidation	2 (12.5)	0	2 (40.0)	0	

occur without respiratory symptoms, and the most commonly reported gastrointestinal symptoms in children are diarrhea, vomiting, and abdominal pain (17). Consistent with the literature, our study found fever to be the most prevalent symptom, while diarrhea, vomiting, and abdominal pain were observed less frequently. Furthermore, vomiting and diarrhea were the most prevalent symptoms following fever in patients with a severe clinical presentation. Although there is no specific laboratory finding exclusive to pediatric patients with coronavirus disease, common laboratory results include leukopenia, leukocytosis, and lymphopenia. Different studies have reported varying prevalence rates of these laboratory findings. Some studies have highlighted lymphopenia as the most common finding, while others have identified leukopenia and lymphopenia as the predominant findings. In some studies, leukocytosis and lymphopenia were reported as the most common findings (11,18-22). In a meta-analysis, leukocytosis and lymphopenia were found to be the most commonly observed laboratory findings (16). Consistent with the literature, our study also identified leukopenia and lymphopenia as the most common laboratory abnormalities. Another meta-analysis that focused on adult patients reported that thrombocytopenia was associated with an increased risk of severe disease and mortality in individuals with coronavirus disease (23). Similarly, in our study, thrombocytopenia was found to be significantly higher in the severe clinical group, supporting the association between thrombocytopenia and disease severity.

Moreover, several studies have reported elevated levels of CRP, procalcitonin, and troponin, along with other laboratory findings, particularly in patients requiring hospitalization or classified as having a severe clinical presentation (24,25). Consistent with the existing literature, our study found elevated levels of these markers in a majority of patients within the severe clinical group.

The utilization of imaging techniques in children with COVID-19 is limited and not routinely recommended. While computed tomography (CT) scans play a crucial role in treatment planning for adults, especially in cases where there is a clinical suspicion but negative SARS-CoV-2 PCR results or delayed access to CoV-2 PCR results, their usage in children is extremely restricted (26,27).

In comparison to studies conducted on adults, pediatric patients exhibit a much lower incidence of abnormal findings on chest computed tomography (CT) scans (28). Furthermore, caution

is warranted due to the potential risk of radiation-induced malignancies associated with CT scans (29). In our study, chest X-rays were performed in 74.3% of the patients, and 89.3% of these X-rays were interpreted as normal. Among the severe patient group, consolidation was observed in all cases on chest radiographs. Additionally, 16 patients (1.5%) underwent chest tomography, with 8 of them (50%) displaying abnormal findings. In a study evaluating children, 64.9% of coronavirus disease patients were diagnosed with radiologically confirmed pneumonia (11). However, we did not observe such findings in our study.

Pediatric patients with coronavirus disease typically exhibit an asymptomatic or mild symptomatic course, while those with comorbidities and younger age groups tend to experience a more severe course. The prevalence of asymptomatic pediatric cases of coronavirus disease varies between 10.7% and 56.6%, often observed in individuals who have been in contact with infected individuals. These variations in rates are likely attributed to differences in protocols across hospitals within and between countries (30). In another study, the rate of asymptomatic patients was reported as 62%, while severe cases accounted for 12% (31). A multicenter study reported rates of asymptomatic and mild cases ranging from 80% to 90% (26). A study conducted in China, involving 2143 children with a median age of 7, reported that 41% of the children had pneumonia with a moderate clinical course, while 2.5% exhibited a severe clinical course (8). Consistent with the literature, our study found that 91.7% of cases were mild or asymptomatic, and these children had a statistically significantly younger median age compared to other groups.

Hospitalization rates for pediatric patients with coronavirus disease vary due to differing criteria in different countries. A study conducted in Greece reported a hospitalization rate of 26.6%, with a higher proportion of hospitalized cases observed among children under the age of 5 (32). In a study conducted in the United States between February 12 and April 2, which included 149.082 cases diagnosed with coronavirus disease, only 1.7% of the cases were in the age range of 0-18, and 5.7% of pediatric patients required hospitalization and follow-up (5). In a similar study conducted in Italy involving 28 centers, the hospitalization rate was 57.7% (26). In our study, the hospitalization rate was 10.3%. In the early days of the pandemic, our hospital served as the reference hospital, and all pediatric patients with coronavirus disease were admitted, including asymptomatic patients.

The most significant limitation of our study is its single-center nature and the retrospective collection of data from computer records. However, it is worth noting that the study period included a substantial number of cases, as our hospital was the first in our country to collect pediatric cases of coronavirus disease.

In conclusion, although coronavirus disease tends to manifest with asymptomatic or mild symptoms in children, it is crucial to recognize that severe cases and even fatalities can occur, albeit rarely. Detecting asymptomatic cases is particularly important for preventing transmission, especially to vulnerable populations such as the elderly and individuals with underlying health conditions

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Musculoskeletal Involvement in Pediatric Behçet's Disease: A Single Center Experience

Pediatrik Behçet Hastalığında Kas İskelet Sistemi Tutulumu: Tek Merkez Deneyimi

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ABSTRACT

Objective: Behçet's disease (BD) is an inflammatory disease characterized by recurrent oral ulcers, genital ulcers, ocular manifestations, and vascular involvement. Musculoskeletal symptoms are common both at the time of presentation and throughout the course of BD. This study aims to report the frequency and characteristics of musculoskeletal involvement in pediatric Behçet's disease (PEDBD) followed by our clinic.

Material and Methods: This retrospective medical record review included patients diagnosed with PEDBD before the age of 16 between January 2010 and December 2022.

Results: Of the 90 patients included in the study, 48 (53.3%) were female. Their mean age at diagnosis was 12.4 ± 3 years. All patients (100%) had recurrent oral ulcers, while 55 (61.1%) had genital ulcers, 44 (48.9%) had musculoskeletal involvement, 37 (41.1%) had skin manifestations, 19 (21.1%) had ocular involvement, 17 (18.9%) had neurological involvement, and 17 (18.9%) had vascular involvement. Among the patients with joint involvement, 27 (65.9%) had arthritis, 41 (100%) had arthralgia, 37 (90.1%) had oligoarticular joint involvement, and 29 (70.7%) had asymmetrical involvement. The most frequently affected joints in patients were knee (63.4%), ankle (31.7%), wrist (19.5%), sacroiliac joints (14.6%), hands (12.2%) (Involvement of the metacarpophalangeal joint in one patient and the proximal interphalangeal joint in four patients), elbow (9.8%) and feet (4.9%) (One of the patients had metatarsophalangeal joint involvement and the other had proximal interphalangeal joint involvement).

Conclusion: Musculoskeletal symptoms are common in PEDBD and can be observed as an early sign of the disease at the time of diagnosis. Therefore, it is important to thoroughly inquire about possible BD in children with musculoskeletal symptoms.

Key Words: Arthralgia, Arthritis, Pediatric Behçet's disease, Musculoskeletal system

ÖZ

Amaç: Amaç: Behçet hastalığı (BH) tekrarlayan oral ülserler, genital ülserler, oküler bulgular ve vasküler tutulum ile karakterize inflamatuvar bir hastalıktır. Kas-iskelet sistemi semptomları hem başvuru sırasında hem de Behçet hastalığının seyri boyunca yaygındır. Bu çalışmanın amacı, kliniğimiz tarafından pediatrik Behçet hastalığı (PEDBH) tanısı ile takip edilen hastalarda kas-iskelet sistemi tutulumunun sıklığını ve özelliklerini bildirmektir.

Gereç ve Yöntemler: Bu retrospektif tıbbi kayıt incelemesi, Ocak 2010 ile Aralık 2022 tarihleri arasında 16 yaşından önce PEDBH tanısı alan hastaları kapsamaktadır.

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Ethics Committee Approval / *Etik Kurul Onayı*: Ethics Committee of Ankara Bilkent City Hospital (Ethics Committee Approval No/Date: E2-23-3123/04.01.2023)

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Bulgular: Çalışmaya dahil edilen 90 hastanın 48'i (%53.3) kadındı. Ortalama tanı yaşı 12.4±3 yıldı. Tüm hastalarda (%100) tekrarlayan oral ülserler, 55'inde (%61.1) genital ülserler, 44'ünde (%48.9) kas-iskelet sistemi tutulumu, 37'sinde (%41.1) deri bulguları, 19'unda (%21.1) göz tutulumu, 17'sinde (%18.9) nörolojik tutulum ve 17'sinde (%18.9) vasküler tutulum vardı. Eklem tutulumu olan hastaların 27'sinde (%65.9) artrit, 41'inde (%100) artralji, 37'sinde (%90.1) oligoartiküler eklem tutulumu ve 29'unda (%70.7) asimetrik tutulum vardı. Hastalarda en sık etkilenen eklem diz (%63.4) olurken, bunu ayak bileği (%31.7), el bileği (%19.5), sakroiliak eklemler (%14.6), eller (%12.2) (Bir hastada metakarpofalangeal eklem ve dört hastada proksimal interfalangeal eklem tutulumu vardı), dirsek (%9.8) ve ayaklar (%4.9) (Hastalardan birinde metatarsofalangeal eklem tutulumu ve diğerinde proksimal interfalangeal eklem tutulumu vardı) takip etti.

Sonuç: Kas-iskelet sistemi semptomları PEDBH'de yaygındır ve tanı anında hastalığın erken bir belirtisi olarak gözlemlenebilir. Bu nedenle, kas-iskelet sistemi semptomları olan çocuklarda olası BH'nin ayrıntılı bir şekilde araştırılması önemlidir.

Anahtar Sözcükler: Artralji, Artrit, Pediatrik Behçet hastalığı, Kas iskelet sistemi

INTRODUCTION

Behçet's disease (BD) is an etiology unknown inflammatory disease characterized by recurrent oral ulcers, genital ulcers, ocular manifestations, skin lesions, gastrointestinal, neurological, musculoskeletal, and vascular involvement, which can affect all organs and systems (1,2). BD often occurs between the second and fourth decades of life. BD can also be observed in children. In fact, studies show that 4-26% of BD patients appear in childhood (3). There is increasing awareness about pediatric Behçet's disease (PEDBD), but information of PEDBD is still limited in the literature. Musculoskeletal symptoms are common both at the time of presentation and throughout the course of BD (4). The most common musculoskeletal symptoms in BD are arthritis and arthralgia, followed by enthesopathy, avascular necrosis, myalgia, and myositis (5). Arthritis occurs in 20-40% of PEDBD cases, is usually oligoarticular and non-erosive, but erosive arthritis is rarely seen in BD (6-9). BD commonly affects the knees, ankles, wrists, and elbows, and rarely causes sacroiliitis (8). Localized myositis is not common in BD and has only been reported in a few children (8).

This study aims to report the frequency and characteristics of musculoskeletal involvement in PEDBD followed by our clinic.

MATERIAL and METHODS

This retrospective medical record review included patients diagnosed with PEDBD before the age of 16 between January 2010 and December 2022. Patients diagnosed with PEDBD before 2016 were evaluated according to the International Study Group for Behçet's Disease (ISG) and International Criteria for Behçet's Disease (ICBD) criteria, while those diagnosed with PEDBD after 2016 were evaluated according to Pediatric Criteria (PedBD) (10-12). Before conducting the study, the diagnoses of all patients were confirmed by experts (BÇA, EÇ, ZET) according to the PedBD criteria. Table I shows the diagnostic criteria for BD. Patients with incomplete medical data, those who did not attend regular follow-up visits, and those diagnosed with BD after the age of 16 years were not included in the study.

The patients' demographic, clinical, laboratory (complete blood count, C-reactive protein, erythrocyte sedimentation rate), and treatment-related data were recorded from their electronic files. Their musculoskeletal symptoms including arthritis, arthralgia, enthesopathy, myalgia, and myositis were noted in the study.

Joint involvement was defined as the presence of joint pain [None of the patients had metabolic (such as electrolyte imbalance) or structural (such as hypermobility, deformity) reasons to explain joint pain], swelling, and/or limited joint mobility, while muscle system involvement was defined as the presence of muscle pain and/or signs of inflammation in the muscle (13).

Laboratory data were examined for the presence of antinuclear antibodies (ANA) and human leukocyte antigen-B51 (HLA-B51).

This study was approved by the Ethics Committee of Ankara Bilkent City Hospital (Ethics Committee Approval No/Date: E2-23-3123/04.01.2023) and conducted in accordance with the Helsinki principles.

Table I. Diagnostic criteria for Behçet's disease

ISG (Adult)*
ROA (mandatory) at least 3 pieces/year
GU
Skin lesions
Ocular involvement
Pathergy test positivity
ICBD (Adult)†
ROA (2 points) at least 3 pieces/year
GU (2 points)
Skin lesions (1 point)
Ocular involvement (2 points)
Vascular involvement (1 point)
Neurological involvement (1 point)
PEDBD (Pediatric)‡
ROA (1 point) at least 3 pieces/year
GU (1 point)
Skin lesions (1 point)
Ocular involvement (1 point)
Vascular involvement (1 point)
Neurological involvement (1 point)

GU: *Genital ulcer,* ***ICBD:*** *International Criteria for Behçet's disease,* ***ISG:*** *International Study Group,* ***PEDBD:*** *Pediatric Behçet's Disease,* ***ROA:*** *Recurrent oral aphthosis* ****** *Mandatory criteria and at least 2 of the others,* ***†:*** *4 and over points,* ***‡:*** *3 and over points*

Statistical analysis

The data were evaluated using the SPSS version 22. Descriptive statistics were used to present quantitative variables as mean± standard deviation (SD) if they had normal distribution, or as median (minimum-maximum) if they did not. Categorical variables were presented as numbers and percentages. When comparing quantitative data, the Student-t test was used for parametric data and the Mann-Whitney U test for non-parametric data. The chi-square test was used to compare categorical variables. The correlation between variables was examined using Pearson's correlation analysis. A p value less than 0.05 was considered statistically significant.

RESULTS

Demographic, clinical, and laboratory parameters

A total of 90 patients, 48 (53.3%) of whom were female, were included in the study. Their mean age at diagnosis was 12.4 ± 3 years. Their median time to diagnosis was 1 year (0-12), and their median follow-up duration was 3 years (1-13). All patients had recurrent oral ulcers, while 55 (61.1%) had genital ulcers, 44 (48.9%) had musculoskeletal involvement, 37 (41.1%) had skin manifestations, 19(21.1%) had ocular involvement, 17 (18.9%) had neurological involvement, 17(18.9%) had vascular involvement, and 6(6.7%) had epididymitis. In addition, HLA-B51 positivity was present in 48(53.3%) patients, and ANA positivity was present in 6 (6.7%) patients. A family history of BD was found in 38(42.2%) patients. Table II summarizes the patients' demographic, clinical, and laboratory parameters.

Musculoskeletal involvement

Musculoskeletal involvement was present in 44(48.9%) patients. Among these patients, 32(72.7%) had musculoskeletal symptoms at the time of diagnosis, and 18 (40.9%) had recurrent musculoskeletal involvement. Regarding the distribution of musculoskeletal symptoms in PEDBD patients, 41(45.6%) had joint involvement, 20(20.2%) had myalgia, and 11(12.2%) had enthesitis.

Among the patients with joint involvement, 27(65.9%) had arthritis, all (n=41, 100%) had arthralgia, 37(90.1%) had oligoarticular joint involvement, and 29(70.7%) had asymmetrical involvement. The most commonly affected joints the patients are the knees (26 patients, 63.4%), followed by the ankle (13 patients, 31.7%), the wrist (8 patients, 19.5%), sacroiliac joints (6 patients, 14.6%), hands (5 patients,12.2%) (Involvement of the metacarpophalangeal joint in one patient and the proximal

Table II: Demographic, clinical and laboratory characteristics of paediatric patients with Behcet's disease

	All patients	Musculoskeletal involvement	Non-musculoskeletal involvement	p
Age at diagnosis years*	12.4 (2-16)	13.5 (5-16)	14 (2-16)	0.620
Age at onset of symptoms years median (min-max)	10.3 (2-15)	10.5 (2-15)	11 (2-15)	0.780
Time to diagnosis years median (min-max)	1 (0-12)	1 (0-12)	1 (0-10)	0.747
Gender†				
Male	42 (46.7)	19 (21.1)	23 (25.6)	0.534
Female	48 (53.3)	25 (27.7)	23 (25.6)	
ROA†	90 (100)	48 (53.3)	42 (46.7)	
GU†	55 (61.1)	24 (26.7)	31 (34.4)	0.280
Skin lesions†	37 (41.1)	16 (17.8)	21 (23.3)	0.284
Ocular involvement†	19 (21.1)	11 (12.2)	8 (8.9)	0.444
Vascular involvement†	17 (18.9)	5 (5.6)	12 (13.3)	0.175
Neurological involvement†	17 (18.9)	10 (11.1)	7 (7.8)	0.593
Epididymitis†	6 (6.6)	2 (2.2)	4 (4.4)	0.429
Pathergy test positivity†	29 (32.2)	15 (16.7)	14 (15.5)	0.822
WBC ($x10^9$ /L)*	7.8 (3.6-25.4)	7.6 (4.6-12.9)	8.1 (3.6-25.4)	0.064
Neutrophils ($x10^9$ /L)*	4.5 (1.4-21.4)	4.3 (2.1-10.3)	4.8 (1.4-21.4)	0.153
Lymphocytes ($x10^9$/L)*	2.3 (0.9-6.3)	2.3 (0.9-3.5)	2.2 (1.1-6.3)	0.551
Thrombocytes, ($x10^9$ /L)*	278 (124-583)	289 (177-583)	264 (124-563)	0.061
CRP (mg/dL)*	4.8 (0-43)	4.6 (0-13.2)	4.9 (0-43)	0.888
ESR (mm/saat)*	10 (2-113)	10 (3-54)	10.5 (2-113)	0.642
HLA B-51†	48 (53.3)	24 (26.7)	24 (26.7)	0.673
Family history†	38 (42.2)	20 (22.2)	18 (20)	0.670

*****median(min-max)*, **†***n(%)*, **CRP:** C-reactive protein, **ESR:** erythrocyte sedimentation rate, **GU:** Genital ulcer, **HLA:** Human leukocyte antigen, **ROA:** Recurrent oral aphthosis, **WBC:** White blood cells*

interphalangeal joint in four patients), the elbow (4 patients, 9.8%), and the feet (2 patients, 4.9%) (One of the patients had metatarsophalangeal joint involvement and the other had proximal interphalangeal joint involvement).

All patients with musculoskeletal involvement received colchicine treatment, and additional non-steroidal anti-inflammatory drugs (NSAIDs) were given to 36.6% of patients. Four patients who did not respond to colchicine and NSAID treatment required additional therapy. One patient with sacroiliitis was started on sulfasalazine and achieved clinical and radiological remission in the third year of treatment, leading to discontinuation of therapy. One patient with polyarticular joint involvement was started on azathioprine, but joint restrictions persisted in the first year. The patient with no evidence of active arthritis received a physiotherapy programme for restriction. Methotrexate treatment was initiated for one patient with involvement in the knee joint, and treatment was discontinued in the second year when complete remission was achieved. Another patient with bilateral knee involvement received two intra-articular steroid treatments at one-year intervals, and adalimumab was started during follow-up. Although the patient did not show active arthritis symptoms in the first year of treatment, there was still restriction in both knees. The patient with no evidence of active arthritis in the knees was entered into a physiotherapy programme for restriction.

