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Overview

The Journal of Pediatric Academy is the official publication of the Kayseri Children Health Association. The Journal of Pediatric Academy is an international, peer-reviewed, open-access electronic and conventional published journal in the English language. The Journal of Pediatric Academy is publishing as 3 issues per year. Only for 2020, the Journal of Pediatric Academy will be published in July, September, December. After 2021 the Journal of Pediatric Academy will be published regularly as April, August, and December. The journal accepts original research articles, invited review articles, clinical reports, and case reports in all areas of pediatric research, which summarize recent developments about a particular subject based on standards of excellence and expertise.

Information About the Journal

J. Pediatr. Acad. (JPA) was established in 2020 as open access and peer-reviewed journal that accepts articles in English. J. Pediatr. Acad. (JPA) is published 3 times a year. Articles submitted should not have been previously published or be currently under consideration for publication any place else and should report original unpublished research results. The journal does not expect any fees for publication. All articles are available on the website of the journal with membership.

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Manuscript Preparation Guidelines

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Instructions for Authors

Scope

Journal of Pediatric Academy (JPA) reports on major advances in the diagnosis and treatment of diseases in children. Each issue presents informative original research articles, review articles, case reports, image corners, and letters to the editor from leading clinicians and investigators worldwide.

Ethical/Legal Considerations

A submitted manuscript must be an original contribution not previously published (except as an abstract or a preliminary report), must not be under consideration for publication elsewhere, and, if accepted, must not be published elsewhere in a similar form, in any language. Each person listed as an author is expected to have participated in the study to a significant extent. Although the editors and referees make every effort to ensure the validity of published manuscripts, the final responsibility rests with the authors, not with the Journal, its editors, or the publisher. All manuscripts must be submitted on-line through the journal's Web site at https://wwwjournalpediatricacademy.com/

Journal metrics:

External peer review of manuscripts is completed within 8-10 weeks of submission, and accepted papers are typically published within 8 months. The journal publishes editorial comments, original articles describing experimental and clinical research, reviews, case reports, image corner, letters to the editor. JPA is published in print and online and distributed free of charge.

JPA is publishing as 3 issues per year. Only for 2020, It will be published in July, September, December after 2021 the JPA will be published regularly as April, August, and December.

Each issue will include at least 4 original research articles, and approximately 4 other types such as editorial comment, invited review, case reports, image corner, and letters to the editor.

Patient Anonymity and Informed Consent

It is the author's responsibility to ensure that a patient's anonymity is carefully protected and to verify that any experimental investigation with human subjects reported in the manuscript was performed with informed consent and following all the guidelines for experimental investigation with human subjects required by the institution(s) with which all the authors are affiliated. The authors should mask patients' eyes and remove patients' names from figures. Photographs with bars placed over the eyes of patients can not be used in publication unless they obtain written consent from the patients and submit written consent with the manuscript.

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Conflicts of interest

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Authors: Please click the login button from the menu at the top of the page and log in to the system as an Author. Submit your manuscript according to the author's instructions. You will be able to track the progress of your manuscript through the system. If you experience difficulties using the system, please contact editorinchief@journalpediatricacademy.com. Requests for help and other questions will be addressed in the order received.

Preparation of Manuscript: Manuscripts that do not adhere to the following instructions will be returned to the corresponding author for technical revision before undergoing peer review.

Title Page: Include on the title page (a) complete manuscript title; (b) authors' full names, highest academic degrees, affiliations, and ORCID numbers; (c) name and address for correspondence, including fax number, telephone number, and e-mail address; (d) address for reprints if different from that of the corresponding author; and (e) all sources of support, including pharmaceutical and industry support, that require acknowledgment. The title page must also include disclosure of funding received for this work.

Highlights: Highlights are mandatory for original articles, invited review as they help increase the discoverability of your article via search engines. They consist of a short collection of bullet points that capture the novel results of your research as well as new methods that were used during the study (if any). Highlights should be submitted in a separate editable file in the online submission system. Please use 'Highlights' in the file name and include 3 to 5 bullet points (maximum 85 characters, including spaces, per bullet point).

Unstructured Abstract and Keywords: Limit of the abstracts are given in the table. It must be factual and comprehensive. Limit the use of abbreviations and acronyms, and avoid general statements (eg, "the significance of the results is discussed"). List three to five keywords or phrases.

Text: Organize the manuscript into four main headings: Introduction, Materials and Methods, Results, and Discussion. Define abbreviations at first mention in the text and each table and figure. If a brand name is cited, supply the manufacturer's name and address (city and state/country). All forms of support, including pharmaceutical industry support, must be acknowledged in the Acknowledgment section.

Abbreviations: For a list of standard abbreviations, consult the Council of Biology Editors Style Guide (available from the Council of Science Editors, 9650 Rockville Pike, Bethesda, MD 20814) or other standard sources. Write out the full term for each abbreviation at its first use unless it is a standard unit of measure.