Out of the 44 patients with musculoskeletal involvement, 42 (95.5%) were in complete remission regarding musculoskeletal symptoms, while 2 (5.5%) patients with while 2 patients with arthritis had restriction in the joints.

There were no significant differences between the patients with musculoskeletal involvement and those without musculoskeletal involvement in terms of demographic, clinical, and laboratory data (Table II).

DISCUSSION

Musculoskeletal symptoms can be observed as an early manifestation of BD in 20-40% of children with BD (14). This study focused on musculoskeletal involvement in PEDBD, and found that musculoskeletal symptoms were present in approximately one-third of the patients at the time of diagnosis. Arthritis and arthralgia were the most common musculoskeletal symptoms among the patients with BD. Some of the patients had oligoarticular and asymmetrical joint involvement. Complete remission of musculoskeletal symptoms was achieved with treatment in 95.5% of patients.

Joint involvement is common in patients with BD. Although it may not be included in the diagnostic criteria, joint involvement is an important component of BD and can sometimes be the sole presenting symptom (15). The frequency of joint involvement in BD patients varies between 5.2% and 60.1% in Türkiye (16). This may be because some studies do not consider arthralgia as joint involvement but only consider arthritis as joint involvement (16). Davachi et al. (17) reported an incidence of joint involvement of 39.4% in the study of 6.075 BD patients . Sarıcaoğlu et al. (18) evaluated 30 PEDBD patients and reported that arthritis and/or arthralgia were present in 50% of them. Peripheral arthritis was detected in 47.4% of patients in a PEDBD cohort (14). Studies have reported that arthritis in BD generally shows a recurrent, acute, self-limiting course without deformity or erosion, and follows a mild and transient course, primarily affecting large joints such as knees and ankles (8,19). In this study, similar to those in the literature, joint involvement was present in 45.6% of PEDBD patients, and joint involvement was predominantly oligoarticular, with knees and ankles being the most commonly affected joints (7,8).

There are several studies suggesting a higher presence of acneiform skin lesions in BD patients with arthritis (20,21). Although the mechanism of arthritis in BD is not fully understood, the coexistence of acne and arthritis raises the possibility of a pathogenic connection (5,8). Many researchers have emphasized the clustering of cutaneous manifestations with arthritis (21,22). Gaggiano et al. (22) reported a higher prevalence of mucocutaneous clustering in children with BD who initially presented with musculoskeletal symptoms. Our study found no relationship between acneiform skin lesions and arthritis symptoms. Yurtkuran et al. (23) evaluated 57 adult BD patients and reported that hand joint involvement correlated with disease duration. Permanent arthropathies are rare in BD patients (8). Destructive arthropathies have been reported in case reports or limited case series for BD. Frikha et al. (24) evaluated a total of 553 adult BD patients and reported that 1.4% of them had destructive arthritis. In our study, sequela lesions were present in 2.2% of the patients. Early onset of joint involvement may increase the frequency of sequela lesions. However, definitive conclusions can be reached through studies comparing large patient groups of adults and children.

Sacroiliac joint involvement and enthesopathy can also be observed in BD patients (14). Although the prevalence of enthesopathy has been reported to be as high as 38% in some clinical studies, low rates such as 3.4% have also been reported in some other studies (5). The wide variation in reported frequency of enthesopathy in BD patients can be attributed to the lack of sensitive methods for detecting enthesopathy through radiography and physical examination, as well as differences in the selected study populations (5). Özelçi et al. (25) found a frequency of 21.1% for sacroiliitis in BD patients. In the present study, sacroiliitis was present in 14.6% of the patients, while enthesopathy was not detected among them. This may be because the rate of enthesopathy is also found to be very low in the literature.

In BD, arthritis is self-limiting and usually resolves within 2-3 weeks, so drug treatment may not be necessary in most cases (26). Colchicine and NSAIDs are the preferred medications

for the treatment of non-erosive arthritis in BD (27-30). However, various therapeutic alternatives are available for destructive arthritis, including local corticosteroid injections and low-dose systemic corticosteroids. Azathioprine and tumor necrosis factor-alpha (TNF-α) blockers may be effective in rare cases resistant to treatment (5). In this study, four patients resistant to colchicine and NSAID treatment received sulfasalazine, azathioprine, methotrexate, adalimumab, and intra-articular steroid treatments. Complete remission in terms of musculoskeletal involvement was achieved in 97.8% of the patients. Similar to other studies in the literature, persistent arthritis in BD was rare in our study.

The main limitations of the study are that it is a single-center study with a retrospective design, and that BD is less common in childhood than in adults. However, considering the limited number of studies on musculoskeletal involvement in PEDBD, this study will contribute to the literature.

In conclusion, musculoskeletal symptoms are a self-limiting, benign, and common finding in children with BD, which can be considered an early manifestation of the disease. Therefore, it is important to thoroughly inquire and evaluate children with musculoskeletal complaints for possible BD.

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Perspectives of School-Aged Overweight/Obese Children and Their Parents on "Healthy Nutrition Period": A Qualitative Study

Okul Çağındaki Fazla Kilolu/Obez Çocukların ve Ebeveynlerinin "Sağlıklı Beslenme Sürecine Yönelik" Bakış Açıları: Nitel Bir Çalışma

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ABSTRACT

Objective: It is aimed to illuminate the experiences of healthy nutrition counseling given to school aged overweight/obese children and their parents.

Material and Methods: Interviews were conducted with 8 children (and their parents) who received healthy nutrition counseling from Bandırma, Türkiye. Themes were validated by study participants. Experiences with the process were analyzed using thematic analysis.

Results: Children expressed their experiences during the healthy nutrition period with different emotions. The main themes of our study were determined as (a) shortcomings, (b) outputs, (c) challenges, (d) coping strategies, (e) suggestions. By synthesizing the themes and sub-themes, it has been determined that facilitators, indicators and obstacles are intertwined, and communication, motivation, taking concrete steps and cooperation are the needs of the healthy nutrition period.

Conclusion: Our study highlights the issue of family-child collaboration in the healthy nutrition period and presents needs to alleviate barriers. Developing coping strategies, increasing motivation, and supporting the taking of concrete steps could provide a suitable environment for a healthier future.

Key Words: Child, Child Nutrition Sciences, Parents, Pediatric obesity

ÖZ

Amaç: Okul çağındaki fazla kilolu/obez çocuklara ve ebeveynlerine verilen sağlıklı beslenme danışmanlığı sürecinde katılımcıların deneyimlerinin aydınlatılması amaçlanmıştır.

Gereç ve Yöntemler: Bandırma'da (Türkiye) yapılan çalışmada, sağlıklı beslenme danışmanlığı alan 8 çocuk (ve ebeveynleri) ile görüşmeler yapılmıştır. Temalar çalışma katılımcıları tarafından doğrulanmıştır. Süreçle ilgili deneyimler tematik analiz kullanılarak analiz edilmiştir.

Bulgular: Çocuklar sağlıklı beslenme dönemindeki deneyimlerini farklı duygularla ifade etmiştir. Çalışmamızın ana temaları (a) eksiklikler, (b) çıktılar, (c) zorluklar, (d) başa çıkma stratejileri, (e) öneriler olarak belirlenmiştir. Temalar ve alt temalar sentezlendiğinde kolaylaştırıcıların, göstergelerin ve engellerin iç içe geçtiği, iletişim, motivasyon, somut adımların atılmasının ve iş birliğinin sağlıklı beslenme döneminin ihtiyaçları olduğu belirlenmiştir.

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

Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. This study was approved by Bandırma Onyedi Eylul University Health Sciences Non-Interventional Research Ethics Committee (11.04.2022/2022-39).

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

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Sonuç: Çalışmamız, sağlıklı beslenme döneminde aile-çocuk iş birliği konusuna dikkat çekmekte ve engellerin kaldırılmasına yönelik ihtiyaçları ortaya koymaktadır. Başa çıkma stratejilerinin geliştirilmesi, motivasyonun artırılması ve somut adımlar atılmasının desteklenmesi, daha sağlıklı bir gelecek için uygun ortamı sağlayabilir.

Anahtar Sözcükler: Çocuk, Çocuk Beslenmesi Bilimleri, Ebeveynler, Pediatrik obezite

INTRODUCTION

Childhood obesity is one of the most serious public health problems of the 21st century, which continues to increase rapidly in developed, developing, and even low-income countries (1,2). In a study conducted with school-age children (6-10 years old) in our country, 14.3% of the children were overweight and 6.5% obese (3). In the Türkiye Childhood Obesity Survey (COSI-TUR 2016), 9.9% of the 2nd-grade primary school students were found to be obese and 14.6% to be overweight (4). Childhood obesity increases the risk of many chronic diseases, including adult obesity and related heart disease, type 2 diabetes, and cancer, and reduces the quality of life. Therefore, developing more effective interventions to prevent childhood obesity has become a priority in many countries (5,6).

In addition to genetic and complex sociocultural, economic, environmental, and psychosocial factors, the effect of parents on children's nutrition habits is considered among the important causes of the development of childhood obesity (7). As a matter of fact, children's nutrition habits are shaped in the home environment, and parents' attitudes and knowledge about healthy eating habits greatly affect children's nutrition habits (8,9). It is stated that the inclusion of parents in body weight management strategies plays a key role in the management of childhood obesity and its long-term effects are quite critical (9,10). In addition, while it is recommended that this process covers the whole family, it is accepted that the effect of the microenvironment is undeniable in the treatment process (10,11). In this context, it is extremely important to identify the barriers to healthy nutrition of children and parents, to develop healthy eating habits in children and ultimately to prevent childhood obesity (12).

In relation to the increasing obesity in the pediatric population, treatment guidelines focus on lifestyle and behavioral changes and intervention, and pharmacotherapy and surgical methods are presented as alternatives for resistant patients (13). Although intervention studies in nutrition management in childhood obesity are often directed at modifiable risk factors, evidence-based individual and environmental risk factors should also be considered (14). It is known that parents perceive this situation as a public health problem and have difficulties in daily life for prevention and intervention (15). It is known that obesity between the ages of 6-18 is important for the development of obesity preventive public health interventions, since it is the school age period. Because obesity between the ages of 6-18 is school age, it is important in the development of public health interventions to prevent obesity (16). Obesity, which starts at the age of 4-11 and continues into adulthood, increases the burden of chronic disease, as a matter of fact, childhood obesity has been an important health problem in the growth monitoring report of the 6-10 age group in Türkiye (17,18). The barriers that parents encounter when changing their children's nutritional habits are known as parental-self-efficacy, motivation, and readiness to change (19). In a review in which intervention strategies for obesity were examined, it was emphasized that clinical studies were needed for the causality of the gaps in the reflection of knowledge in practice, the definition of the obesogenic environment and the needed interventions should be clarified (20). Quantitative studies on childhood obesity mainly emphasize that there are problems in children's adaptation to lifestyle changes and completion of obesity treatment (21-23). Qualitative studies investigating families' views on interventions to treat childhood obesity point to common facilitators (entertainment, communication with healthcare professionals, social support, etc.) and barriers (time, negative effects from family members, sustainable habits after the intervention, etc.) (24-26). On the other hand, it is predicted that using qualitative methods to understand children's perceptions of healthy nutrition and shaping these perceptions in the early stages of life will have a significant impact on reducing morbidity and health expenditures caused by chronic nutrition (27,28). In addition, it is thought that determining all experiences in the implementation of healthy nutrition education given to children will be an important step in improving healthy nutrition counseling services. In this direction, this study was carried out to qualitatively evaluate the experiences of both children and parents, the difficulties they encounter, and the positive aspects of the process, with healthy nutrition counseling given to overweight school-age children (6-10 years old) and their parents.

MATERIALS and METHODS

Research design

In this study, which was conducted to qualitatively evaluate the factors that overweight school-age children (6-10 years old) and their parents evaluate as positive/negative regarding the phenomenon (receiving healthy nutrition counseling service due to being overweight), and the factors that they believe facilitate/difficult this process, the traditional content analysis approach was applied (29).

The sampling process was continued until sufficient information was obtained about the questions in the semi-structured form used in the research, and data collection ended when data saturation was reached. At the same time, the sampling was

stopped because it did not affect the results of the research, since there may be communication problems with the participants due to the approach of the summer vacation and the children's patterns in the summer period may be different compared to the school period. In the interviews conducted within the scope of the research. Plain questions were asked with a literature-based semi-structured form. The interviews lasted for an average of 45 minutes (min 30, max 60 minutes). Data were collected between April and June 2022.

The participant selection process consisted of the inclusion and exclusion criteria of those who applied for the advertisement, without skipping their order. 36 volunteers applied to our research center and there were 22 children who met the criteria. All of them were included in the healthy eating process, thematic analyzes of the interviews were made after each child's 4-week period, the data were found to be repetitive in 8 interview transcriptions, and the research was terminated due to data saturation. Research process chart is presented in Figure I. The first recruitment for this study was through a series of online advertisements (Instagram, Facebook, web announcements) to parents of children diagnosed with obesity in the relevant Bandırma Onyedi Eylul University Healthy Nutrition and Life Research Center clinics between April and June 2022 (Research announcement link: https://sabesya.bandirma.edu.tr/tr/sabesya/Duyuru/Goster/Cocuklar-6-10-yas-arasi-Icin-Saglikli-Beslenme-Danismanligi-Duyurusu-22251). Inclusion criteria were school-age children and parents who participated in a healthy nutrition program as parents of an obese or overweight child; Exclusion criteria are children who discontinued a healthy nutrition program and who were diagnosed with any chronic disease during the study or who started to take obesity-specific medical drug therapy. The researchers contacted the volunteers and planned face-to-face interviews of 30 to 60 minutes. A standard educational content for children is explained one by one, based on the Türkiye Nutrition Guide (nutrients that should be consumed daily, their amounts and cooking methods). In this way, the 4-week healthy eating period started. Each participant was interviewed twice, at the beginning of the study and at the end of the 4-week healthy eating period. The healthy eating period is a period in which there are alternative lists prepared in accordance with the child's age, development, and general nutritional habits, and children are compatible with parental guidance. Families are a guide for the preparation, selection and cooking of foods. After the completion of the process in cooperation with family-child education, a qualitative interview was held. Interviews were held in a separate interview room when parents and children were together. In general, the questions were open-ended and did not search for a specific answer. The main question of the interview is based on the studies in the literature, "What are your experiences and opinions in your Healthy Eating Period?" is oriented (21-23). Due to the nature of the qualitative research, it continued spontaneously without directing the participants. During the period, they were asked spontaneously how the first week and the last week went for 4 weeks, what kind of situations

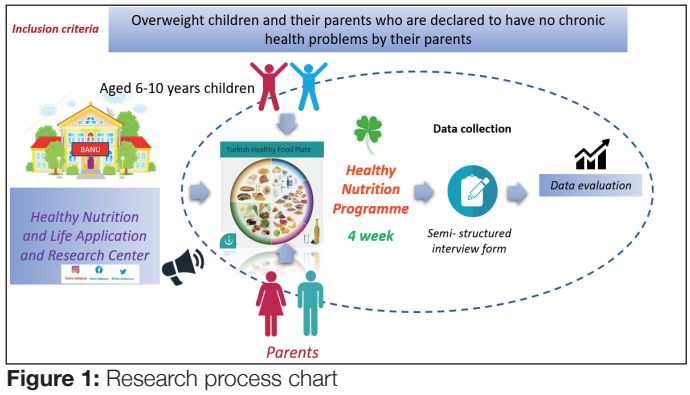

Figure 1: Research process chart

they encountered, what solutions they produced for different situations they encountered, and what they would recommend to those who started this process like themselves. Parents and children were asked the same questions, each other's answers fed the interview during the interview. No medical evaluation was made in the study, and their medical histories were taken regarding the declaration. Middle class family selection was not made, it is known that all of the children, including all the children who applied in the first place, are in the middle social class. These inferences are based entirely on participant statement. During the data collection phase, the data reached saturation as a result of 8 child and 10 parent interviews (both parents of two children were interviewed). Transcription of the audio tapes and analysis of the manuscript was completed by the researchers. Qualitative analysis was performed on the transcript.

Data analysis

Traditional data analysis has been done in five steps; the steps were followed by reading the text several times, dividing it into meaningful titles, abstracting the condensed meaning units, reconciling the abstracted units with the study purpose, comparing the meaning units, and dividing them into themes and sub-themes.

All interviews were audio-recorded and professionally transcribed with the respondent's permission. The transcripts were then transcribed verbatim by independent researchers. The thematic analysis method was chosen because it offers in-depth understanding and versatile perspective, which is known as an ideal method for qualitative research (30-33). During the thematic analysis, the transcripts were first coded, then the following steps were followed by three independent researchers: the steps were followed by reading the text several times, dividing it into meaningful titles, abstracting the condensed meaning units, reconciling the abstracted units with the study purpose, comparing the meaning units, and dividing them into themes and sub-themes.

Reflexivity

While working on the methodology on this research question, the researchers could plan the funding by considering the economic conditions and design projects to minimize the

income differences that may occur during the healthy eating process. It can use qualitative and quantitative research methods together to determine the demographic status of the research group. The frequency of meeting with children and parents could have been higher. Caregivers other than the mother and father and even the teachers of the children could be included in the process and their opinions could be taken. In order to prevent potential biases of researchers, it may be more appropriate to conduct training on healthy eating process and qualitative interviews and transcriptions independently from each other.

This study was approved by Bandırma Onyedi Eylul University Health Sciences Non-Interventional Research Ethics Committee (11.04.2022/2022-39). Before participating in the study, explanations covering ethical issues such as the purpose of the study, confidentiality, the right to withdraw, obtaining information and informed consent were given to the children and parents separately, accompanied by an informed voluntary consent form.

RESULT

During the study, 15 children were included in the healthy nutrition program, but some of them did not want to continue further interviews (n=7). After interviewing 8 participating children (and their parents) during the research, we reached thematic saturation and recruitment was suspended. In the study, 8 children and their parents were interviewed. While mother-child interviews were frequently conducted, the father also accompanied the interviews in two cases. Participants were between the ages of 6-9. The percentile evaluation of body mass indexes of all children was >95th percentile. It is known that there is about 0.5-2% weight loss during the process.

Table I: The Qualitative research results on the Healthy Nutrition Period: main and sub-themes

Main themes **Sub-themes**
Outputs
Food label reading
Wellbeing
Academic performance
Regular sleep ^ Snoring
Intestinal health
Motivation ^ Physical activity + Weight management
Meal planning ^ Night eating
Portion control
Avoid binge eating
Meal replacement
Healthy food choices
Saying “no”
Dietitian requirement ^ Reduced parental burden ^ Child’s responsibility
Shortcomings
Hopelessness
Lack of motivation
Physical activity
Adaptation to meal times
Snack of regret
Interview fear
Challenges
Picky eating
Stigma of obesity
Lack of family support v Paternal support + Siblings + Grandmothers + Working mothers ^ Cooking
Taste of vegetables
Unwillingness
Parent child conflict
Special occasions
Attractiveness v Packaged foods + Ads +Delicious foods
Deprivation
School v Peers + Timing +Canteen ^ Unhealthy foods
Habits v Big portions
Lack of satiety v Big portions
Out of home consumption
Out of home consumption
Unhealthy menus
Social life
Food variety
Lack of sale of vegetables
Sale of animal foods
Fast-food
Sale of bakery products
Coping strategies
Carrying homemade food
Self control
Limiting social life
Food preference
Fasting
Food frequency
Self deception
Changing cooking methods
Alternative recipes
Persistent parenting behavior
Permanency
Negotiation
Suggestions
Communication skills
Reward system
Adherence to diet v Parents
Adherence to diet ~ Being respect v Grandparents
Food culture v Vegetable recipe
Healthy food marketing v Reducing the sale of sugary foods
Canteen improvement
Parental attitudes
Motivators v Collaboration with organizations + Healthy cartoons + Education curriculum+ Dietitian support+ School-parent cooperation

^ : Sub-sub-themes, v: Coexistence of sub-themes, +: Sub-sub-sub themes, ~: Interaction

Their experiences regarding the healthy nutrition period are presented in Figure II. During to period, it has been observed that children have different moods such as restless, angry or

Table II: Free text comments associated with some sub-themes.

Outputs	Wellbeing	C: "With the weight loss, I started to feel more dynamic and I can do sports more comfortably."(C)
Outputs	Saying "no"	P: "We were able to say no to grandma's food treats."(P)
Shortcomings	Interview fear	"I am worried about counseling for health, I am afraid that the dietitian will draw blood and I do not want to come because of this fear"(C)
Shortcomings	Hopelesness	"I thought my child couldn't make it" (P)
Challenges	Attractiveness-Delicious foods	"I can't even imagine eating without butter"(C)
Challenges	Habits-Big portions	"Soup is healthy and it won't hurt if I drink too much, I'm used to drinking it in a big bowl" (C)
Coping strategies	Food preference	"I eat oats instead of bagels." (C) "I eat pasta with yogurt instead of pasta with sauce"(C)
Coping strategies	Self deception	"If I eat a very high-calorie meal at one meal, I eat a low-calorie meal for the next meal."(C) "My friend gave me tiny chips, I smashed it well, threw it in my mouth, made do with it and did not continue to eat"(C)
Coping strategies	Alternative recipes	"I developed a vegetable pie recipe to be able to eat vegetables."(P)
Coping strategies	Persistent parenting behaviour	"First the vegetables (beans) will be finished, then you can eat chicken rice"(P)
Coping strategies	Persistent parenting behaviour	"You will eat healthy, fast food is prohibited"(P)
Coping strategies	Permanency	"Once I eat junk food, my diet will be ruined, I don't want to break the rule, so the effort should not go to waste"(C)
Suggestions	Adherece to diet-Parents	"As his mother, I pay attention, but his father takes him to the market to buy snacks"(C)
Suggestions	Motivators	"I can't stand my child, I need support"(P)
Suggestions	Reward system	"I would threaten my child, practice with the reward system, vomit if you eat unhealthy foods or vomit if you eat healthy foods, I will take you to the park"(P)
Who says:		C: Child; P: Parents

hopeless. Two of our cases were exposed to biopsychosocial conditions such as illness and death within four weeks period. Specific evidence has also been presented regarding the consumption of junk food in children during the pre-diet period and the existence of a heritage weight problem. In one case, had a conflict with her mother during the process, and one of our cases reported that she was exposed to social exclusion at school. Another one, had the opportunity to try various sports branches throughout the process. One of our cases had difficulties with the opposite junk foods. The other one, also showed resistance to eating vegetables seriously during the process (Table I and Figure 2).

During the Healthy Nutrition Period, 5 main topics were formed from the interviews with families and children. Shortcomings, outputs, challenges, coping strategies, suggestions. In the title of challenges, a main problem related to out of home consumption was identified and it was also considered as the main title, and a total of 6 main titles were presented (Table I and Figure 3).

Some free text comments associated with some sub-themes are given in Table II. Regarding the outputs of the process, with the support of the dietitian, the parents reported that their responsibilities have decreased somewhat, and it is very beneficial for the children to take responsibility. In the process, it was emphasized that the dietitian relieved the participants in physical activity and weight management with motivational support. It has been reported that the frequency of night eating decreases with the regulation of food times. In the process, there were positive returns regarding regular sleep and reduction in snoring in children who lost weight due to a healthy diet for 4 weeks. Improvement of gut health, increase in academic performance, and positive effects on well-being are among the effects obtained as a result of the interview. Learning to say "no" in the words of the participants during the process is also among the stated outputs.

At the beginning of the shortcomings reported in the process, the children came to the interviews with prejudice in the interviews. Children applied fear to consult a dietitian, especially the fear of donating blood for biochemical tests. Since there was no interventional procedure during the process, this situation was reflected in the outputs's well-being. Challenges of the period linked to stigmatization, pick eating, reluctance due to dislike of vegetable flavor, conflict with family, the attractiveness of delicious foods and packaged foods, deprivation due to fear of hunger, peer influence, encountering unhealthy foods in the canteen during breaks, inability to leave old habits, the habit of

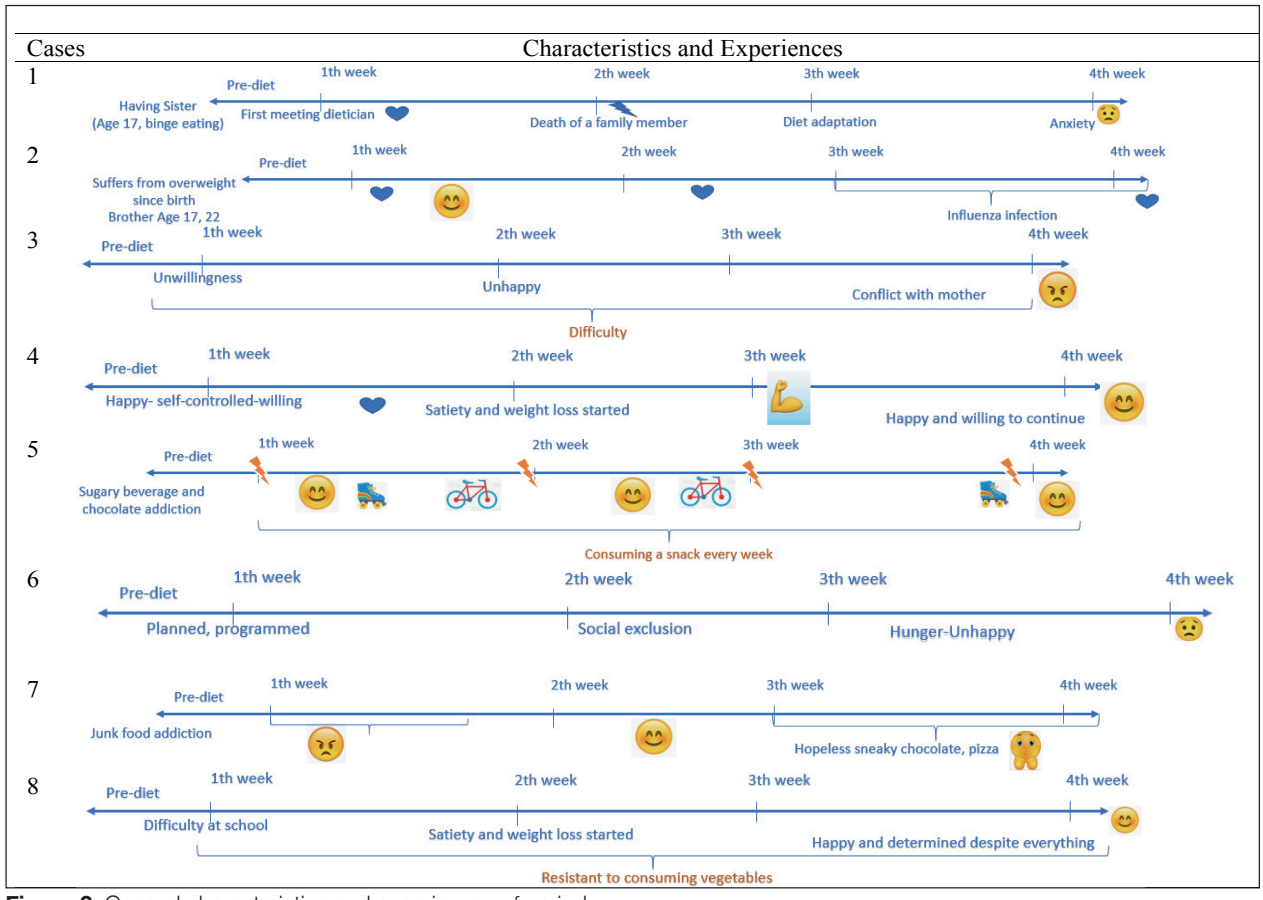

Figure 2: General characteristics and experiences of period.

consuming large portions. It has been reported as wanting to be continued and out of home consumption. The sub-themes that emerged under the heading of out of home consumption in the inductive evaluations revealed to us that out of home consumption is actually a single theme. Reasons such as unhealthy alternatives encountered outside the home, lack of food diversity, low sales of vegetables, especially the prevalence of animal and bakery foods, the prevalence of fast food, and the maintenance of social life were the difficulties experienced by the participants and mothers.

In terms of coping strategies, they resorted to carrying homemade food, self-control, limiting social life, adapting to changes in food preferences, self-deception, and developing alternative cooking methods. Developing alternative recipes, especially for vegetable consumption, has been a frequently emphasized strategy. Vegetable pancakes and mixed cereals with vegetables should be on the children's menus. The families emphasized that it is very effective to have a persistent and determined attitude and to be in negotiation throughout the process.

Families and children also had suggestions for the system. There were sayings that communication techniques were very effective during the diet. The importance of increasing the support of extended family and relatives other than the nuclear family and increasing dietary compliance in a respectful manner was emphasized. Many children reported that while they consume healthy food, they want other family members to consume healthy food in the same way and not to consume packaged food secretly. They demanded that the spread of vegetable recipes in food culture, canteens, and all food marketing services support the sale of healthy food and limit the sale of sugary foods. In addition to the general attitudes of the families, it has been reported that the unity of many organizations, the development of the healthy cartoon-series sector, the education environment, the support of the dietitian, the support of the school-parent union are the motivators of the healthy nutrition period.

When all the themes obtained within the scope of the interviews are brought together, we can draw a conceptual framework on the experiences of children and parents during the Healthy Nutrition Period. The conceptual framework drawn for the process is presented in Figure 4. Regarding the process, facilitators, indicators, and barriers are intertwined. Some variables can be found at the intersection of one or more clusters. Self-control is both a facilitator and an indicator. Strategies determined for the process, some strategies such as eating outside the home and producing alternative solutions have been both barriers and facilitators. In any case, child and

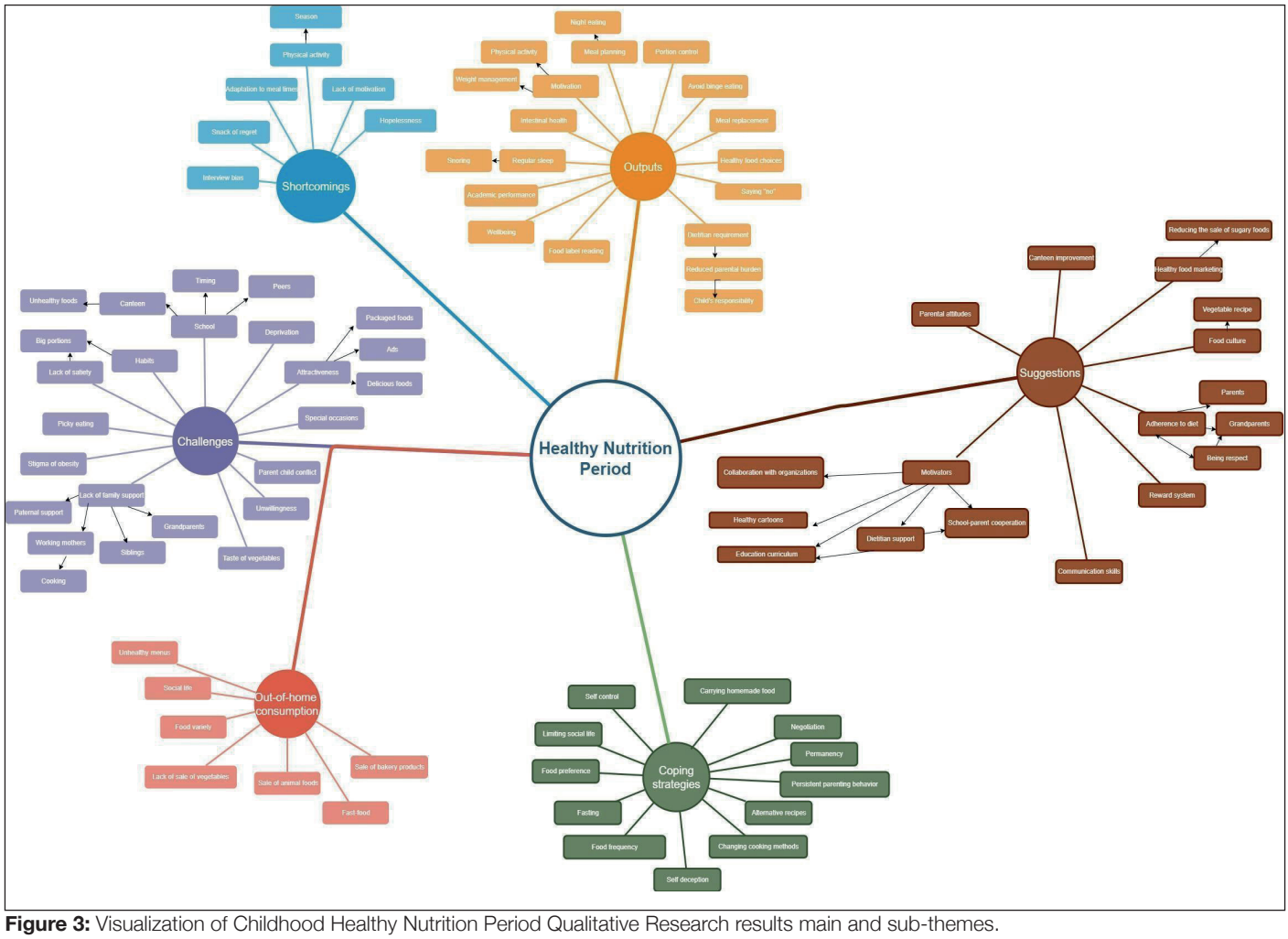

Figure 3: Visualization of Childhood Healthy Nutrition Period Qualitative Research results main and sub-themes.

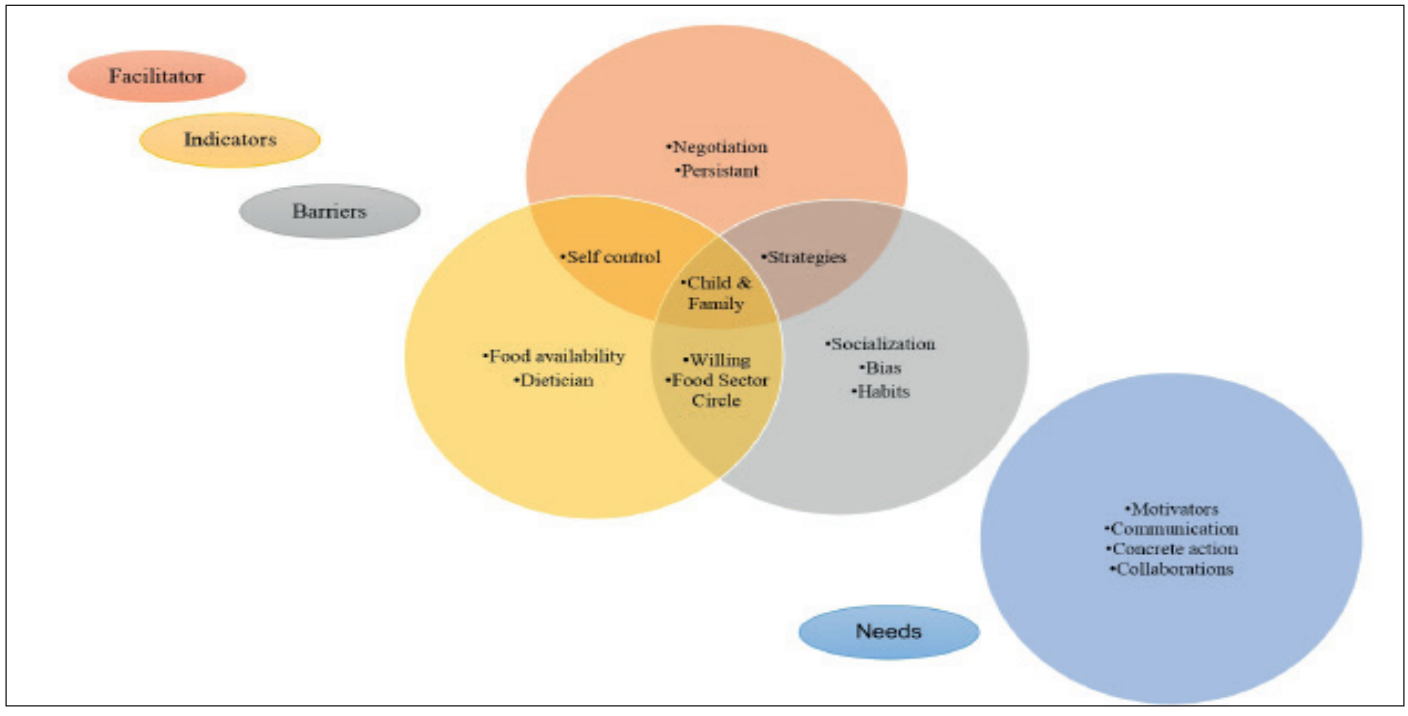

Figure 4: Visualization of Childhood Healthy Nutrition Period Qualitative Research results main and sub-themes.

family cooperation is the intersection point of clusters and any obesity intervention for children cannot be effective without the participation of the family. On the other hand, a negotiator is one of the indicators of creating permanent life behaviors. Food availability and dietitian support indicate the process. Participants often need support in purely technical matters such as not being able to find the food they are looking for, not being able to find vegetables, or developing a recipe with vegetables. The need for socialization is one of the most challenging issues. Eating can be seen as perhaps the strongest barrier, as it is seen as a means of socialization. The prejudices and habits of the people associated with it are also barriers to the process. When the needs are interpreted as a result of this intervention, the concepts of communication, motivation, concrete actions, and cooperation come to light.