Manuscript Types

JPA publishes the types of articles briefly described below.

Editorial Comment:

Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with a high reputation in the topic of the research article published in the journal. The authors are selected and invited by the journal to provide such comments. The text should contain 1500 words or fewer. it includes 5 figures and/or tables or fewer and 15 references or fewer.

Research Articles:

This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with an Introduction, Methods, Results, Discussion, Conclusion, and References subheadings. Please see Table 1 for limitations for Research Articles.

Statistical analysis is usually necessary to support conclusions. Statistical analyses must be conducted by 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 on 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.

Units should be prepared by the International System of Units (SI).

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

Invited Review:

Invited reviews prepared by authors who have extensive knowledge of a particular field and whose scientific background has been translated into a large volume of publications with a high citation potential are welcomed. Submissions from such authors may also be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies.

Case Reports:

Clinical observations may include case histories that demonstrate novel findings or associations, important clinical responses when a larger study is not needed to address a specific issue, or a unique laboratory observation linked to clinical care and/or practice. The text should contain 1500 words or fewer, with a brief abstract of 200 words or fewer. Abstracts outline background, observation(s), and conclusions. Include 5 figures and/or tables or fewer and 15 references or fewer.

Image Corner:

For educational purposes, the journal publishes original, interesting, and high-quality clinical images having a brief explanation (maximum 500 words excluding references but including figure legends) and of educational significance. The figure legend should contain no more than 100 words. It can be signed by no more than 5 authors and can have no more than 5 references and 3 figures or tables. Any information that might identify the patient or hospital, including the date, should be removed from the image. An abstract is not required with this type of manuscripts. The main text of clinical images should be structured with the following subheadings: Case, and References.

Letters To The Editor:

Letters to the editor should pertain to articles published within the Journal of Pediatric Academy or highlight important new clinical or laboratory insights. The text should contain 1000 words or fewer.

Table 1
Limitations for each manuscript type

Manuscript Type	Word Limit	Abstract Word Limit	Reference Limit	Table Limit	Figure Limit
Editorial comment	1500	No abstract	15	2	5
Original Article	3500	300	50	6	6
Invited Review	5000	350	100	6	10
Case Report	1500	200	15	2	5
Image corner	500	No abstract	5	-	3
Letter to the Editor	1000	No abstract	5	1	1

References:

The authors are responsible for the accuracy of the references. Key the references (double-spaced) at the end of the manuscript. Cite the references in the text in the order of appearance. Cite unpublished data—such as papers submitted but not yet accepted for publication and personal communications, including e-mail communications—in parentheses in the text. If there are more than three authors, name only the first three authors and then use et al. Refer to the List of Journals Indexed in Index Medicus for abbreviations of journal names, or access the list at http://www.nlm.nih.gov/tsd/serials/lji.html. Sample references are given below:

Journal Article:

1. Ang KK, Price RE, Stephens LC, et al. The tolerance of primate spinal cord to re-irradiation. *Int J Radiat Oncol Biol Phys*. 1993;25:459–464.

Journal Article published in non-English Languages:

2. Arıcı C, Oğuz V. [Surgical Treatment Options According to Inferior Oblique Hyperfunction in Superior Oblique Palsy]. *Turkiye Klinikleri J Med Sci* 2011;31:1160–1166

Book Chapter:

3. Dimery IW. Chemotherapy in head and neck cancer. In: Myerhoff WI, Rice DH, eds. Otolaryngology: head and neck surgery, 2nd ed. Philadelphia: WB Saunders, 1992:1027–1045.

Entire Book:

4. Virchow R. Cellular Pathology. Philadelphia: JB Lippincott, 1863.

Software:

5. Epi Info [computer program]. Version 6. Atlanta, GA: Centers for Disease Control and Prevention; 1994.

Online Journals:

6. Friedman SA. Preeclampsia: a review of the role of prostaglandins. Obstet Gynecol [serial online]. January 1988;71:22–37. Available from: BRS Information Technologies, McLean, VA. Accessed December 15, 1990.

Database:

7. CANCERNET-PDQ [database online]. Bethesda, MD: National Cancer Institute; 1996. Updated March 29, 1996.

World Wide Web:

8. Gostin LO. Drug use and HIV/AIDS [JAMA HIV/AIDS Web site]. June 1, 1996. Available at: http://www.ama-assn.org/special/hiv/ethics. Accessed June 26, 1997.

URL (Uniform Resource Locator)

9. (J. M. Kramer, K. Kramer [jmkramer@umich.edu], e-mail, March 6, 1996).

Figures and Tables

Figures and tables should be numbered using Arabic numerals. The same information should not appear in both a figure and a table. Each table and figure must be cited in the text and should be accompanied by a legend on a separate sheet.

Authors are responsible for all statements made in their work, and for obtaining permission from copyright owners to reprint or adapt a table or figure or to reprint quotations from one source exceeding the limits of fair use.