DISCUSSION

It is thought that determining the experiences of children and their parents during the implementation of healthy nutrition education will be an important step in improving healthy nutrition counseling services. Based on the lack of knowledge about the experiences of parents and children regarding the healthy nutrition model implementation process and the difficulties they encounter in the literature, we aimed to qualitatively evaluate the experiences of overweight/obese school-age children and their parents in the healthy nutrition period.

In a study on family-based childhood obesity, family involvement, awareness of responsibility, and gradually reaching realistic goals were reported as factors facilitating healthy behavior change. In the qualitative focus group discussions, the willingness of the children aged 9-12 and their parents towards the behavior change intervention was evaluated as an encouraging factor (33). In this research, the child's willingness to healthy nutrition and exhibit self-control behavior to achieve this has been both the determinant and facilitator of the process. Parents' active roles in working life, their dislike of preparing and cooking food, and the feeling of being punished due to the restriction of the foods they want to consume have been described as personal barriers to behavior change (33). Similar to previous studies, the majority of the parents interviewed in this study were mothers, and it was stated that the mother's working life created difficulties in terms of cooking and producing alternative recipes (34,35). In addition, as in our study, other studies emphasized the lack of support and motivation for healthy behavior change (33-36).

In our study, the whole healthy nutrition period includes factors related to the family. Family support, parents' food choices, meal times, etc. While his firm attitude on issues was a facilitating factor, the fact that family members were not included in the process made the process difficult. Burchett et al. reported that aiming at family-wide behavior change in healthy nutrition and involving both parents and children play a key role in this process (10). Similarly, Alexander et al. (37) emphasized the importance of encouraging the family to the body weight management process. The theme of communication, which is one of our findings consistent with the study of Wagner et al. (35) which emphasizes the importance of communication in childhood obesity, was found to be very important for the successful outcome of the process. The parent and child's agreement on food and nutrition was evaluated as a coping strategy and positively affected the process. However, habits such as picky eating and packaged food consumption have caused parent-child conflict in this process. Watson et al. (33) reported that parent-child association and a supportive environment are factors that facilitate behavior change. We think that the active role of families in this process and effective communication with parents are one of the key factors in preventing childhood obesity.

In a study, even four years after obesity treatment, children still struggle to maintain healthy nutrition behaviors outside the home; grandparents, teachers, and friends have been reported to facilitate their healthy routines (36). Similarly, in this study, food consumption and socialization outside the home were considered as an obstacle to the process, but it was stated that the number of family elders (grandmother), friends, and even siblings made the process difficult. In this direction, children and parents stated that they limit their social life as a coping strategy. In a study conducted in China, it was reported that grandparents' misconceptions about nutrition, such as that obese children are healthier and better cared for, are one of the factors that cause childhood obesity. However, this attitude has been described as an obstacle to encouraging children to eat healthy (38). In our study, children were able to oppose these attitudes of their grandmothers (saying "no") and were able to prevent "breaking the chain" in maintaining a healthy diet.

One of the important indicators of the process is exposure to peer pressure and social stigma at school. Having social support makes the process successful (10). Murphy et al. (39) emphasized internal factors as the cause of obesity in the theme of marginalization of obesity. On the other hand, Giovanni et al. (40) reported that social anxiety is severe in overweight and obese adolescents. A better understanding of childhood obesity factors through qualitative research can improve process-oriented interventions and provide an enabling environment for a healthier future.

The necessity of family, school, dietitian interaction, and cooperation was emphasized by the parents. In a study, general practice staff working in primary health care services stated that it is difficult to detect overweight children and they reported that they have limited interaction with these children. They emphasized that schools can take a more active role in detecting and interacting with overweight children (41). Another important point emphasized by parents in our study is that school canteens being made up of unhealthy foods is an important obstacle and concrete steps should be taken to

eliminate unhealthy food environments. In a study conducted with adolescents, it was revealed that school meal programs facilitate healthy nutrition practices. Limited accessibility to healthy foods has been shown as the biggest obstacle to healthy eating (42). In addition, it has been stated that a more informative school curriculum about healthy nutrition can help prevent the development of wrong attitudes towards nutrition in children (27). As a matter of fact, in our study, parents made suggestions to increase motivation in the healthy nutrition period, such as improving school canteens, improving school-family cooperation, and providing nutritionist / dietitian support to schools.

von Hippel and Workman reported that the prevalence of obesity and being overweight in children increases significantly due to inactivity in the summer months, but weight management is better with a regular meal plan, physical activity, and sleep routine during the school period (28). Similarly, in another study, it was reported that the risk factors that cause obesity are exacerbated by the effect of staying away from school and spending more time at home in the summer months (43). In this study, sampling was stopped in order not to affect the results of the research, based on the reason that children's patterns may be different in the summer period compared to the school period. In the interviews, the parents stated that the physical activity of the children is less compared to the summer months due to seasonal conditions, and there are deficiencies in promoting physical activity during the healthy nutrition period. In this context, they emphasized the importance of cooperating with organizations in order to process more sustainable and to support it with physical activity. Similarly, in the study evaluating body weight management programs for childhood obesity, it was emphasized that providing children with food consumption-physical activity sessions and providing social support for both parents and children (10).

Strengths

Studies on healthy nutrition counseling often focus on retrospective views after the intervention. In this study, experiences in the intervention period are included. In addition, the experiences related to healthy nutrition period were evaluated from both the child's and parent's perspectives.

Limitations

Since the research was conducted in a single center, the findings cannot be generalized to different institutions and regions in our country. Similar to other studies in the literature in terms of ease of data collection, the planned time frame is short-term and does not provide an opportunity to evaluate the sustainability of healthy nutrition habits recommended for childhood obesity.

CONCLUSION

Qualitative research gives an in-depth literature of issues that are difficult to capture. This research provides an overview of the experiences of overweight/obese school-age children and their parents during the healthy nutrition period. While there are some insights about nutrition in school-age children, there are many factors that cause them to display wrong attitudes. A better understanding of these factors, developing coping strategies by revealing the situations that prevent healthy nutrition, using communication language that will maintain motivation, and taking concrete steps to cover public health can provide a suitable environment for a healthier future.

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Türkiye Çocuk Hastalıkları Dergisi

A Rare Case Report: Pediatric Aural Myiasis Composed of Multiple Live Larvae

Nadir Bir Olgu Sunumu: Çok Sayıda Canlı Larvadan Oluşan Pediatrik Aural Miyazis

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ABSTRACT

Aural myiasis is a rare otorhinolaryngological disease, which is usually seen in children or mentally retarded patients under poor hygiene conditions and is caused by the infestation of fly larvae in the tissues of vertebrates. A 3-year-old girl presented to the emergency service with her father with the complaint of bloody discharge and moving maggots in the left ear for a week. 23 living larvae were removed from the left ear of the patient who was consulted to the Otorhinolaryngological Clinic. In this article, a rare case of aural myiasis is presented with clinical findings, diagnosis, management of cases and treatment process, in the light of current literature.

Key Words: Children, Ear, Myiasis

ÖZ

Aural miyazis, kötü hijyen koşullarında genellikle çocuklar ya da mental retarde hastalarda görülen, omurgalı canlıların dokularına sinek larvalarının yerleşmesiyle oluşan nadir bir kulak burun boğaz hastalığıdır. 3 yaşındaki kız hasta bir haftadır olan sol kulakta kanlı akıntı ve hareketli kurtlar gözükmesi şikayeti ile babasıyla birlikte acil servise başvurdu. Kulak Burun Boğaz Kliniği'ne konsülte edilen hastanın sol kulağından 23 adet canlı larva temizlendi. Bu makalede nadir görülen aural miyazis olgusu klinik bulgular, tanı, vakaların yönetimi ve tedavi süreci ile birlikte güncel literatür eşliğinde sunulmuştur.

Anahtar Kelimeler: Çocuk, Kulak, Miyazis

INTRODUCTION

Myiasis is the invasion of human tissues by fly larvae (Dipthera). Poor hygiene conditions, low socioeconomic status, mental retardation, diabetes, chronic suppurative otitis media, elder age, children under 10 years age, rural areas, humid and hot climate can be counted as predisposing factors for human myiasis (1-4). Myiasis can be seen in the head and neck region, ears, mastoid region, nasal cavity, paranasal sinuses, oral cavity and eyes (5). In the literature, such a high number of live larvae in aural myiasis cases have rarely been encountered. In this article, a case of aural myiasis in a 3-year-old girl who had 23 live larvae cleared from the left external ear canal is presented with clinical findings, diagnosis and treatment process, in the light of current literature.

CASE REPORT

A 3-year-old girl living in a rural area, with a low socioeconomic level and poor personal hygiene, was admitted to the emergency service by her father with complaints of restlessness, constant crying, discharge from the left ear, bleeding and many moving

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Figure 1: Obliterated external auditory canal with larvae

Figure 2: Some of the removed larvae

maggots (Figure 1). In the physical examination of the patient who was consulted to the Otorhinolaryngology Clinic, the left external auditory canal was completely obliterated with living larvae. Right ear and other otolaryngological examinations were normal. It was stated that there was no known ear disease or systemic disease. She has never had ear discharge or similar complaints before. With the help of otomicroscopy, 23 live larvae with an average length of 10-15 mm were removed from the left external ear canal and middle ear using alligator forceps and aspirator (Figure 2).

It was observed that the external ear canal was edematous, with foul-smelling hemorrhagic purulent discharge, and the eardrum was perforated. Washing was done with saline irrigation. No pathological appearance was detected in the left middle ear, ossicles and mastoid cells in the temporal bone computed tomography imaging taken after the larvae were removed. Subsequently, systemic (14 mg/kg cefdinir) and topical (ciprofloxacin) antibiotics were prescribed and close follow-up was recommended. Microbiological examinations could not be performed in our center for the species analysis of the larva. In the follow-ups, no growth was detected as a result of the culture taken from the external ear canal. At the end of the first week, it was observed that the discharge in the external ear canal had completely resolved, and topical and systemic antibiotic therapy was terminated. It was observed that the perforation in the eardrum of the patient, who was followed closely for four weeks, was closed at the end of the fourth week. As a result of the brainstem evoked response audiometry (BERA) test performed in an external center in the first month, it was seen that hearing was within normal limits.

DISCUSSION

Myiasis occurs when fly larvae settle in the tissue and organ cavities of a living vertebrate and these larvae feed on living and dead tissues, body fluids or undigested nutrients in the host. The most common are cutaneous and wound myiasis. This is followed less frequently by myiasis of the body cavities (oral, nasal, aural, ophthalmic, urogenital) that open outward (3,6).

Myiasis cases are frequently seen in people who live in rural areas, have low socioeconomic status, and have poor personal hygiene. Its incidence increases especially in humid and hot climates. Elder age, childhood, mental retardation, and diabetes can be counted among the predisposing factors for myiasis in these individuals (4,5). Most of the cases with aural myiasis have chronic suppurative otitis media (1). Our three-year-old patient had poor personal hygiene and lived in a rural area. The patient, who did not describe ear discharge before, applied to the hospital in the summer season.

The symptoms of aural myiasis are quite diverse. These symptoms include ear pain, bleeding, itching, ringing, humming, decreased hearing, malodorous otorrhea, eardrum perforation, a moving object sensation in the ear, the appearance of larvae in the external auditory canal, and dizziness. In rare cases, neurological symptoms due to intracranial involvement may be seen. Myiasis is a self-limiting disease, as the larvae leave the host when they are fully mature, but if left untreated it can rarely lead to fatal complications. In cases of intracranial involvement in nasal and aural myiasis, a mortality rate of 8% has been reported (1,2,4). In our case, the patient was brought to the

hospital by her father with complaints of restlessness, crying, bloody and foul-smelling ear discharge, and the appearance of moving maggots in the external ear canal.

Since the larvae are usually in the external ear canal, anamnesis and physical examination are sufficient for diagnosis. In cases of clinical suspicion, computed tomography can be performed to investigate complications such as mastoid cavity invasion or intracranial spread (4,5). In the temporal bone computed tomography imaging taken from our patient, no pathological appearance was detected in the left middle ear, ossicles and mastoid cells.

Since aural myiasis is usually self-limited, the treatment is simple, but early intervention should be performed to prevent complications (2,6). Treatment consists of removing the larvae and washing the external ear canal with 10% chloroform, 70% ethanol, saline, iodine, oil, ivermectin. If tympanic membrane perforation is observed, only saline irrigation and simultaneous aspiration should be applied. Prophylactic antibiotics are recommended to prevent secondary bacterial infections (1,5). In our patient, after cleaning the larvae under otomicroscopy, perforation of the eardrum was observed, and topical and systemic antibiotics were prescribed after washing with saline.

It should be evaluated whether the eardrum is intact or not. Hearing levels should be measured before and after treatment. Surgical treatment should be performed as soon as possible in cases of widespread disease, middle ear involvement, prolonged disease course despite treatment, suspected residual disease, and suspected intracranial involvement. Compliance with hygiene rules and close follow-up of patients is significant in terms of reducing recurrences and preventing complications (3,4,5). Our patient was followed for four weeks, and no recurrence was observed during the follow-up, and it was observed that the perforation in the eardrum was closed. As a result of the BERA test performed in an external center, it was observed that hearing was within normal limits.

CONCLUSION

In conclusion, although aural myiasis is rare, it should be remembered in cases of unexplained ear pain, discharge, and hearing loss in children, elderly, mentally retarded, poor hygienic conditions and risk group patients living in rural areas. Although the diagnosis and management is simple, it can lead to serious complications in cases where treatment is delayed.

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Prosthetic Treatment of Pediatric Patients with Ectodermal Dysplasia: Two Case Reports

Ektodermal Displazili Çocuk Hastaların Protetik Tedavisi: İki Olgu Raporu

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ABSTRACT

Ectodermal dysplasia (ED) is a hereditary disorder characterized by anomalies in the ectodermal structures. The most common dental anomalies are oligodontia and/or anodontia of the primary and permanent dentition. Therefore, pediatric patients with ED may be need prosthetic rehabilitations. Several prosthodontics treatment options, such as complete, removable partial, overdenture, fixed and implant-supported dentures are avaible to rehabilate patients with ED. The aim of this clinical case report is to present the clinical characteristics and prosthetic treatment of two cases with ED.

Key Words: Dental prosthesis, Ectodermal dysplasia, Pediatric dentistry

ÖZ

Ektodermal displazi (ED), ektodermal yapılardaki anomalilerle karakterize kalıtsal bir hastalıktır. En yaygın görülen diş anomalileri, süt ve daimi dişlerin oligodontisi ve/veya anodontisidir. Bu nedenle ED'li çocuk hastalarda protetik rehabilitasyona ihtiyaç duyulabilir. ED'li hastaları rehabilite etmek için tam, hareketli parsiyel, overdenture, sabit ve implant destekli protezler gibi çeşitli protetik tedavi seçenekleri mevcuttur. Bu olgu raporunun amacı, ED'li iki olgunun klinik özelliklerini ve protetik tedavisini sunmaktır.

Anahtar Kelimeler: Dental protez, Ektodermal displazi, Çocuk diş hekimliği

INTRODUCTION

Ectodermal Dysplasia (ED) comprises clinical and inherited heterogenous group of disorders affecting at least two or more ectodermal-derived tissues, such as nails, hair, sweat glands, and teeth with or without the involvement of the other organs (1). ED can be inherited in various genetic patterns: e.g. autosomal-recessive, autosomal-dominant or X-linked modes, and it affects males more commonly and severely compared with females (2). The estimated incidence of ED is 1 in 100.000 births and considered to be relatively rare. Nearly 200 clinically different pathologic conditions have been identified as ED (3).

ED has two major types considering the number and function of the sweat glands:

1. Hypohidrotic (HED)/anhidrotic ED is characterized by sweat glands that are either missing or severly decreased in number (Christ-Siemens-Touraine syndrome),
2. Hydrotic ED is characterized by normal sweat glands and autosomal-dominant inheritance (Clouston's syndrome) (3,4).

While the dentition and hair are similarly affected in both types, inheritance patterns, nail and sweat gland manifestations tend to differ (5). General clinical findings in patients with ED include dry-lightly pigmented skin, alopecia or hypotrichosis (sparse, shiny hair or eyelashes), nail dystrophy, absence of sweat glands, and palmar-plantar hyperkeratosis (2,5). Complete or partial anodontia of the primary and permanent dentition and tooth malformations are the most common dental findings.

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Furthermore, incisors and canines are typically conical in shape, whereas, second molars, if present, are predominantly affected by taurodontizm (6). Due to multiple missing teeth, the alveolar ridge of both maxilla and manbidula are reduced, which leads to a decrease in the vertical dimension of occlusion (7). As a result, affected children often exhibit an old-age appearance (8). Other orofacial characteristics of ED include a prominent supraorbital ridge and frontal bossing, midfacial hypoplasia, a depressed nasal bridge, disappeared vermillion border and protuberant lips (9,10). Additionally, xerostomia can occur when the major salivary glands are affected in ED patients (10).

Early oral and prosthetic rehabilitation of ED patients is necessary to restore function and esthetics, as well as speech, psychosocial development and well-being (10). A multidisciplinary team involving pediatric dentist, orthodontist, prosthodontist, oral-maxillofacial surgeon, and speech therapist is essential to achieve successful results for the treatment of patients with ED (6,7,11). This case report aimed to present characteristic dental findings and prosthetic treatment of two pediatric patients with ED.

CASE REPORTS

Case 1:

An 11-year-old male patient was referred to Pamukkale University, Faculty of Dentistry, Department of Pediatric Dentistry with a complaint of inability to masticate with previous prosthesis, which be applied two years earlier. He had been diagnosed with HED when he was four years old, and displayed characteristic features of ED including brittle and fine blonde hair, narrow eyeblow-eyelashes, depressed nasal bridge, prominent forehead, periorbital pigmentation, and protuberant lips (Figure 1). An intra-oral examination showed mandibular anodontia, low alveolar ridges, and presence of hypoplastic conic-shaped maxillary central incisors (Figure 2A). Panoramic radiography also verified mandibular anodontia and the absence of maxillary teeth except of two permanent maxillary central incisors (Figure 2B).

Figure 1: Extra-oral view of case 1.

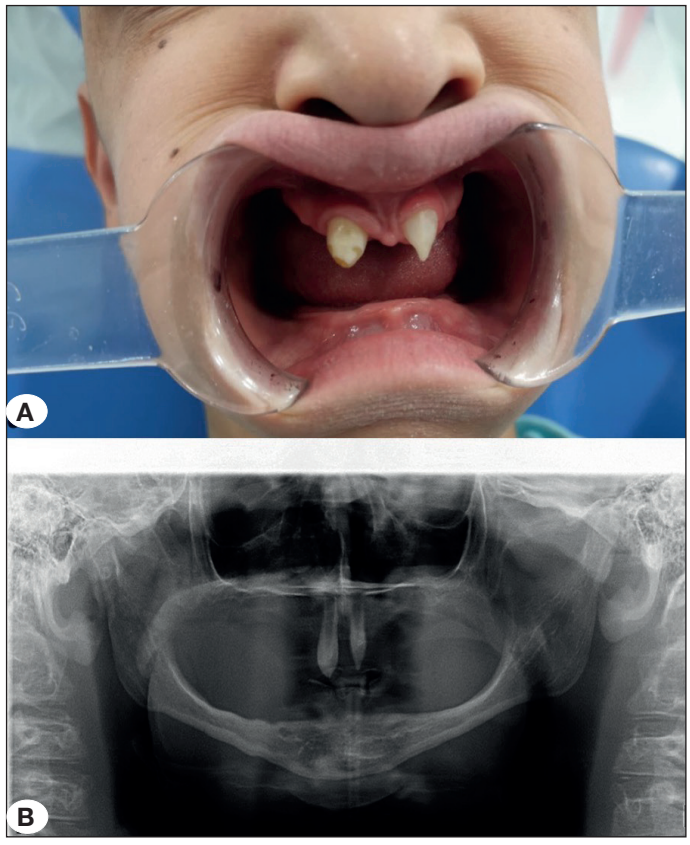

Figure 2: A) Intra-oral view of maxilla and mandibula (conic-shaped maxillary central incisors and mandibular anodontia). **B)** Panoramic radiography of case 1.

Figure 3: Prosthetic treatment of case 1 with a maxillary overdenture and a mandibular complete denture.

Dental treatment plan was discussed with patient and his parents, and informed consent was obtained. To improve function, esthetics, and speech, a tooth-supported maxillary overdenture and a mandibular complete denture were considered the preferred treatment options. After preparing both conic-shaped

permanent maxillary central incisors, preliminary impressions were made using irreversible hydrocolloid (Cavex Tulip, Cavex Holland BV, Haarlem, Holland), and then custom trays were fabricated for functional impression. Occlusal relationship was recored using wax occlusal rims, and the models were mounted on a semi-adjustable articulator. Prosthetic permanent denture teeth (Eray, Eray Inc., Türkiye) were set to provide proper lip support and ensure bilateral balance occlusion. After assessing retention, occlusion and esthetics of trial dentures, dentures were fabricated heat-activated acrylic resin (Imicryl®, Konya, Türkiye). The dentures were inserted and required adjustments were made (Figure 3). Instructions about to maintain a soft diet for the first few days, oral hygiene procedures, and wearing dentures throughout the day except for brushing and sleeping were given to parents. During follow-up visits the patient and his parents reported improvements in mastication, appearance, speech, and social behaviour after prosthetic rehabilitation. Follow-up visits at 3-month intervals were scheduled for adjustments of the dentures, to evaluate growth and development, as well as oral hygiene.

Case 2:

An 11-year-old female patient was referred to Pamukkale University, Faculty of Dentistry, Department of Pediatric Dentistry with the same complaint of case 1. It was revealed through parental history that the patient was intolerant to heat, and her mother and uncle also presented oligodontia. Extra-oral examination revealed typical features of ED including dry anhidrotic skin, diffusely sparse hair, narrow eyebrow-eyelashes, depressed nasal bridge, prominent forehead, periorbital and perioral pigmentation, protuberant lips, and old-age appearance (Figure 4). An intra-oral and radiographic examination showed

Figure 4: Extra-oral view of case 2.

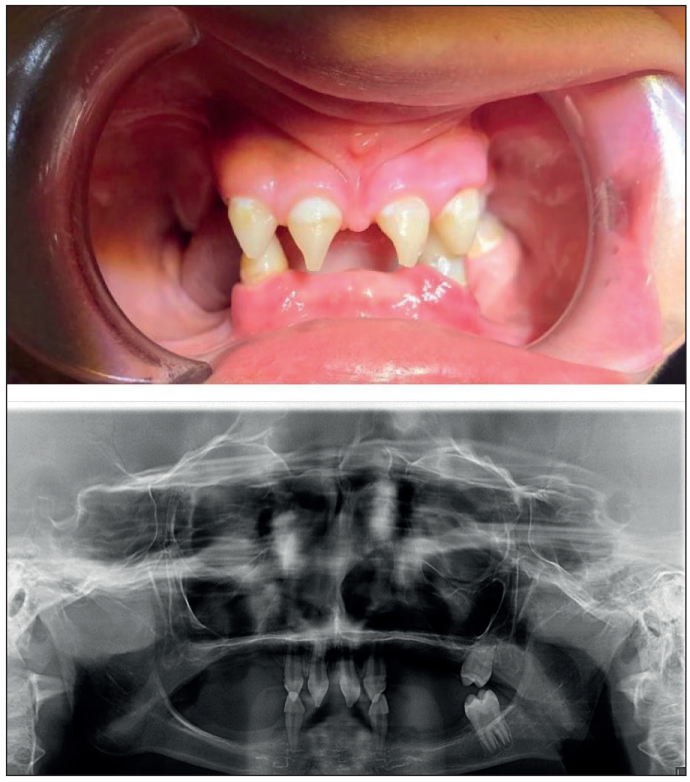

Figure 5: Clinical intra-oral frontal view of case 2. Panoramic radiograph revealing absence of 24 permanent teeth.

Figure 6: The maxillary and mandibular removable partial dentures of case 2.

that only four conic-shaped permanent maxillary anterior teeth, both permanent mandibular canines, left permanent maxillary and mandibular first molars had erupted (Figure 5). The patient also presented low alveoler ridges, loss of vertical dimension, and reduced sulcus depth in the posterior region of the maxilla and mandibula. Caries lesions were detected in both permanent mandibular canines, and her oral hygiene was poor.

Treatment plan included maintaining of appropriate oral hygiene, restoration of carious permanent mandibular canines and conic-shaped permanent maxillary anterior teeth,

and fabricated maxillary and mandibular removable partial dentures. The dental treatment plan was explained to the patient and her parents, and informed consent was obtained. After carious permanent mandibular canines were restored with composite resin (Clearfil MajestyTM Anterior; Kuraray Medical Inc., Okuyama Japan), and conic-shaped permanent maxillary incisors reconstructed with strip crowns (TDV Dental Ltda. Brussels, Belgium), preliminary impressions were made using irreversible hydrocolloid (Cavex Tulip, Cavex Holland BV, Haarlem, Holland). Following fabricated of custom trays, border-molding was established and final impression were made using polyvinylsiloxane impression material. Occlusal record was obtained with the same procedures as in the first case. Prosthetic permanent denture teeth (Eray, Eray Inc., Türkiye) were arranged to ensure age-appropriate appearance, and bilateral balance occlusion was given. Four wrought wire clasps were positioned on the permanent maxillary lateral incisors, permanent maxillary first molar, and permanent mandibular first molar (Figure 6). Removable maxillary and mandibular partial dentures were fabricated as previously described, then inserted and required adjustment were made. Recall appointments were scheduled as described for case 1. Despite the patient and her parents reported improvements in mastication, appearance, speech, and social behaviour during follow-up visits, the patient was unable to maintain proper oral hygiene. The patient was instructed to maintain proper oral hygiene, and further follow-up visits were scheduled every 3-months to evaluate growth and development, and oral hygiene.

DISCUSSION

Patients with ED present a significant challenge with regard to mastication ability, speech problems, esthetic concerns, and potential impacts on social and psychological development (10). Therefore, prosthetic treatment is essential for ED patients to provide improvements in function, speech, and esthetics, as well as increased self-esteem and psychological development. Several prosthetic treatment options including removable (complete/partial or overdentures), fixed partial, and implant-supported dentures are avaible for patients with ED. Treatment choice depends on patient's age, clinical findings, developmental stage, patient's individualised needs, patient's motivation, and also parents' social status (11). It is generally recommended that the first dental prosthesis should be delivered prior to school-age, though there is no certain time period to start dental treatment (9). In general, early prosthetic treatment is recommended from the age of 5, but depending on the cooperation of the patient, dentures can also be made at the age of 3 to 4 (8). As a result, it contributes to normalize the function of the masticatory and perioral muscles, resulting in proper growth of the basal bones, and psychologically improves the child's self-image (12).

Fixed dentures are rarely used in ED patients because of minimal number of teeth, and furthermore, if these dentures cross the dental midline, the rigid connectors may interfere with normal jaw growth in actively growing patients (9). Implant-supported dentures are recommended as a treatment option for adolescents over 12 years (7,8). In a growing child, early placement of implants may lead to cosmetically unfavorable results due to the implants acting like ankylosed teeth. The vertical growth of the jaws may cause implant over-structures to not contact with the opposite teeth, which may lead to prosthetic infraocclusion (7). In 2013, consensus meeting focusing on the rehabilitation of patients with ED was held, and expert teams decided that the earliest age for implant therapy should be 7-8 years old for the anterior mandible, while older ages should be considered for the maxilla (13). When implant therapy is considered as a treatment option, the primary challenge is lack of sufficient bone. The alveolar ridges and basal bone may be insufficient, especially in the maxilla. Therefore, in ED patients who suffering from alveolar deficiency, if bone atrophy progresses severe extent, implant placement may not be achievable without bone grafting (8). Consequently, when implant therapy is considered as a treatment option, it requires extra consideration to determine if there is sufficient bone level to placement the implants, and whether there is sufficient vertical bone dimension to support to implants (14).

Removable dentures (complete/partial or overdentures) are the most common preferred options for the prosthetic rehabilitation of the pediatric ED patients due to their ease of modification during the rapid growth period (3,9). However, retention and stability of dentures can be compromised due to insufficient bone support, dryness of oral mucosa, and the irregular tooth shape (8,13). Conversely, overdentures offer more retentive options when teeth are present to support them, and have several advantages, such as preserving alveolar bone, providing greater support and stability for dentures, improving proprioception and neuromuscular feedback, and increased comfort when compared to complete dentures (10,15).

In both cases, implant therapy was not considered as a treatment option because of ongoing growth and development as well as alveolar deficiency. In case 1, the treatment consisted of a maxillary overdenture and a mandibular complete denture. Due to the conical shape of the maxillary central incisors and their positioning, they were used as abutments for the overdenture. These dentures can preserve sensorial input of periodontal receptors, preserve alveolar bone structure, provide increased retention, stabilization, mastication performance, and also have psychological benefits for the children (11). In case 2, maxillary and mandibular removable partial dentures with wire clasps were fabricated to provide increased retention. Following prosthetic treatment of both patients, notable improvements in esthetics, speech, mastication performance were achieved. However, in case 2, the patient failed to maintain appropriate

oral hygiene at her 1-month follow-up. Oral hygiene instructions were reinforced, and follow-up appointments were scheduled to evaluate oral hygiene, and assess the need for any prosthetic modification/renewal of dentures at 3-month intervals due to ongoing development.

CONCLUSIONS

The management of ED patients is challenging and requires multidisciplinary approach involving pediatric dentist, orthodontist, prosthodontist, maxillofacial surgeon, and speech therapist. When deciding on the choice of treatment, the patient's age, intraoral condition, and patient's/parent's demands should be considered. Prosthetic rehabilitation of pediatric ED patients with removable partial/overdenture or complete denture is a suitable and cost-efficient option that can improve esthetics, speech, and mastication performance. Periodic follow-up is essential to assess the need for any modification or renewal of dentures due to ongoing development. Fixed or implant-supported dentures may be considered as a treatment option after skeletal growth is complete.

Consent

A written informed consent was obtained from all patients and their parents for publication of clinical data and images.

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Ophthalmological Findings in Metabolic Diseases

Metabolik Hastalıklarda Göz Bulguları

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ABSTRACT

Inherited metabolic diseases are rare genetic disorders caused by synthesis disorders affecting protein, carbohydrate and lipid metabolisms, impaired enzyme activity, and deficiency of cofactors or transporters. More than 1000 inherited metabolic diseases have been reported. The prevalence of each disease is rare. However, the overall prevalence is not rare as expected. Inherited metabolic diseases can occur at any age, from prenatal to adulthood. The clinical features are mostly progressive when left untreated. Most diseases occur at young ages and often with more than one organ involvement. In Inherited metabolic diseases, eye involvement may be primary or secondary, and the findings may be local or systemic. The toxic effect of abnormal metabolites or accumulation of normal metabolites is usually responsible for the pathogenesis. Early recognition of treatable inherited metabolic diseases is important as it may change the treatment outcome of the patient. Ophthalmological findings may be in the form of cataract, corneal clouding, retinitis pigmentosa, cherry red spot and optic atrophy. Bilateral symmetrical involvement is expected. In this article, eye findings that can be seen in hereditary metabolic diseases will be discussed.

Key Words: Ophthalmological findings, Inherited metabolic disorders, Rare Diseases

ÖZ

Kalıtsal Metabolik Hastalıklar; protein, karbonhidrat ve lipid metabolizmalarını etkileyen sentez bozukluklarından, bozulmuş enzim aktivitesi, kofaktör veya taşıyıcı protein eksikliğinden kaynaklanan nadir görülen genetik bozukluklardır. 1000'den fazla hastalık bildirilmiştir. Metabolik hastalıklar her biri ayrı ayrı düşünüldüklerinde seyrek görüldükleri düşünülse de toplu olarak düşünüldüğünde önemli bir grup hastalığı oluşturmaktadır. Kalıtsal metabolik hastalıklar doğum öncesi dönemden yetişkinliğe kadar her yaşta ortaya çıkabilir. Klinik özellikler tedavi edilmediği taktirde çoğunlukla ilerleyicidir. Çoğu hastalık; genç yaşlarda ve sıklıkla birden fazla organ tutulumu ile ortaya çıkar. Kalıtsal metabolik hastalıklarda göz tutulumu primer veya sekonder olabileceği gibi bulgular lokal veya sistemik olabilir. Patogenezden genellikle anormal metabolitlerin toksik etkisi veya normal metabolitlerin birikimi sorumludur. Tedavi edilebilir kalıtsal metabolik hastalıkların erken tanınması, hastanın tedavi sonucunu değiştirebileceği için önemlidir. Oftalmolojik bulgular katarakt, korneal bulanıklık, retinitis pigmentoza, kiraz kırmızısı leke ve optik atrofi şeklinde olabilir. Bilateral simetrik tutulum beklenmektedir. Bu makalede kalıtsal metabolik hastalıklarda görülebilecek göz bulguları tartışılacaktır.

Anahtar Kelimeler: Göz bulguları, Kalıtsal metabolik hastalıklar, Nadir Hastalıklar

INTRODUCTION

The eye is the most specialized organ and enables us recognize the world around us. It has important physiological connections with the central nervous system (CNS), it gives symptoms in diseases affecting the CNS. Since the eye is a complex organ, one or more structural or functional components may affect vision. Several studies have shown that; Ocular manifestations occur in approximately one-third of inherited metabolic disorders. The occurrence of eye pathologies is not yet clear, but may be by direct toxic mechanisms of abnormal metabolic products or by the accumulation of normal metabolites. Eye involvement is not life-threatening, but may cause vision loss and affect the patient's quality of life. Eye pathologies are detected as an additional finding of hereditary metabolic

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disease in the follow-up or the patient presents with primary eye findings and may indicate a hereditary metabolic disease. Symmetrical bilateral involvement is the rule in inherited metabolic diseases. Detailed clinical evaluation is essential to identify inherited metabolic disease. Congenital severe visual impairment is usually not noticed until about 2 months of age, when normal children can make eye contact. Severe visual impairment should be detected in the first weeks of life (1,2). Common eye findings that may occur in inherited metabolic diseases are as follows: corneal clouding, lens abnormalities, retinal degeneration, cherry red spot and optic atrophy.

CORNEAL CLOUDING

Anterior segment abnormalities of the eye can be easily detected on rapid eye examination using a slit lamp microscope. Ophthalmic phenotypes are corneal clouding or lens opacity. Corneal tissue consists of three components such as epithelium, stroma and Descemet's membrane. IMDs often show corneal opacities or clouding. Corneal transparency is dependent on collagen fibers and proteoglycans. Corneal opacities are common in lysosomal storage disorders such as X-linked Fabry disease because more than 70% of patients have corneal verticillata. Yellowish-gray deposits of glycosaminoglycan deposits in all layers of the cornea have been reported frequently in MPS I, IV and IV patients, and rarely in MPS II patients. This feature is also not detected in MPS III patients. A ring of copper can be seen in Descemet's membrane of the cornea in patients with Wilson's disease. In patients with cystinosis, cystine crystals in the cornea appear after 1 year of age. While renal complications predominate in the early forms of cystinosis, corneal cystine deposition will manifest in all patients with cystinosis. Inherited metabolic diseases affecting the cornea are numerous and severe. Lysosomal storage diseases are one of the most common inherited metabolic diseases that cause corneal clouding (3) (Table I).

Mucopolysaccharidoses (MPS) are a rare group of lysosomal storage diseases characterized by the accumulation of incompletely degraded glycosaminoglycans in many organs, including the eye. Ocular findings seen in MPS often result in visual impairment. Ocular complications are retinopathy, corneal opacity, and increased intraocular pressure. It is very difficult to detect corneal opacification due to mental problems, thickening with glaucoma and ocular hypertension in MPS patients. All patients with MPS types I, IV, and VI are affected by progressive corneal opacities. In MPS IS (Scheie's disease) and MPS II, corneal clouding is mild. It rarely requires corneal transplantation. Corneal clouding is not a prominent feature for MPS III (Sanfilippo syndrome). Progressive corneal opacification is seen in MPS VII (Sly syndrome). In MPS IV (Morquio's disease), keratan sulfate accumulates in the cornea. The accumulation of glycosaminoglycans in the corneal stroma causes a progressive increase in corneal thickness. In MPS VI and VII, the corneal epithelium is normal or minimally affected as in MPS I. Edema in the cornea is not a pathological feature. Corneal clouding is the result of storage in stromal keratocytes. Other ocular manifestations such as cataract, pigmentary retinopathy, glaucoma, and optic atrophy are also quite common in MPS In the past, the ocular pathology of many patients with MPS was inadequately treated. In recent years, treatments such as enzyme replacement therapy and bone marrow transplantation have provided a better quality of life for many MPS patients. These treatments do not completely remove ocular pathologies, but they are effective in reducing or stabilizing the symptoms (3).