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All manuscripts are scanned with a plagiarism checker to deter and prevent plagiarism issues before submission. The similarity rate should be less than 20%.

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Manuscripts will be evaluated based on style as well as the content. Some minor copyediting may be done, but authors must take responsibility for clarity, conciseness, and felicity of expression. PDF proofs will be sent to the corresponding author. Changes of content or stylistic changes may only be made in exceptional cases in the proofs.

Prerequisites Requiring Special Attention

1. Discrimination based on age should be avoided.
2. High lights must be added to the manuscript.
3. Each table and figure must be cited in the text and should be accompanied by a legend on a separate sheet.
4. Each reference cited in the text should be listed in the References section.

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Contents

Journal of Pediatric Academy

Editorial Comment

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The Journal of Pediatric Academy is Launching

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Editorial Comment

Dear Colleagues,

Erciyes University Faculty of Medicine, Department of Pediatrics has been serving with great enthusiasm and success to protect Child Health and treat pediatric diseases in our country for half a century. We are proud to have raised a great number of pediatricians and sub-specialists serving as physicians, physician-scientists and academics all over our country and across the globe.

We proudly present our newly established journal, The Journal of Pediatric Academy (JPA). We would like to share our scientific experiences with the national and international medical experts through JPA. Our aim is to be a permanent publication indexed in National and International indexes without sacrificing the quality, ethical and scientific principles.

The Journal of Pediatric Academy aims to be publish novel articles in general pediatrics and pediatric subspecialties (Emergency Medicine, Allergy and Immunology, Endocrinology, Gastroenterology, Hepatology and Nutrition, Genetics, Cardiology, Hematology-Oncology, Infectious Diseases, Metabolism, Nephrology, Neurology, Rheumatology, Pulmonology, Social Pediatrics, Newborn, Critical Care Medicine, Ethics and Health Service Research), as well as relevant specialties such as Pediatric Surgery, Child and Adolescent Psychiatry, Pedodontics, Pediatric Nursing and Family Physicians.

We are aware that we started our publishing life during these difficult times due to COVID 19 pandemic. However, having a highly motivated and diligent team in the kitchen of the magazine helped us overcome these difficulties.

In our first issue, we come before you with articles of great importance and original topics and case reports in pediatrics field.

Dr. Çiçek & Kısaarslan[1] reviewed the clinical guidelines for rheumatic COVID-19 children in their review article.

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In this issue Kurtoğlu et al[2] reported the first study that show body mass index (BMI), fat mass (FM), fat free mass (FFM), and body fat % in Turkish children and adolescents. Their study sample has consisted of more than 4 000 children and adolescent. The result of this study can be regarded as a base the final product of the data of Determination of Anthropometric Measures of Turkish Children and Adolescents (DAMTCA II) study. Beside reference values, they also checked the age specific contribution of fat mass index (FMI), fat free mass index (FFMI) to BMI and fat % with Hattori chart. Both in screening and clinical practice use of FMI and FFMI together with BMI would significantly contribute to detection and follow-up of adiposity rebound, puberty precious, delayed puberty, overweight and obesity.

Dr. Yel et al[3] determined the etiological reasons and frequency of prenatal determined hydronephrosis and evaluated the renal functions in 48 patients.

Dr. Çıraklı et al[4] reported the clinical and electrophysiological features, treatment, and outcome of 15 children with hot water epilepsy.

Dr. Vatansever et al[5] reported their experience of 126 critically ill children with hyperglycemia in pediatric intensive care unit. The effect of thiamine pyrophosphate level on mortality and morbidity in patients with hyperglycemia at the time of application was evaluated.

In addition, two interesting case reports by Dr. Kara[6], Dr. Aydın[7] were also included in the first issue of the JPA.

We wish best of luck to JPA family and looking forward to the valuable contributions of our colleagues in the coming period.

References

1. Özdemir Çiçek S, Paç Kısaarslan A. Pediatric rheumatologists' perspective on corona virus disease 19 J Pediatr Acad 2020; 1(1): 3-7.
2. Kurtoğlu S, Mazıcıoğlu MM, Öztürk A, Hatipoğlu N, Çiçek B, Zararsız G. Fat and fat free mass index reference percentiles of healthy Turkish children and adolescent in Turkey. J Pediatr Acad 2020; 1(1): 8-15.
3. Yel S, Poyrazoğlu H. One-year follow-up results of patients with prenatally diagnosed hydronephrosis and evaluation of renal functions. J Pediatr Acad 2020; 1(1): 16-20.
4. Çıraklı S, Kaçar Bayram A, Akdemir A, Canpolat M, Kumandaş S, Gümüş H, Per H. Clinical and EEG features, treatment, and outcome of hot water epilepsy in pediatric patients. J Pediatr Acad 2020; 1(1): 21-24.
5. Vatansever Z, Özsoylu S, Kendirci M, Akyıldız B. The effect of thiaminepyrophosphate levels on mortality and morbidity ın patients with stress hyperglycemia. J Pediatr Acad 2020; 1(1): 25-29.
6. Kara B, Kartal A, Öztürk M, Köksal Y. Wernicke Encephalopathy Due to Prolonged Total Parenteral Nutrition in A Child with Signet Ring Cell Gastric Carcinoma. J Pediatr Acad 2020; 1(1): 30-33.
7. Aydın F, Altay D, Görükmez O, Hafo Kiraz A, Karaman F, Özcan A, Yılmaz E, Kurtsoy, A, Özkan KU, Deniz K, Per H, Karakukcu M, Ünal E, Patıroğlu T. Glioblastoma and Colorectal Adenocarcinoma in an Adolescent Girl with Constitutional Mismatch Repair Deficiency syndrome mimicking Neurofibromatosis Type-I. J Pediatr Acad 2020; 1(1): 34-38.