Table I: Inherited Metabolic Diseases with Corneal Clouding

Lysosomal Storage Disorders
Mucopolysaccharidosis
Mucolipidosis
Mannosidosis
Farber's disease
Fucosidosis type III
Multiple sulfatase deficiency
Fabry disease
Cystinosis
Lipid metabolism disorders
Fish eye disease
Lecithin: cholesterol acyltransferase deficiency
Homozygous familial hypercholesterolemia
Disorders of amino acid metabolism
Alkaptonuria
Tyrosinemia type II
Metal transport disorder
Wilson's disease

Fabry disease also known as Anderson-Fabry disease is an X-linked lysosomal storage disease caused by insufficient activity of lysosomal α-galactosidase. Multiorgan involvement is seen. Estimated worldwide prevalence is 1:40,000 to 1:117,000. One of its local manifestations is the development of dystrophic changes in the structure of the cornea. Cornea, lens and conjunctival-retinal vessels are involved. In Fabry disease, there is a progressive accumulation of glycosphingolipids in the eye 'Cornea verticillata'. The prevalence of cornea verticillata is similar in different age groups. Cornea verticillata is seen in 80% of Fabry patients and is recognized by slit lamp examination. In early stages, fine horizantal lines are seen progressing to curving lines. Generally, vision is not affected. Differential diagnosis of Cornea verticillata includes the chronic use of medications like amiadorone and chloroquine. There are two types of cataracts (anterior and radial posterior subcapsular cataracts) described. These eye pathologies can be detected by slit lamp examination. Conjunctival and retinal vascular lesions, which are part of systemic vascular involvement, are also quite common. Irregularities of vessels (conjunctival and retinal vessels) occur by deposition of globotriaosylceramide (Gb3). This results in vascular tortuosity. Other ocular abnormalities rarely seen in Fabry disease are lid edema, chemosis, dry eye, papilledema and optic atrophy. Enzyme replacement therapy does not

change the ocular manifestations of Fabry disease (4).

Corneal involvement is also an early sign in other lysosomal storage diseases. Visual impairment and corneal clouding are evident in Mucolipidosis type IV. First, corneal clouding, then retinal degeneration and blindness may develop. Cytoplasmic membranous bodies are found in a variety of tissues. Patients are often mentally handicapped. In late-onset alpha-mannozidosis; hearing loss, corneal clouding, cataract and bone findings can be seen. The clinical findings of late onset forms of galactosialidosis are coarse face, mental retardation, hearing loss, growth retardation, joint stiffness, cardiac involvement, vertebral anomalies and seizures. In the second decade of life, loss of visual acuity, corneal clouding, bilateral cherry-red spots, dotted lens opacities, and color blindness are seen. In steroid sulfatase deficiency, corneal opacities, small punctate or filiform lesions are seen (5).

Cystinosis is a multisystem metabolic disease caused by mutations in the CTNS gene, which encodes the lysosomal carrier protein cystonin. Conjunctiva, cornea, iris, choroid and retinal pigment epithelium are affected due to the accumulation of cystine in lysosomes. Polychromatic corneal crystals extending from the periphery to the center are found in the anterior stroma. Photophobia is seen as a result of crystal deposition in the front camera. The first sign of the disease may be an ocular sign. Eye pathologies can be seen before nephropathy, eye examination is very important in patients with cystinosis. Corneal crystal accumulation can cause erosions. As a result of erosions of the corneal epithelium; eye watering, photophobia and blepharospasm may develop. In a severe form of the disease, cataracts, pigmentary retinopathy and blindness can occur. Cysteamine eye drops are used to reduce crystal deposits in the cornea. Corneal transplantation can be performed for visual rehabilitation (6).

Hypoalphalipoproteinemia such as Tangier disease, Lecithin cholesterol acyltransferase deficiency and apoprotein A-1 (Apo A-I) deficiency, is an inherited dyslipidemia characterized extremely low HDL-C values. Rare complications may include corneal opacities that typically do not affect vision. In patients with cyclomicronemia (hypertriglyceridemia), lipemia retinalis can be seen. Ocular findings are creamy discoloration of retinal vessels. Lipemia retinalis also does not affect the visual acuity. Familial hypercholesterolemia is an autosomal dominant disorder of lipid metabolism. Arcus cornea is an important sign and appears as single grayish ring parallel to the limbus. It is caused by lipid deposits in corneal stroma (7-10).

Tyrosinemia Type II, is an extremely rare autosomal recessive inherited metabolic disorder also called oculocutaneous tyrosinemia occurs due to deficiency of cytosolic tyrosine aminotransferase (TAT). Main manifestations of this enzyme deficiency are bilateral corneal erosions as well as palmar and plantar hyperkeratosis. Common complications are corneal opacity, glaucoma, corneal plana, nystagmus, visual impairment and amblyopia. Treatment consists of phenylalanine and tyrosine restricted diet. The target is to keep the tyrosine blood level at <500 micromol (11). Eye symptoms improve in a few weeks with treatment.

Alkaptonuria is a rare autosomal recessive metabolic disease caused by deficiency of homogentisate 1,2-dioxygenase (HGD) that results in harmful abnormal deposits in various tissues. Deficiency of HGD enzyme causes accumulation of homogentisic acid, tyrosine and phenylalanine. Oxidized pigment derivative bind collagen, causing their deposition in the connective tissue of the nose, sclera and earlobes. The ocular manifestations may occur as the renal and joint involvement. Eye pathologies occur in 70% of patients. Hyperpigmentation of the sclera can present and can be identified with gross examination without using any equipment. Wilson's disease is an autosomal recessive disease that causes copper to accumulate in the liver, kidneys, and nervous system. The characteristic ocular finding is Kayser-Fleischer ring typically starts without symptoms at the vertical poles of the cornea due to the deposition of copper in its deeper layers and progresses circumferentially. It may be visible to the naked eye as a golden-brown ring when it develops, but early stages can be seen by magnified examination with slit lamp examination. The ring decrease with treatment when serum copper levels become normal values. Similar rings can be seen in other causes of liver failure, such as carotenemia and multiple myeloma, in asymptomatic affected individuals. Therefore, it is certainly not pathognomonic for Wilson's disease. Rings can heal after copper chelation therapy (12).

LENS ABNORMALITIES

Cataract

Congenital cataracts are rare but the most important reason of treatable childhood blindness. Cataract is the opacity within the lens. Cataract and lens dislocation are frequently seen in inherited metabolic diseases. If lens opacities are not diagnosed or treated at birth, they can cause blindness or amblyopia (13). When the patient is 3 months old, bilateral cataract causes irreversible nystagmus and amblyopia. For this reason, cataracts must be surgically removed within the first few weeks of life. Some inherited metabolic diseases also manifest themselves with cataracts (Table II). Unilateral cataracts are often associated with eye malformations whereas bilateral cataracts are more often associated with genetic metabolic disorders (14,15). Due to the lack of systemic associations in unilateral cataract, it is generally agreed that these children do not require further work up. Systemic work-up is necessary in children with bilateral cataracts (16,17).

Classic galactosemia is a disorder of the galactose metabolism and is inherited as autosomal recessive manner. It is caused by deficiency of GALT enzyme. Galactose-1-phosphate uridyltransferase (GALT), galactose1-phosphate epimerase and galactokinase are the three enzymes involved in galactose metabolism. In the early stage, "oil droplet" cataracts are seen,

Table II: Inherited metabolic diseases with cataract
Galactosemia Zellweger syndrome Rhizomelic chondrodysplasia punctata Lowe's syndrome Sorbitol dehydrogenase deficiency
Aldose reductase deficiency
Fabry disease Neuronal ceroid lipofuscinosis (juvenile form) Oligosaccharidoses:α-mannosidosis; sialidosis
Lysinuric protein intolerance Ornithine aminotransferase deficiency
Sjogren-Larsson syndrome Neutral lipid storage disorder Cerebrotendinous xanthomatosis Smith – Lemli – Opitz syndrome Conradi-Hunermann syndrome Mevalonate kinase deficiency
Sengers syndrome Methylglutaconic aciduria Mitochondrial DNA mutations
Menkes disease Wilson's disease

which are not true cataracts but produce refractive changes in the lens. The lesion appears as a floating oil droplet in the center of the lens (13). Galactitol, a metabolite of galactose, accumulates in the lens. Galactitol is impermeable and causes deterioration of the lenticular structure. Hepatic failure, jaundice and tubulopathy are seen in GALT deficiency. Diagnosis is made by measurement of GALT enzyme activity in erythrocytes and molecular analysis for confirmation. Epimerase deficiency is caused by GALE gene defects and three forms have been defined. The polyol pathway consists of two enzymes; aldose reductase and sorbitol dehydrogenase. Aldose reductase reduces hexose sugars such as glucose and galactose to sorbitol and galactitol. As a result of polyol accumulation; lens swelling, increased membrane permeability, electrolyte abnormalities and increased intracellular fluid are seen. This causes cataracts. In sorbitol dehydrogenase deficiency, cataract occurs as the only finding at birth. Determination of galactose metabolizing enzymes, sorbitol dehydrogenase in lens, may help in determining the mechanism of formation of cataracts. Cataract may also develop in glucose-6-phosphate dehydrogenase deficiency (G6PD), which is noted with hemolytic anemia. Glucose-6-phosphate dehydrogenase has an essential role in the defense against cellular injury. The most common manifestations of G6PD deficiency is jaundice and hemolysis. Cataract is less known finding described with G6PD deficiency. Oxidative stress is responsible in the pathogenesis of cataract (18,19).

Among the known membranes, the membrane with the highest cholesterol content is the lens membrane. It is of great importance that cholesterol metabolism is normal in the continuity of the lens. It is manifested by disorders of cholesterol biosynthesis and a wide and variable distribution of congenital anomalies. Cataracts can be seen in very severe forms in the early period. In mild forms, cataracts may not develop. In Cerebrotendinous xanthomatous; xanthomas are associated with progressive neurological ataxia syndrome, cognitive impairment, pyramidal manifestations, epilepsy, peripheral neuropathy and eye pathologies such as bilateral, irregular, corticonuclear, anterior polar or posterior capsular cataracts that occur in the first decade. It may be related to the opacities of the crystalline lens. Cataracts can also be seen in patients with Sjögren-Larsson syndrome and neutral lipid storage disorder characterized by ataxia, myopathy, hepatomegaly and ichthyosis. Vacuolated lymphocytes are a common finding in peripheral smear (7,20).

Zelweger spectrum disorders are heterogenous group of autosomal recessive disorders characterized by a defect in peroxisome formation. Mutations in *PEX* genes cause a deficiency of functional peroxisomes. Ocular abnormalities like retinopathy, cataracts and glaucoma often leading to blindness could be seen (21). Measurement of plasma very long chain fatty acids is helpful in diagnosis but molecular genetic analysis should be done for accurate diagnosis (22). It is important to initiate proper supportive therapy to improve quality of life.

Cataracts can also be seen in other aminoacidopathies such as ornithine aminotransferase (OAT) deficiency (gyrate atrophy of the choroid and retina) and lysinuric protein intolerance. In Lowe's (oculo-cerebro-renal) syndrome, cataract is a prominent finding in the disease. Severe neurological involvement such as muscle hypotonia, areflexia, renal involvement (Fanconi syndrome) and mental retardation are other clinical findings of Lowe's syndrome (23,24).

Lens Dislocation

Lens dislocation is a common and characteristic feature of both Marfan syndrome and homocystinuria. Marfan syndrome is a rare inherited disorder of the connective tissue with autosomal dominant mode of inheritance. Microfiber abnormalities are seen in the lens capsule due to changes in microfibers caused by mutations of the fibrillin-1 (*FBN1*) gene in Marfan syndrome. The clinical findings are are tall stature with a large arm span, kyphosis, congenital lens dislocation and cardiac manifestations. In homocystinuria, lens subluxation is most common downward, whereas in Marfan syndrome, the lens usually subluxes upwards. However, it can be in any direction in both diseases (25,26) (Table III). Most patients with Isolated sulfite oxidase deficiency develop microcephaly, feeding difficulties and dislocated ocular lenses. In patients with homocystinuria, subluxation of the ocular lens occurs in more than 90% of patients and is very characteristic. As it can be seen before 3 years of age, it usually presents until the first 10 years of age. Worsening myopia, astigmatism, and glaucoma may also occur. Cataracts may occur in the lens. Optic atrophy may develop following retinal detachment and central retinal artery occlusion. Hypermethioninemia is an important finding. Diagnosis is made by measuring cystathionine β-synthetase enzyme activity in fibroblast culture, lymphoblasts and mutation analysis. In patients diagnosed with newborn screening, diet

Table III: Inherited metabolic diseases with Lens Dislocation
Marfan Syndrome
Homocystinuria
Sulfite oxidase deficiency
Molybdenum Cofactor deficiency

therapy (low in methionine) and pyridoxine should be started. Thus, it is possible to prevent lens dislocation in early detected patients (26).

RETINAL DEGENERATION

The retina is a target for defects of oxidative phosphorylation. Retinal involvement occurs as retinitis pigmentosa or optic atrophy. Diseases characterized by the presence of retinal pigmentation as a prominent feature of retinal degeneration are overviewed. Retinitis pigmentosa and optic neuropathy are very frequent in mitochondrial disorders.

Retinitis Pigmentosa is a group of inherited diseases in which progressive loss of photoreceptor and pigment epithelial function occurs. The genetic defect is expressed in the rods, but in most affected people the cones finally degenerate resulting in loss of central vision. Bilateral peripheral vision loss, rod dysfunction and progressive loss of photoreceptor function are diagnostic criteria. RP usually begins in early childhood or infancy. The earliest ophthalmoscopic findings are a thread-like appearance of retinal arteries and a weak retinal reflex. Anomalies in RP can be detected by electroretinogram before they have fundoscopic findings. It can be divided in two groups as primary and secondary RP. Gyrate atrophy of the choroid and retina caused by OAT deficiency can be given as an example to the first group. RP is frequently associated with some genetic disorders impairing mitochondrial OXPHOS. Two of them are neurogenic muscle weakness with retinitis pigmentosa (NARP) and sporadic Kearns-Sayre syndrome (KSS). Retinitis pigmentosa can also be seen in lipid metabolism disorders such as abetalipoprotenemia and lysosomal storage disorders as shown in Table IV.

Gyrate atrophy of the choroid and retina is a rare metabolic disease caused by deficiency of the enzyme ornithine aminotransferase (OAT) which is pyridoxal 5-phosphate dependent and located in mitochondrial matrix. Elevated concentration of ornithine occurs in body leads to characteristic ocular abnormalities. Patients usually present to the ophthalmologist with night blindness or myopia in late childhood or adolescence. Posterior subcapsular cataract develops in the twenties. In the third decade, most of the fundus is involved and pigmentation increases in the macular region. The optic disc is pink. Visual acuity and visual fields gradually decrease. In OAT deficiency, ornithine level increases 10-15 fold in all body fluids including aqueous humor along with a small reduction in glutamine, lysine and creatine and causes lesions

Table IV: Inherited metabolic diseases with retinitis pigmentosa
Lysosomal storage diseases
Lipid metabolism disorders
Mitochondrial diseases
Peroxisomal disorders

in photoreceptors. Treatment is not curative and depends on life long dietary modifications (arginine restriction and lysine supplementation) and vitamin B6 administration which aims to increase plasma pyridoxal 5-phosphate level (24-28). Inherited metabolic diseases causing secondary retinitis pigmentosa are described in Table IV.

Neuronal Ceroid lipofuscinoses (NCLs) are among gray matter neurodegenerative disorders. NCLs are a group of progressive encephalopathies characterized by neural and extraneural accumulation of autofluorescent ceroid and lipofuscin material. NCL types that cause RP are divided according to clinical and genetic variants (29,30).

1. ***Palmitoyl protein thioesterase-1 related NCL (CLN1):*** Common presenting findings included motor delay or regression, abnormal movements, visual impairment, microcephaly and myoclonic epilepsy are seen.
2. ***Tripeptidyl-peptidase-1 related NCL (CLN2):*** Clinical findings start between the ages of 2-4; regression in mental abilities, ataxia, convulsions, optic atrophy on fundus examination and pathological electroretinogram and visual evoked potentials (VEP) are seen.
3. ***Juvenile neuronal ceroid lipofuscinosis (CLN3):*** The majority of the patients suffer from neurological degeneration in the first decade and rapid visual decline after 5 years of age due to retinal degeneration. It limits the life expectancy to 20 years of age.

Retinitis pigmentosa can also be seen in different lipid metabolism disorders such as abetalipoproteinemia, malabsorption of fat-soluble vitamins, especially vitamins A and E. The most common clinical symptoms are diarrhea and growth retardation. Peripheral neuropathy, spinocerebellar ataxia, and muscle weakness are also seen. Retinal dystrophy usually occurs in late childhood. Fundus examination may be normal in the early period, then there may be peripheral pigmentary retinopathy. Retinal and neurological complications can be prevented by early supplementation of vitamin E (31,32).

CHERRY RED SPOT

A cherry red spot is formed due to ganglioside deposition in retinal ganglion cells. Sialidosis is an autosomal recessive disorder resulting from mutations in NEU1 gene. There are two forms defined. Sialidosis I is often referred as myoclonus-cherry red spot syndrome presenting in second decade of life with visual decline. Type II is more severe acute fulminant

form. Galactosialidosis is also autosomal recessive inherited metabolic disease caused by mutations in *CTSA* gene leading to combined deficiency of neurominidase and beta-galactosidase. Common clinical features are coarse face, skeletal abnormalities, myoclonus, cherry red spot in macula and seizures. Cherry red spot is also a common feature of other lysosomal storage disorders such as Tay-Sachs disease, Sandhoff disease and Niemann Pick disease. GM1 gangliosidosis is a lysosomal storage disorder caused by low activites of beta- galactosidase enzyme and pathogenic mutations in *GLB1* gene. The clinical features are psychomotor regression, visceromegaly, extensive Mongolian spots on the trunk, coarce facial appearence, retinal cherry red spot and skeletal abnormalities. GM2 gangliosidosis include Tay-Sachs disease, Sandhoff disease and GM2 activator protein deficiency. Sandhoff disease is an autosomal recessive lysosomal disorder resulting in GM2 gangliosidoside storage due to deficiency of Beta-hexosaminidase B (*HEX-B*). There are three clinical phenotypes exist. Most common subtype is infantile onset one which is characterized by axial hypotonia, startle response, macrocephaly, seizures and macular cherry red spots and finally died before 5 years of age. Farber disease is an ultra-rare lysosomal disorder caused by acid ceramidase deficiency encoded by *ASAH1* gene. Cardinal clinical findings include subcutaneous nodules, joint contractures, and hoarce voice. Ophtalmic symptoms such as formation of cherry red spot, storage pathology in retinal ganglion cells, corneal opacities and nystagmus may be present in patients with Farber disease. Pigment retinopathies are one of the ocular findings seen in many lysosomal storage diseases. The absence of ganglion cells in the fovea causes a red stain surrounded by white cells filled with storage material. As the ganglion cells die, the cherry-red spot disappears, optic atrophy becomes evident. In the differential diagnosis, mainly lysosomal storage diseases should be considered. It can be detected early in GM2 gangliosidosis and GM1 gangliosidosis. Electroretinogram is normal, but VEP is abnormal. The cortical response usually disappears from the first months of life (33,34). In Niemann-Pick disease type A, corneal opacification and dislocation of the anterior lens capsule are seen. In sialidosis (mucolipicosis type I), cherry- red spot is seen. Irregular pale cherry red spot is also seen in Farber's disease, Gaucher's disease type II and GM2 activator protein deficiency (5,35) (Table V). Retinal degeneration can also be seen in intracellular cobalamin metabolism defects and congenital glycosylation defects.