Journal of Pediatric Academy

Invited Review

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Pediatric Rheumatologists' Perspective on Corona Virus Disease 2019

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Abstract

Corona Virus Disease 2019 (COVID-19) has become a pandemic affecting the entire the world. Rheumatologists may play an important role in the management of COVID-19 cases owing to their experiences on inflammation and macrophage activating syndrome (MAS), one of the most important complications of COVID-19. Here, we present the applicability of pediatric rheumatology treatment methods on COVID-19 therapy, and management of children with rheumatic diseases using immune suppressive treatments, in this pandemic season. COVID-19 causes severe acute respiratory distress syndrome (SARS) in about 20% of infected patients. The virus specifically recognizes the angiotensin converting enzyme 2 (ACE2) receptor by its spike protein. In patients whose immunomodulatory capacities are not strong enough, the virus can trigger a severe cytokine storm. The rheumatologist may play an important role to avoid this complication with a timely treatment. In COVID-19 patients, by detecting elevated serum ferritin levels, cytokine storm syndrome can be recognized early, and the necessary treatments can be initiated on time. Anti-rheumatic drugs, such as hydroxychloroquine, colchicine, interleukin-1 and interleukin-6 blockers, JAK inhibitors, TNF inhibitors are used in the treatment of COVID-19 at different stages of the disease. Another very important issue is the management of patients with rheumatic diseases in this pandemic season. The increased risk of infection is an important concern in patients with rheumatic disease who are receiving immunosuppressive drugs. Various rheumatism associations have recommended the continuation of anti-rheumatism treatments to control of chronic inflammatory status, based on the experience so far.

Keywords: Corona virus disease 2019, cytokine storm syndrome, inflammation, pediatric, rheumatology

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Introduction

Corona Virus Disease 2019 (COVID-19) presented with severe acute respiratory distress syndrome (ARDS) has rapidly spread all over the world. Data from China have indicated that about 20% of patients developed severe ARDS. Particularly, older adults with serious underlying health conditions are at higher risk than younger ones. A minority of patients have presented with respiratory failure, septic shock, and multi-organ dysfunction, resulting in a fatality of 4%.[1] Although children with COVID-19 presents with mild symptoms, patients with chronic diseases who on immunosuppressive medications are at higher risk.

Researches in COVID-19 pathogenesis and treatment options have led to a rapid rise of publications in the medical literature. In line this with, it has been realized that experiences in rheumatology are particularly applicable to COVID-19 complications such as cytokine storm, i.e macrophage activation syndrome, and inflammation associated treatments with hydroxychloroquine, anakinra, tocilizumab, and baricitinib. In this paper, we present a review of 31 manuscripts indexed in PubMed database until April 17 about COVID-19 in rheumatology patients.

Highlight

- Pediatric rheumatologists' experience in cytokine storm and associated treatments may help to guide inflammatory complications of COVID-19.
- We recommend that a notably elevated ferritin value should alert clinicians for cytokine storm syndrome in hospitalized patients with COVID-19.
- During the pandemic season for rheumatic disease, the most important issues are the control of chronic inflammatory status and continuity of rheumatologic treatment.

Pathogenesis of COVID 19

The first step of the COVID-19 pathogenesis is that the virus specifically recognizes the angiotensin converting enzyme 2 (ACE2) receptor by its spike protein.[2,3] In addition, the cellular serine protease TMPRSS2 for HCoV-19 spike protein priming is also essential for the host cell entry and spread.[3] The ACE2 receptor is widely distributed on the human cells surface, especially the alveolar type II cells (AT2) which highly express TMPRSS2[4,5] and capillary endothelium. More recently, enterocytes have been shown to express ACE2 and target of virus.[6] However, in the bone marrow, lymph nodes, thymus, and the spleen, immune cells, such as T and B lymphocytes, and macrophages are consistently negative for ACE2.[4] The findings suggest that immunological therapy may be used to treat the infected patients. If host has not enough immunomodulatory capacity to control viral infection, the virus can trigger a severe cytokine storm especially with IL-2, IL-6, IL-7, GSCF, IP10, MCP1, MIP1A, and TNFα in the lung. The cytokine storm can stimulate the mechanisms resulting in pulmonary edema, dysfunction of the air exchange, acute respiratory distress syndrome, acute cardiac injury and a secondary infection.[7] Therefore, avoiding the cytokine storm may be the key for the treatment of COVID-19 patients.[1,8]

The Rheumatologist's Role in COVID-19

Rheumatologists are familiar with the treatment of cytokine storm syndrome (CSS)/ macrophage activation syndrome (MAS) in patients with Still's disease, systemic juvenile idiopathic arthritis, autoinflammatory diseases, systemic lupus erythematosus, juvenile dermatomyositis, and Kawasaki disease. Therefore, they can support the screening, diagnosis, and the treatment of CSS among COVID-19 patients. A set of diagnostic criteria is not available for the diagnosis of CSS in the COVID-19 currently. The CSS criteria used in hematologic and rheumatologic diseases can certainly be a guide to clinicians for the diagnosis of COVID-19.[9-12] These criteria were compared in **Table 1**. The serum ferritin measurement, which is a simple, cheap, readily available, and fast screening method, should be performed every hospitalized COVID-19 patient.[13] A notably elevated ferritin value (e.g. >700 ng/

Table 1.
Comparison of cytokine storm syndrome criteria in previously reported with COVID-19 patients

	HLH-04 criteria (9)	HScore (10)	MAS criteria in SJIA (11)	Covid-19 (13)
Fever	Yes	Yes	Yes	Yes
Splenomegaly	Yes	Yes		Unknown
Hepatomegaly		Yes		Unknown
Anemia	Yes	Yes		Yes
Thrombocytopenia	Yes	Yes	Yes	Yes
Neutropenia	Yes	Yes		Yes
Hypertriglyceridemia	Yes	Yes	Yes	Unknown
Hypofibrinogenemia	Yes	Yes	Yes	Yes
High AST		Yes	Yes	Yes
Hemophagocytosis	Yes	Yes		Unknown
Low NK cell activity	Yes			Unknown
Hyperferritinemia	Yes	Yes	Yes	Yes
Elevated soluble CD25	Yes	Yes		Yes
		Elevated serum GGT		High ALT
		Underlying immunosuppression		

HLH: Hemophagocytic lymphohistiocytosis, GGT: glutamic oxaloacetic transaminase, ALT: Alanin aminotransferase, AST: Aspartat aminotransferase

mL) should alert clinicians to additional diagnostic work-up so that therapeutic approaches can be considered without significant delay.[13]

Anti-rheumatic Agents in Treatment of COVID-19

Non-steroid anti-inflammatory drugs

Since the commonly used ibuprofen is believed to increase the expression of ACE2, using ibuprofen should be avoided during this pandemic if possible.[14-16]

Corticosteroids

In SARS and MERS cases, no association between use of corticosteroids and improved survival in patients was found. On the other hand, it was shown that the viral clearance from respiratory tract and blood was delayed by corticosteroids.[17] Therefore, corticosteroids are not recommended for patients with COVID-19.[18]

Hydroxychloroquine sulfate and chloroquine phosphate

Two antimalarial drugs act by blocking viral entry by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. Additional immunomodulatory effects were found through inhibition of cytokine production, autophagy, and lysosomal activity in host cells.[18,19] Two trials one from China, another from France report some benefit to the COVID-19 patients, although both studies have been scrutinized with regard to methodology.[20,21] Other reports do not support efficacy of hydroxychloroquine.[22,23] More trials with larger cohorts under way and will be more informative. Nevertheless, the current protocols for COVID-19 treatment in Turkey or elsewhere include hydroxychloroquine.

Colchicine

Colchicine is used routinely in Familial Mediterranean Fever (FMF). It could inhibit both neutrophil recruitment to the sites of inflammation and the secretion of IL-1β. Trials using colchicine in COVID-19 cases were reported by Italian Medicines Agency (AIFA) (ClinicalTrials.gov identifiers: NCT04326790, NCT04328480, NCT04322565, NCT04322682).[24,25] As a result of these studies, treatment with colchicine of patients affected by COVID-19 may prove to be a viable path.

Anakinra

Anakinra, a blocker of IL-1β plays a central role in the pathogenesis of CSS and it has been recommended for the treatment of CSS.[24,25] In this treatment, the window of opportunity is the key point to the success of the treatments (**Figure 1**).

Tocilizumab

The high plasma IL-6 levels were reported in severe COVID-19 cases.[26,27] Tocilizumab was recommended as the first choice of treatment for CSS in the window of opportunity[25] (**Figure 1**).