Table V: Inherited metabolic diseases with cherry-red spot

Tay–Sachs disease
Sandhoff disease
Niemann–Pick disease type A
Gaucher disease type II
Farber's disease
Sialidosis types I, II
Galactosialidosis
GM1 gangliosidosis
GM2-activator protein deficiency

OPTIC ATROPHY

Optic atrophy is a manifestation of the degeneration of ganglion cell axons forming the optic nerve or the supporting microvascular tissue surrounding the optic nerve. Decreased visual acuity, visual field defects and/or color vision disturbances are seen. The early stage of optic atrophy before clinical signs appear is called optic neuropathy. It is a general term for optic nerve dysfunction. Progression of optic atrophy can be stopped by treating an underlying cause. However, there is no effective treatment. Genetic defects are responsible for a significant portion of optic atrophy. The lesion may be the only clinical feature (primary) or it may be associated with various symptoms (secondary) (36).

Optic atrophy is often the only clinical feature of the disease. Examples of primary causes are Leber's hereditary optic neuropathy (LHON) and Costeff syndrome (37).

Leber hereditary optic neuropathy (LHON) is an inherited metabolic disease of mitochondrial inheritance. The pathogenesis involves a primary point mtDNA mutation resulting in failure of the oxidative phosphorylation pathway. Vision loss that mostly affects young men. It is typical of mitochondrial optic neuropathies. Rapid, painless loss of central vision in one eye is characteristic. It usually starts with discoloration in one eye, and then a similar involvement is seen in the other eye and visual acuity stabilizes within a few months. Visual field defect in the form of centrocecal absolute scotoma is seen (37). The symptomatic phase of LHON is characterized by an acute or subacute bilateral painless central vision loss associated with swelling of the nerve fiber around the disc and telangiectatic microangiopathy in peripapillary region without leakage on fluorescein angiography. The optic disc appears hyperemic, sometimes with peripapillary hemorrhages, and axonal loss quickly leads to transient atrophy of the optic disc. Over time, the optic disc becomes pale. Optic atrophy occurs with permanent severe central vision loss but with relative preservation of the pupillary light reflex. However, over time, visual acuity improved spontaneously. Visual function may suddenly improve with the contraction of the scotoma or the reappearance of small islets of vision (fenestration) in it. In long-term LHON, dimpling of the optic disc can often be a manifestation of the chronic stage of the pathological process. LHON typically results from homoplasmic mtDNA mutations with wide variability in phenotypic penetration (38). The diagnosis of LHON can be made based on patient and family history, as well as neuroophthalmologic examination and mDNA genetic analysis. Confirmation of the diagnosis is very important because of the clinical course, prognosis and hereditary pattern of the disease. Idebenone is a synthetic water-soluble analog of co-enzyme Q10, the approved therapy for LHON. Approved treatment in LHON is limited, preclinical studies in gene therapy will be done (39).

Table VI: Inherited metabolic diseases with optic atrophy
Mitochondrial diseases
Peroxisomal diseases
Lysosomal storage diseases
Other metabolic disorders Homocystinuria Cobalamin C/D disorders Propionic acidemia Mevalonic aciduria Smith – Lemli – Opitz syndrome Alexander's disease Canavan's disease Menkes Pelizaeus-Merzbacher disease

Costeff optic atrophy syndrome (OPA 3), is a disease consisting of early-onset bilateral optic atrophy and late-onset spasticity, extrapyramidal dysfunction, and cognitive problems.

Secondary optic atrophies are commonly caused by mitochondrial, peroxisomal, lysosomal and other metabolic diseases (Table VI) (40-44). Due to the crucial involvement of Krebs cycle in the maintenance and survival of retinal ganglion cells, patients with mitochondrial disease are prone to have optic atrophies.

Optic atrophies are described also in a variety of inherited metabolic disorders and may not be a permanent finding. Biotinidase deficiency, Menkes disease, homocystinuria, inherited disorders of cobolamin metabolism, Smith- Lemli-Opitz syndrome, congenital glycosylation defects and organic acidemias are examples of diseases that cause secondary optic atrophy.

CONCLUSION

Ocular symptoms often occurs in inherited metabolic diseases. Accurate examination of the eye with the aid of an ophthalmoscope and slit lamp can detect pathognomonic abnormalities such as corneal clouding, lens abnormalities, retinal degeneration, cherry red spot, cataract and optic atrophy. Ophthalmological evaluation are often non-invasive and provides important clues in the diagnosis of many inherited metabolic diseases. Inherited metabolic diseases should always be suspected when more common etiologies have been ruled out. Early management of ocular symptoms can improve the patient's quality of life.

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Turkish Journal of Pediatric Disease

Türkiye Çocuk Hastalıkları Dergisi

17. Vol Author Index / *Cilt: 17. Yazar İndeks*

Aslı Nur ÖZKAYA PARLAKAY	4/324
Abduljabar ADI	4/279
Abdurrahman BİTKAY	4/298
Adem DURSUN	5/418
Adnan DAĞÇINAR	1/68
Ahmet ATICI	1/52
Ahmet ÖZTÜRK	2/139
Ahmet ÖKTEM	5/335
Ahmet Sefa GÜMÜŞSOY	6/466
Ahmet Serkan ÖZCAN	3/187
Ahmet Vedat KAVURT	1/30
Ahmet Yasin GÜNEY	4/324
Ali FETTAH	1/56
Anar QURBANOV	6/451
Arif BOLACA	6/501
Arzu Meltem DEMİR	4/309
Asburce OLGAÇ	2/101
Aslı ÇELEBİ TAYFUR	1/1
Aybegüm KALYONCU AYÇENK	6/461
Aybüke YAZICI	3/187
Aydan BİRİ	5/428
Aydın YAĞMURLU	6/451
Ayhan PEKTAŞ	4/257
Ayla AKÇA ÇAĞLAR	6/433
Aylin GÜLTEKİN KURU	6/501
Aylin KILINÇ UĞURLU	4/298
Aynur KÜÇÜKÇONGAR YAVAŞ	5/428
Ayse METİN	2/166
Ayse RODOPMAN ARMAN	2/106
Ayse Selcen OĞUZ ERDOĞAN	2/171
Ayse TOKSOY AKSOY	2/106
Aysel HAJİYEVA	4/272
Aysel ÜNLÜSOY AKSU	4/309
Aysenur DEMİR	1/25
Ayşe ÇITAK	4/257
Ayşe Derya BULUŞ	3/219
Ayşe Gül ALIMLI	5/363
Ayşe Gül GÜVEN	5/387
Ayşe METE YEŞİL	4/272
Ayşegül BÜKÜLMEZ	4/257
Ayşegül DEMİR	3/207
Ayşegül ZENCİROĞLU	5/380
Azize Pınar METBULUT	2/166
Bahar AKINTUĞ	6/476
Banu ÇELİKEL ACAR	1/7,3/194,5/347, 5/369,6/483
Baran GÜL	4/257
Barış GÜLLER	3/233
Begum AVCI	2/91
Begüm SOYALAN	4/257
Belgin GÜLHAN	4/324
Beste ÖZSEZEN	1/62,5/363
Betül BÜYÜKTİRYAKİ	1/13,6/439
Betül ORHAN KILIÇ	4/279
Betül SİYAH BİLGİN	3/187
Beyza Nur KUZAN	1/68
Bilal OZELCE	1/30
Binnaz ÇELİK	5/418
Burak BEKGÖZ	3/182
Burcak KURUCU	1/56
Burcu Ceylan CURA YAYLA	1/25,6/476
Burcu HIDIMOĞLU	4/309
Burçin BEKEN	5/424
Bülent GÜNEŞ	5/375
Büşra BAHADIR	5/354
Çağla İLBASMIŞ	2/106
Can AKAL	5/335
Can İhsan ÖZTORUN	1/71,2/171
Can Naci KOCABAŞ	1/13,6/439
Caner KARA	4/263
Çiğdem Seher KASAPKARA	2/101
Cüneyt KARAGÖL	1/7,3/194,5/347, 5/369,6/483
Cüneyt UĞUR	4/267
Çağla ÖZDEMİR	4/285
Çiğdem Seher KASAPKARA	6/506
Deniz DURMUŞ	4/257
Deniz KARAKAYA	5/341
Deniz YILMAZ	1/1
Denizhan BAGRUL	1/30
Derya CENSUR	1/1
Derya GÜMÜŞ DOĞAN	4/291
Derya SULUHAN	3/243
Derya TEPE	4/298
Didar GüRSOY	1/52
Didem ARDIçLI	1/1,1/45
Dilek KONUKSEVER	2/85,4/279
Dilek YILDIZ	3/243
Doğuş GÜNEY	2/171
Dursun ALEHAN	5/335
Duygu İSKENDER MAZMAN	4/309
Ecem SAĞIROĞLU	3/243
Eda ÖZAYDIN	4/320,5/354
Efe SEVİM	4/279
Elif AKÇAY	3/207,5/354
Elif ARSLANOĞLU AYDIN	3/214
Elif BENDERLİOĞLU	6/433
Elif ÇELİKEL	1/7,3/194,5/347, 5/369,6/483
Elif Emel ERTEN	1/71
Elif N. ÖZMERT	4/272
Emel ÖMERCİOĞLU	4/272,5/380
Emine Bilge AYNI	5/424
Emine DİBEK MISIRLIOĞLU	1/13,2/166,6/439
Emrah GÜN	6/451
Emrah ŞENEL	1/71,2/171,3/243, 6/433
Emre ÖZER	4/298

Emregül IŞIK	4/298
Erbu YARCI	3/233
Ergin ÇİFTCİ	6/451
Ergun ERGÜN	6/451
Ersoy CİVELEK	1/13,1/39,6/439
Ervin MAMBET	2/147
Esra BAĞLAN	3/214
Esra ÇÖP	3/207, 5/354
Esra FIRAT OGUZ	1/56
Eşay KIRAN YENİCE	4/263
Evra ÇELİKKAYA	5/341
Evrim KARGIN ÇAKICI	5/341
Eylem GÜL ATEŞ	4/279
Eyüp SARI	3/182
Fatih DURAN	4/309
Fatih GÜRBÜZ	4/298
Fatma AYDIN	1/7,5/369
Fatma ESEROGLU	1/25
Fatma Gül DEMİRKAN	5/406
Fatma Şemsa ÇAYCI	2/91, 3/194
Fatma YAZILITAŞ	5/341
Ferhat YAYLACI	3/233
Feyza SEVER	5/412
Feyzullah Necati ARSLAN	4/291
Funda BAŞTUĞ	5/418
Funda Seher ÖZALP ATEŞ	5/354
Gamze ÖZTÜRK YILMAZ	6/498
Gizem ATAKUL	4/304
Gokhan Berktug BAHADIR	2/147
Gökçe Dilek İŞCAN	6/476
Gökçen Dilşa TUĞCU	5/363
Gökhan YILMAZ	6/498
Gönül BÜYÜKYILMAZ	4/298
Gönül YARDIMCI	4/298
Gulenay KORKMAZ	2/147
Gülşah ALYAR	2/96
Günay TUNCER ERTEM	1/25
Gürses ŞAHİN	1/56
Gül ARGA	6/451
Gülendam BOZDAYI	5/428
Gülnur GÖLLÜ	6/451
Gülser ŞENSES DİNÇ	3/207,5/354
Gülsüm İclal BAYHAN	4/324
Günay EKBERLİ	3/253,4/315,5/394
Güzin CİNEL	5/363
H. Hakan AYKAN	5/335
Hakan CENSUR	1/1
Hakan GÜVENİR	1/13
Halil ÖZDEMİR	6/451
Halil Tuna AKAR	3/250
Halise AKÇA	3/182,6/433
Haluk ÖZTÜRK	2/147
Harun BAĞCI	1/19
Harun DEMİRCİ	2/160
Hasan ARI	1/13
Hatice GÜNEŞ	2/133
Hatice Kübra KONCA	6/451
Hatice ÜNVER	2/106
Hazım Alper GÜRSU	1/30,4/328
Hilal AYDIN	2/113
Hüseyin Emre ATASEVER	2/147
Hüsniye YÜCEL	3/201
İbrahim ECE	1/30
İbrahim Hakan BUCAK	2/113
İbrahim İlker ÇETİN	1/30
İbrahim YILDIRIM	2/147
İlke Evrim SEÇİNTİ	1/52
İrem CİHANYURDU	2/106
İbrahim EKER	4/257
İlhami SURER	2/147,2/154
İlker ERTUĞRUL	5/335
İlknur BAĞRUL	3/214
İlknur FİDANCI	6/476
İlknur KÜLHAŞ ÇELİK	6/439
İnci ERGÜRHAN İLHAN	6/455
İrem Damla ÇİMEN	6/466
İshak SAN	3/182
Jale KARAKAYA	1/25
Johannes HAEBERLE	2/101
Kadri Cemil ULUBULUT	2/147
Kezban ŞAHİN	6/488
Keziban TOKSOY ADIGÜZEL	4/298
Kübra AYKAÇ	1/25,6/476
Kutay SEL	5/335
Kübra DEVECİ	3/250
Latife GÜDER	4/324
Leman AKÇAN YILDIZ	6/433
Luai SHAABAN	4/279
M. Levent KAYAALP	2/133
Medine Ayşin TAŞAR	1/25,5/387,6/476
Medine Ezgi ÖCAL	1/71
Mehmet Bahadır CALIŞKAN	2/147,2/154
Mehmet BOYRAZ	4/298
Mehmet BÜLBÜL	3/214,5/341
Mehmet ÇELEĞEN	4/257
Mehmet Emin ÇELİKKAYA	1/52
Mehmet Oğuz ÇEVİK	2/147
Melih İlhan DEMİRCİLER	6/501
Meliha SEVİM	5/387
Melike Mehveş KAPLAN	1/7,3/194,5/347, 5/369,6/483
Melissa KARATAŞ	4/257
Meltem BİNGOL KOLOĞLU	6/451
Meriç KAYMAK CİHAN	6/455
Merve Cansu POLAT	3/194,5/347,5/369, 6/483
Merve ONAT	3/207,3/243
Merve YOLDAŞ ÇELİK	6/439
Mesut KOÇAK	3/219
Mihriban İNÖZU	2/91
Mina HIZAL	5/363
Miray TÜMER	6/433
Müge SEZER	1/7,3/194,5/347, 5/369,6/483
Müge TOYRAN	1/13,1/74,6/439
Müjdem Nur AZILI	2/171
Murat ÇAPANOĞLU	1/39
Murat ÇAKMAK	6/451
Murat DOĞAN	5/418
Murat YURDAKÖK	5/335
Mustafa BERKAY KILIÇ	6/476
Mustafa KILIÇ	2/101
Mustafa Orhan DUYAR	5/418
Mustafa SAKAR	1/68
Nejmiye AKKUŞ	6/445
Neriman SARI	6/455
Nesibe Gökce KOCAMAZ	3/214
Nevin UZUNER	4/304
Nevzat Can SENER	3/253
Nihat SAPAN	2/118
Nilgün EROĞLU	4/257
Nilüfer TEKGÖZ	1/7,3/194,5/347, 5/369,6/483
Nimet ÖNER	3/194,5/347, 5/369,6/483
Nuray AKTAY AYAZ	5/406
Nuri BAKAN	2/96
Nurinnisa ÖZTÜRK	2/96
Nursel DAL	6/488
Ömer GÜNHAN	2/154
Öner ÖZDEMİR	2/118
Onur KAŞLI	3/219

Osman SAYIN	4/267
Oya KIREKER KÖYLÜ	6/506
Özcan EREL	1/56,4/309
Özge DEDEOĞLU	1/45
Özge Nur TURKERI	2/96
Özgür YÖRÜK	2/96
Özlem EKİCİ	2/147
Özlem Yüksel AKSOY	2/91
Ömer GÜNEŞ	4/324
Özge ATAY	4/304
Özge BOYACIOĞLU KANGALLI	4/304
Özge PARLAK GÖZÜKARA	5/354
Özge YILMAZ TOPAL	3/227
Özkan KARAMAN	4/304
Özlem KALAYCIK ŞENGÜL	5/424
Özlem MUSTAFAOĞLU	4/324
Özlem Yüksel AKSOY	5/418
Pari KHALILOVA	6/451
Pelin ÖZYAVUZ ÇUBUK	6/445
Pınar BAYRAKTAR	4/324
Pınar KOCAAY	4/298
Pınar ZENGİN AKKUŞ	4/272
R. Köksal ÖZGÜL	3/250
Sabri DEMİR	3/243
Salih CESUR	1/25
Saliha KANIK YÜKSEK	3/175, 4/324
Saliha SENEL	2/126
Salim NEŞELİOĞLU	4/309
Sami DALATI	4/279
Sanem ERYILMAZ POLAT	5/363
Sare Gülfem ÖZLU	1/19
Secil SAYIN	1/30
Seçil ÇAKIR GÜNDOĞAN	4/298
Seda KÖSE ŞİRİN	4/304
Seda ŞAHiN	4/324
Selcen YUKSEL	1/19
Selim DERECİ	4/309
Selin YİĞİT	5/428
Selma ALİM AYDIN	2/166
Selma ÇAKMAKCI	6/455
Sema ATEŞ	4/320
Sema Nilay ABSEYİ	5/387
Semanur ÖZDEL	3/214
Serdar AL	4/304
Serdar SEZER	5/369
Serhat KILIÇ	4/279
Serkan COŞKUN	1/7,3/194,5/347, 5/369,6/483
Serkan GÜNEŞ	5/394
Serkan ÖZMEN	5/369
Serkan ÖZSOYLU	5/418
Sevgin TANER	3/253,4/315,5/394
Sevim Ecem UNLU BALLI	2/147
Sevim ÜNAL	3/187
Sevinc PUREN YUCEL	2/85
Sinem KORTAY CANALOĞLU	4/291
Songül YALÇIN	5/375
Şükrü ÇEKİC	2/118
Şule YEŞİL	1/56
Süleyman Arif BOSTANCI	1/71
Süleyman Taha ASLAN	2/160
Sümeyye ERDOĞAN	2/113
Suna ASİLSOY	4/304
Suzi DEMIRBAĞ	2/147
Süleyman KELEŞ	4/285
Sümeyye SÖZDUYAR	6/451
Şamil HIZLI	4/309,5/412
Şenay GÜVEN BAYSAL	4/291
Şerife TUNCEZ	3/214
Şeyma ÖZPINAR	5/424
Şuayip KESKİN	5/418
Şule BÜYÜK YAYTOKGİL	1/74
Şule YİĞİT	5/335
Tanıl KENDİRLİ	6/451
Tayfun GİNİŞ	1/13, 6/439
Tevfik KARAGÖZ	5/335
Toghrul JAVADOV	1/68
Tolga Hasan ÇELİK	5/335
Tuba KURT	1/7, 3/194, 5/369
Tuğba GÜLER SÖNMEZ	1/19
Tugba ÖRNEK DEMİR	1/71
Tuğçe KAPUCU	6/466
Turan BAYHAN	6/455
Tülin ÇATAKLI	2/126, 3/201
Tülin GÜNGÖR	5/341
Ufuk ATEŞ	6/451
Uğur Ufuk IŞIN	3/219
Ülkü ÖZTOPRAK SİYAH	1/25
Umut Selda BAYRAKCI	2/91
Utku PAMUK	4/328
Ümran Gül AYVALIK BAYDUR	3/207
Vildan GÜNGÖRER	3/194,5/347, 5/369,6/483
Vildan Selin CAYHAN	2/171
Yakup CANITEZ	2/118
Yasemin ERGÜL	6/488
Yaşar BİLDİRİCİ	5/401
Yeter DÜZENLİ KAR	4/257
Yılmaz YILDIZ	3/250
Yiğit ŞENOL	4/257
Zahide EKİCİ TEKİN	1/7,3/194,5/347, 5/369,6/483
Zehra AYDIN	2/91
Zehra İNCEDAL SONKAYA	2/139
Zeliha YEĞİN	6/466
Zeynep GÖKER	3/207
Zuhal KARALI	2/118