JAK blockers

The SARS-CoV-2 enters targeted cells through receptor-mediated endocytosis. Some of the identified regulators of clathrin-mediated endocytosis are members of the numb-associated kinase (NAK) family, such as AP2-associated protein kinase 1 (AAK1) and cyclin G-associated kinase (GAK).[28] Inhibition of AAK1 may stop the access of the virus into lung cells and also the intracellular assembly of virus particles.[29] Among the JAK blockers, only baricitinib effectively inhibits AAK1 and GAK. Baricitinib is also able to dampen CSS by reducing IL-6 and IFN-γ levels.[30]

TNF inhibitors

The viral spike protein is able to induce a TNF-α-converting enzyme (TACE)-dependent shedding of the ACE2 ectodomain which is crucial for the penetration of the virus into the cell.[31] Since this process seems to be strictly coupled to TNF-α production, it has been postulated that the use of TNF inhibitors may be effective in reducing both COVID-19 infection and the consequent organ damage.[32]

There is no consensus on how to treat COVID-19 patients. Turkish Ministry of Health and the Scientific Board's suggestions and guidelines which are constantly updated can help to manage the disease for clinicians.[33]

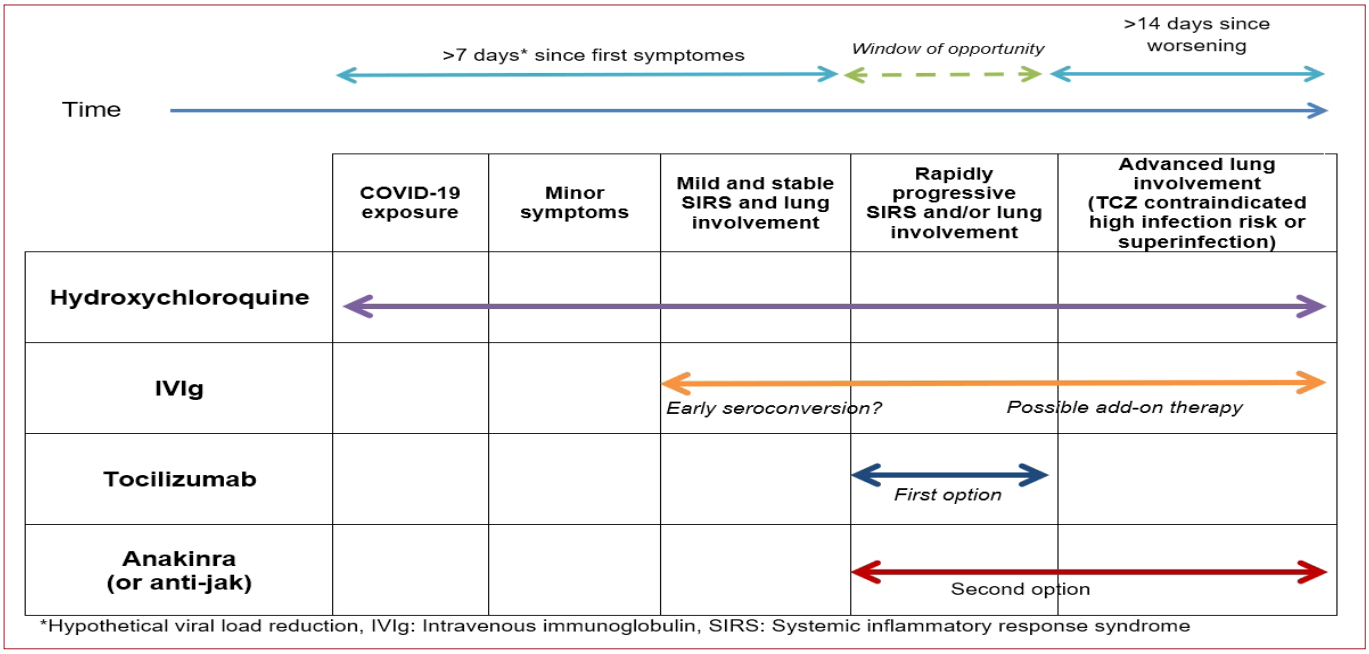

Figure 1. Hypothetical timing of some anti-rheumatic drugs in COVID-19 infection. This figure is adapted from the reference 25.

Management of Patients with Rheumatic Diseases in COVID-19 Season

The rapid and uncontrolled spread of the epidemic creates concerns for rheumatic patients, which are inherently characterized by being under increased risk of infection due to the rheumatic disease itself and to the iatrogenic effect of immunosuppressive agents such as corticosteroids and synthetic or biological disease-modifying drugs they are on.[30]

Risk factors for severe COVID-19 infections are older age, smoking, and underlying chronic diseases such as hypertension, diabetes mellitus, cardiovascular diseases and rheumatic diseases.[16] The American College of Rheumatology (ACR)[34], the European League Against Rheumatism (EULAR)[35] and the Italian Society of Rheumatology (SIR)[36] advise not to discontinue or reduce immunosuppressive therapy in patients with rheumatic diseases. The recommendations from several rheumatology societies were summarized in **Table 2**. According to the experience of COVID-19 so far, the most important point about prevention of the disease is the control of chronic inflammatory status and continuity of anti-rheumatic treatment.[16,25,30,37,38]