Turkish Journal of Pediatric Disease

Türkiye Çocuk Hastalıkları Dergisi

17. Subject Index/ *17. Cilt Konu Dizini*

8-hydroxy-2 deoxyguanosine	2/96
Activity	4/309
Acute kidney injury	2/91
Acute Scrotum	1/52
Acute Urticaria	1/13
Adenotonsillar hypertrophy	2/96
Adolescent	2/106,2/171, 3/207,3/243
Adults	1/25
Age	5/369
Allergic rhinitis	1/39
Ambulance	3/182
Amplatzer occluder device	1/30
Anemia	3/187
Anesthesia	5/412
Antinuclear antibody	1/7,5/347
Antioxidant	4/309
Anxiety	5/394
ARFID	5/354
Arthralgia	6/483
Arthritis	6/483
Asthma	1/39,1/62,2/118, 3/227
Atopic dermatitis	4/304
Atrioventricular (AV) Block	5/335
Avoidant/restrictive food intake disorder	5/354
Awareness	1/19,3/175, 5/387
Baby walker	3/201
BCG vaccine	1/74
Behavior	4/279
Behavior problems	4/272
Behavioral problems	3/233
Biologics	5/406
Biotinidase deficiency	3/250
Brain Atrophy	1/68
Breastfeeding	4/263,5/428,
Bronchitis	1/62
Burn	3/243,5/401
Burn unit	5/401
Burn-out	6/466
CAKUT	4/315
Cancer	6/455
Capillaroscopy	1/7
Cardiac Dysrhythmia	5/428
CDKL5	4/320
Cefoperazone	6/455
Cerebral Blood Flow	2/160
Cerebral palsy	1/45
Chest pain	4/328
Child	1/1,1/13,1/19,1/25,1/39,1/52,1/62,1/71,2/91,2/106,2/113,2/139,2/133,2/147,2/166,3/219,3/182,3/227,3/253,4/258,4/279,4/280,4/309,4/315,4/320,4/324,4/328,5/363,5/401,5/412,5/418,6/433,6/451,6/455,6/461,6/466,6/476,6/488,6/498
Child Development	4/291
Child Nutrition Sciences	6/488
Child psychiatry	3/207
Childhood vaccines	1/74
Chronic Cough	1/62,3/227
Complication	5/380,6/461
Congenital Cytomegalovirus infection	3/175
Consultation	4/267
Coping Strategies	2/106
Coronavirus Diseas	4/258
COVID-19	1/25,2/118,2/106,3/182,4/272,4/299,4/324,5/387,5/428,6/433, 6/476
Craniosynostosis	2/160
Cystic Fibrosis	5/363
Dental prosthesis	6/501
Depression	4/279,5/394
Developmental Behavioral Pediatrics	4/291
DFS 70	5/347
Disease-modifying anti-rheumatic drugs	3/214,5/406
DRESS	5/424
Drug allergy	5/424
Drug Induced Hypersensitivity Syndrome	5/424
Dysmyelinating Disorders	6/445
Ear Childhood Development	6/498
Early Childhood Development	4/291
Ectodermal dysplasia	6/501
Electrical Burn	5/401
Electrolyte Imbalance	2/85
Emphysematous Pyelonephritis	3/253
Empyema	6/451
Endoscopy	5/412
Epilepsy	1/45
Erythema Multiforme	2/166
Erythrocyte transfusion	3/187,5/380
Etiology	1/13
Eye	4/267
Family Environment	4/279
Febrile neutropenia	6/455
Folic acid	2/113
Food allergy	4/304
Foreign body	4/267
Fractional urea excretion	2/91
Gastrointestinal hemorrhage	4/304
Gender Dysphoria	2/133
Gender Identity	2/133
Graft enhancement	2/154
HAV vaccine	1/74
Hemoglobin	1/56
Hepatic failure	5/424

Herpes Simplex Virus	2/166
Home Accident	6/433
Hospitalization	3/207
Human milk	4/263
Human Papilloma Virus	5/387
Hyperammonemia	2/101
Hypertension	1/19
Hyponatremia	5/418
Hypospadias	2/154
Immune thrombocytopenic purpura (ITP)	4/324
Immunization	2/139
Immunoglobulin A	6/439
Immunoglobulin G	6/439
Immunoglobulin M	6/439
Inborn errors of metabolism	3/250
Inborn urea cycle disorders	2/101
Indication	5/380
Infant	2/126,3/201, 4/304
Infantile colic	5/375
Infantile panhypopituitarism	1/68
Infection	1/13
Influenza	1/39
Inguinal hernia	6/461
Inherited metabolic disorders	6/506
Injury	3/201
Inpatients	3/207
Iron deficiency anemia	1/56
Ischemia modified albumin	1/56
İnfluenza vaccine	1/74
Juvenile idiopathic arthritis	3/214,5/406
Knowledge	3/175
Language development	3/233
Laparoscopic	6/461
Leflunomide	3/214
Levetiracetam	4/320
Liver	5/363
Lockdown	2/106
Low immunoglobulin	6/439
Magnetic Resonance	2/160
Malondialdehyde	2/96
Mass Index	4/258
Medical Education	4/291
Medical Students	4/291
Membranous glomerulonephritis	5/341
Migraine	1/1
Minimally Invasive Surgery	2/147
MMR vaccine	1/74
Mothers	2/126
Multisystem Inflammatory Syndrome	4/258
Musculoskeletal system	6/483
Myiasis	6/498
Myomectomy	2/171
Necrotizing Fasciitis	1/71
Neonate	2/101
Nephritic syndrome	5/341
Neurogenic Bladder	3/253,5/394
Newborn	5/380
Newborn screening	3/250
NIAS	5/354
Nonsyndromic	2/160
Nurse	5/412
Nutrition	3/219,4/279
Obesity	3/219,4/299
Omalizumab	2/118
Ophthalmological findings	6/506
Ovarian size	4/299
Oxidative damage	1/56
Parent-child relationship	6/466
Parenting attitude	3/233
Parenting stress	3/233
Parents	5/387,6/488,
Patent ductus arteriosus	1/30
Pediatric	1/7,1/45,3/175, 5/369,5/394
Pediatric Behçet's disease	6/483
Pediatric cardiology	4/328
Pediatric dentistry	6/501
Pediatric Emergency	2/85,3/182, 4/267,6/476
Pediatric obesity	6/488
Pelizaeus-Merzbacher Disease	6/445
People with disabilities	6/466
Percutaneous	6/461
Perfusion Imaging	2/160
Physical Activity	3/219
Platelet	4/258
PLP1 Gene	6/445
Pneumonia	1/62
Postpartum depression	5/375
Potassium	2/85
Pre-school recurrent wheezing	6/439
Pregnancy	5/428
Premature	3/187
Premature infant	1/30
Prematurity	3/233
Prepubertal	2/133
Preschool children	4/285
Preschooler	4/263
pRIFLE	2/91
Proctocilitis	4/304
Prognosis	3/194,4/258
Prolonged crying	5/375
Protein carbonyl	2/96
Psychiatry	5/394
Psychological Effect	2/106
Psychopathology	3/207
Puberty precocious	4/299
Rare Diseases	6/506
Raynaud's Phenomenon	1/7
Recurrence	5/369,6/461
Refractive errors	4/263
Refractory epilepsy	1/45
Reliability	5/354
rhabdomyolysis	4/320
Rheumatology	1/7
Risk factors	1/45
Robot-Assisted Surgery	2/147
Screen exposure	4/285
Screening	3/175
Self-esteem	3/243
Self-regulation skills	4/285
Shear-Wave Elastography	5/363
Sjögren's Syndrome	5/335
SLEDAI-2K	3/194
Sleep	2/126,4/285
Smartphone Use	4/279
Social anxiety	3/243
Sodium	2/85,5/418
Special education	6/466
Subdural hematoma	1/68
Sudden infant death syndrome	2/126
Sulbactam	6/455
Surgey	6/451
Syrian refugee	4/315
Systemic Lupus Erythematosus	5/335,5/347
Systemic lupus erythematosus	3/194
Testicular Torsion	1/52
Tetanus Vaccine	1/71
Thiol	4/309
Thiol/disulfide	1/1,1/56
Thoracoscopic	6/451
Treatment	2/113,3/207
Trigger	1/13

Ulcerative colitis	4/309
Urethra	2/154
Urticaria	2/118
Uterine leiomyoma	2/171
Uterus size	4/299
Uveitis	5/369

Vaccination	5/387
Vaccine	1/39,1/74
Vaccine Hesitancy	2/139
Vaccine Refusal	2/139
Validation	5/354
VATS	6/451

Vitamin B12	2/113
Walking	3/201
Wheezy Infant	3/227
Without petechiae	4/324

Türkiye Çocuk Hastalıkları Dergisi

17. Cilt Konu Dizini

8-hidroksi-2-deoksiguanozin	2/97
Adenotonsiller hipertrofi	2/97
Adolesan	2/171,3/244
Aile Ortamı	4/280
Akıllı telefon kullanımı	4/280
Aktivite	4/310
Akut böbrek hasarı	2/92
Akut skrotum	1/53
Akut Ürtiker	1/14
Allerjik rinit	1/40
Ambulans	3/183
Amfizematöz	3/253
Ampiyem	6/452
Amplatzer tıkayıcı cihaz	1/31
Anemi	3/188
Anestezi	5/413
Ani bebek ölümü sendromu	2/127
Anksiyete	3/395
Anne baba tutumu	3/234
Anne Sütü	4/264,
Anneler	2/127
Antinükleer antikor	1/8,5/348
Antioksidan	4/310
ARFID	5/355

Artralji	6/484
Artrit	6/484
Astım	1/40,1/63, 2/118,3/228
Aşı	1/40,1/74
Aşı Reddi	2/140
Aşı Tereddüdü	2/140
Aşılama	5/388
Atopik dermatit	4/305
Atrioventriküler blok	5/336
B12 Vitamini	2/114
Bağışıklama	2/140
Baş Etme Stratejileri	2/107
BCG aşısı	1/74
Bebek	2/127,3/202
Benlik saygısı	3/244
Besin alerjisi	4/305
Beslenme	3/220,4/280
Beyin atrofisi	1/68
Bilgi Çocuk doktoru	3/176
Biyolojikler	5/406
Biyotinidaz eksikliği	3/250
Bronşit	1/63
CAKUT	4/316

CDKL5	4/320
Cerrahi	6/452
Cinsiyet Hoşnutsuzluğu	2/134
Cinsiyet Kimliği	2/134
COVİD-19	1/26,2/118,2/107,2/148,3/183,4/273,4/299,4/324,5/388,5/428,4/434,6/477
Çocuk	1/2,1/14,1/20,1/26,1/40,1/53,1/63,1/71,2/107,2/114,2/134,2/140,2/166,3/183,3/228,3/220,3/253,4/258,4/273,4/310,4/316,4/320,4/320,4/324,4/328,5/342,5/364,5/402,5/413,5/419,4/434,6/452,6/456,6/462,6/467,6/477,6/489,6/498
Çocuk Acil	2/86,3/183,6/477
Çocuk Beslenmesi Bilimleri	6/489
Çocuk diş hekimliği	6/501
Çocuk Gelişimi	4/292

Çocuk psikiyatri	3/208
Çocukluk çağı aşıları	1/74
Davranış	4/280
Davranış sorunları	3/234,4/273
Demir eksikliği anemisi	1/57
Dental protez	6/501
Depresyon	3/395,4/280
DFS 70	5/348
Dil gelişimi	3/234
Dirençli epilepsi	1/46
Dismiyelinizan Hastalıklar	6/446
Doğum sonrası depresyon	5/375
Doğumsal metabolik hastalıklar	3/250
Doğuştan üre döngüsü bozuklukları	2/102
DRESS	5/424
Drug Induced Hypersensitivity Syndrome	5/424
Düşük immunglobulin	6/440
Ebeveyn-çocuk ilişkisi	6/467
Ebeveynler	5/388
Ebeveynler	6/489
Ebeveynlik stresi	3/234
Ekran maruziyeti	4/286
Ektodermal displazi	6/501
Elektrik Yanığı	5/402
Elektrolit Bozuklukları	2/86
Emzirme	4/264,5/428
Endikasyon	5/381
Endoskpi	5/413
Enfeksiyon	1/14
Epilepsi	1/46
Ergen	2/107,3/208
Erişkin	1/26
Eritema Multiforme	2/166
Eritrosit Transfüzyonu	3/188,5/381
Erken Çocukluk Gelişimi	4/292
Etiyoloji	1/14
Ev kazaları	6/434
Farkındalık	1/20,3/176, 5/388
Febril nötropeni	6/456
Fiziksel Aktivite	3/220
Folik asit	2/114
Fraksiyone üre ekskresyonu	2/92
Gastrointestinal hemoraji	4/305
Gebelik	5/428
Geçerlilik	5/355
Gelişimsel Pediatri	4/292
Göğüs ağrısı	4/328
Göz	4/268
Göz bulguları	6/506
Greft alımı	2/155
Güvenirlik	5/355
Hastalık Aktivitesi	5/370
Hastalık modifiye edici anti-romatizmal ilaçlar	3/215,5/406
Hastane yatışı	3/208
HAV aşısı	1/74
Hemoglobin	1/57
Hemşire	5/413
Hepatik yetmezlik	5/424
Herpes Simplex Virüs	2/166
Hışıltılı Çocuk	3/228
Hipertansiyon	1/20
Hiponatremi	5/419
Hipospadiyas	2/155
Hyperammonemia	2/102
İlaç alerjisi	5/424
İmmunglobulin A	6/440
İmmunglobulin G	6/440
İmmunglobulin M	6/440
İmmün trombositopenik purpura (İTP)	4/324
İnfant	4/305
İnfantil kolik	5/375
İnfantil panhipopituitarizm	1/68
İnfluenza	1/40
İnfluenza aşısı	1/74
İnguinal herni	6/462
İnsan Papilloma Virüsü	5/388
İskemi modifiye albümin	1/57
Jüvenil idiyopatik artrit	3/215,5/370, 5/406
Kaçıngan/kısıtlı yeme bozukluğu	5/355
Kalıtsal metabolik hastalıklar	6/506
Kanser	6/456
Kapilleroskopi	1/8
Karaciğer	5/364
Karantina	2/107
Kardiyak disritmi	5/428
Kas iskelet sistemi	6/484
Kırma Kusurları	4/264
Kistik fibrozis	5/364
Kitle İndeksi	4/258
KKK aşısı	1/74
Komplikasyon	5/381,6/462
Konjenital Sitomegalovirüs enfeksiyonu	3/176
Konsültasyon	4/268
Koronavirüs Hastalığı	4/258
Kraniyosinostoz	2/161
Kronik öksürük	1/63,3/228
Kulak	6/498
Laparoskopik	6/462
Leflunomid	3/215
Levetirasetam	4/320
Malondialdehit	2/97
Manyetik Rezonans	2/161
Membranöz glomerülonefrit	5/342
Migren	1/2
Minimal İnvaziv Cerrahi	2/148
Miyazis	6/498
Multisistem İnflamatuar Sendrom	4/258
Myomektomi	2/171
Nadir Hastalıklar	6/506
Native tiyol	4/310
Nefritik sendrom	5/342
Nefrotik sendrom	5/342
Nekrotizan Fasiit	1/71
NIAS	5/355
Non-sendromik	2/161,
Nörojen Mesane	3/253,3/395
Nüks	5/370
Obezite	3/220,4/299, 6/489
Oksidatif hasar	1/57
Okul Öncesi	4/264
Okul öncesi çocuklar	4/286
Okul öncesi tekrarlayan vizing	6/440
Omalizumab	2/118
Over boyut	4/299
Öz-düzenleme becerileri	4/286
Özel eğitim	6/467
Özel gereksinim	6/467
Patent duktus arteriozus	1/31,
Pediatri	1/8,1/46,5/370, 5/395
Pediatrik acil	4/268
Pediatrik Behçet hastalığı	6/484
Pediatrik kardiyoloji	4/328
Pelizaeus-Merzbacher Hastalığı	6/446
Perfüzyon Görüntüleme	2/161
Perkütan	6/462
Peteşi olmadan	4/324
Piyelonefrit	3/253
PLP1 Geni	6/446
Pnömoni	1/63

Potasyum	2/86
Prematüre	3/188,3/234
Prematüre bebek	1/31
pRIFLE	2/92
Prognoz	3/195,4/258
Proktokolit	4/305
Protein karbonil	2/97
Psikiyatri	3/395
Psikolojik Etki	2/107
Psikopatoloji	3/208
Puberte prekoks	4/299
Rabdomiyoliz	4/320
Raynaud Fenomeni	1/8
Rekürrens	6/462
Risk faktörleri	1/46
Robot Yardımlı Cerrahi	2/148
Romatoloji	1/8
Sefoperazon	6/456
Serebral Kan Akımı	2/161
Serebral palsi	1/46
Shear-wave elastografi	5/364
Sistemik lupus eritamatozus	3/195,5/336, 5/348
Sjögren sendromu	5/336
SLEDAİ-2K	3/195
Sodyum	2/86,5/419
Sosyal anksiyete	3/244
Subdural hematom	1/68
Sulbaktam	6/456
Suriyeli mülteciler	4/316
Tarama	3/176
Tedavi	2/114,3/208
Testis Torsiyonu	1/53
Tetanoz Aşısı	1/71
Tetikleyici	1/14
Tıp Eğitimi	4/292
Tıp Öğrencileri	4/292
Tiyol/Disülfit	1/2,1/57
Torakoskopik	6/452
Trombosit	4/258
Tükenmişlik	6/467
Uretra	2/155
Uterus boyut	4/299
Uterus leiomyomu	2/171
Uyku	2/127,4/286
Uzun süreli ağlama	5/375
Ülseratif kolit	4/310
Ürtiker	2/118
Üveit	5/370
VATS	6/452
Yabancı cisim	4/268
Yanık	3/244,5/402
Yaralanma	3/202
Yaş	5/370
Yatan hasta	3/208
Yenidoğan	2/102,5/381
Yenidoğan taraması	3/250
Yürüme	3/202
Yürüteç	3/202