Table 2.
Summary of recommendations from rheumatology societies for patients with rheumatic diseases during COVID-19 outbreak[34-37]

1. Practicing sneeze/cough hygiene, regular hand washing, avoiding touching the face, keeping away from crowded places, social distancing, avoiding busy public transport and cancelling unnecessary travel is recommended.
2. Use of a mask is recommended for those with suspected and confirmed infection. In such instances, N95 respirators with appropriate fit to the face are advisable.
3. Abrupt discontinuation of glucocorticoid therapy should be avoided, even during active infection. Do not discontinue immunosuppressive treatment.
4. If patients are on disease-modifying anti-rheumatic drugs, including biologics, small molecules, and other immunosuppressive agents, standard practices may be followed to discontinue them should one develop infection.
5. Routine face-to-face appointments should be delayed until the outbreak settles. Both patients and healthcare personnel should consider substituting face-to-face appointments with video appointments if feasible.
6. Patients should be updated about appropriate flu and pneumococcal vaccination practices.

Conclusion

Anti-rheumatic drugs may be useful during the coronavirus COVID-19 pandemic to control viral infection or inflammation associated with rheumatic disease.

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References

1. Zhang W, Zhao Y, Zhang F, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives of clinical immunologists from China. *Clin Immunol.* 2020; 214: 108393. *[CrossRef]*
2. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, et al. Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19. *N Engl J Med.* 2020; 382: 1653-1659. *[CrossRef]*
3. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell.* 2020; 181: 271-280.e8. *[CrossRef]*
4. Hamming I, Timens W, Bulthuis ML, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol.* 2004; 203: 631-637. *[CrossRef]*
5. Iwata-Yoshikawa N, Okamura T, Shimizu Y, et al. TMPRSS2 contributes to virus spread and immunopathology in the airways of murine models after coronavirus infection. *J Virol.* 2019; 93: e01815-18. *[CrossRef]*
6. Lamers MM, Beumer J, van der Vaart J, et al. SARS-CoV-2 productively infects human gut enterocytes. *Science.* 2020; 369; 50-54. *[CrossRef]*
7. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: A clinical-therapeutic staging proposal. *J Heart Lung Transplant.* 2020; 39: 405-407. *[CrossRef]*
8. Leng Z, Zhu R, Hou W, et al. Transplantation of ACE2 mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. *Aging Dis.* 2020; 11: 216-228. *[CrossRef]*
9. Henter JI, Horne A, Aricó M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer.* 2007; 48: 124-131. *[CrossRef]*
10. Fardet L, Galicier L, Lambotte O, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheumatol.* 2014; 66: 2613-2620. *[CrossRef]*
11. Ravelli A, Minoia F, Davì S, et al. 2016 Classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/ American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. *Ann Rheum Dis.* 2016; 75: 481-489. *[CrossRef]*
12. Eloseily EMA, Minoia F, Crayne CB, et al. Ferritin to erythrocyte sedimentation rate ratio: simple measure to identify macrophage activation syndrome in systemic juvenile idiopathic arthritis. *ACR Open Rheumatol.* 2019; 1: 345-349. *[CrossRef]*
13. Cron RQ, Chatham WW. The Rheumatologist's Role in COVID-19. *J Rheumatol.* 2020; 47: 639-642. *[CrossRef]*
14. Day M. Covid-19: European drugs agency to review safety of ibuprofen. *BMJ.* 2020; 368: m1168. *[CrossRef]*
15. Day M. Covid-19: ibuprofen should not be used for managing symptoms, say doctors and scientists. *BMJ.* 2020; 368: m1086. *[CrossRef]*
16. Misra DP, Agarwal V, Gasparyan AY, et al. Rheumatologists' perspective on coronavirus disease 19 (COVID-19) and potential therapeutic targets. *Clin Rheumatol.* 2020; 1-8. *[CrossRef]*
17. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome. *Am J Respir Crit Care Med.* 2018; 197: 757-767. *[CrossRef]*
18. Sanders JM, Monogue ML, Jodlowski TZ, et al. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review *JAMA.* 2020; 323: 1824-1836. *[CrossRef]*
19. Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. *Nat Rev Rheumatol.* 2020; 16: 155-166. *[CrossRef]*
20. Gautret P, Lagier JC, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study. *Travel Med Infect Dis.* 2020; 34: 101663. *[CrossRef]*
21. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. *BMJ.* 2020; 369: m1849. *[CrossRef]*

22. Molina JM, Delaugerre C, Le Goff J, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. *Med Mal Infect.* 2020; 50: 384. *[CrossRef]*
23. Mahévas M, Tran VT, Roumier M, et al. Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data. *BMJ.* 2020; 369: m1844. *[CrossRef]*
24. Barnes BJ, Adrover JM, Baxter-Stoltzfus A, et al. Targeting potential drivers of COVID-19: Neutrophil extracellular traps. *J Exp Med.* 2020; 217: e20200652. *[CrossRef]*
25. Ferro F, Elefante E, Baldini C, et al. COVID-19: the new challenge for rheumatologists. *Clin Exp Rheumatol.* 2020; 38: 175-180. *[CrossRef]*
26. Sarzi-Puttini P, Giorgi V, Sirotti S, et al. COVID-19, cytokines and immunosuppression: what can we learn from severe acute respiratory syndrome? *Clin Exp Rheumatol.* 2020; 38: 337-342. *[CrossRef]*
27. Chen X, Zhao B, Qu Y, et al. Detectable serum SARS-CoV-2 viral load (RNAaemia) is closely correlated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients [published online ahead of print, 2020 Apr 17]. *Clin Infect Dis.* 2020; ciaa449. *[CrossRef]*
28. Sorrell FJ, Szklarz M, Abdul Azeez KR, et al. Family-wide Structural Analysis of Human Numb-Associated Protein Kinases. *Structure*. 2016; 24: 401-411. *[CrossRef]*
29. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet.* 2020; 395: 565-574. *[CrossRef]*
30. Favalli EG, Ingegnoli F, De Lucia O, et al. COVID-19 infection and rheumatoid arthritis: Faraway, so close!. *Autoimmun Rev.* 2020; 19: 102523. *[CrossRef]*
31. Haga S, Yamamoto N, Nakai-Murakami C, et al. Modulation of TNF-alpha-converting enzyme by the spike protein of SARS-CoV and ACE2 induces TNF-alpha production and facilitates viral entry. *Proc Natl Acad Sci USA.* 2008; 105: 7809-7814. *[CrossRef]*
32. Wang W, Ye L, Ye L, et al. Up-regulation of IL-6 and TNF-alpha induced by SARS-coronavirus spike protein in murine macrophages via NF-kappaB pathway. *Virus Res.* 2007; 128: 1-8. *[CrossRef]*
33. Kilic AU, Kara F, Alp E, et al. New threat: 2019 novel Coronavirus infection and infection control perspective in Turkey. *North Clin Istanb.* 2020; 7: 95-98. *[CrossRef]*
34. ACR Announcement: Coronavirus Disease (COVID-19). Available from: https://www.rheumatology.org/announcements
35. EULAR: EULAR Guidance for patients COVID-19 outbreak. Available from: https://www.eular.org/eularguidanceforpatientscovid19outbreak.cfm
36. Pandemia da COVID-19: la SIR rispondeadalcunedomandedeipazienti. *SocietàItaliana di Reumatologia.* Available from: https://www.reumatologia.it/cmsx.asp?IDPg=1087
37. Ceribelli A, Motta F, De Santis M, et al. Recommendations for coronavirus infection in rheumatic diseases treated with biologic therapy. *J Autoimmun.* 2020; 109: 102442. *[CrossRef]*
38. Haşlak F, Yıldız M, Adrovic A, et al. Childhood Rheumatic Diseases and COVID-19 Pandemic: An Intriguing Linkage and a New Horizon. *Balkan Med J.* 2020; 37: 184-188. *[CrossRef]*

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Fat and Fat Free Mass Index Reference Percentiles of Healthy Turkish Children and Adolescent in Turkey

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Abstract

In addition to body mass index (BMI), fat mass (FM), fat-free mass (FFM), and their index may be used to predict metabolic health risks. The aim of this study is to define age- and gender-specific FM, fat mass index (FMI), FFM and fat-free mass index (FFMI) percentiles for heatly Turkish children and adolescents. A total of 4028 (2252 girls, 1776 boys) participant aged 6–17 years were recruited. The body composition was evaluated by bioelectrical impedans. FM, FMI, FFM and FFMI percentiles were produced. FM, FFM, FMI and FFMI percentiles were calculated. FMI and FM were female predominance through 6 to 17 years. The differences in 3rd-97th percentiles of FFMI were 4.06–7.20 kg/m^2 respectively for males, where this difference was 4.06-6.95 kg/m^2 for females. We checked the age-specific contribution of FMI, FFMI to BMI and fat% with Hattori chart and found that children with similar BMI may lie in different fat%. Since FM and FFM are important for the evaluation of body composition, in addition to BMI and body fat%, FM and FFM percentiles are required as local reference. Therefore, this study provides normative data for body FM, FMI, FFM and FFI percentiles.

Keywords: Fat mass, fat mass index, fat-free mass, fat-free mass index, children, adolescents

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Introduction

In addition to secular change in growth, change in body composition should also be considered as an indicator of endocrine and cardiometabolic parameter which needs serious concern.[1] Since the onset of obesity has shifted to an early age, the complication of overweight and obesity in adults can also be observed in childhood.[1-5]

Early onset overweight and obesity in childhood is not only an endocrine and cardiometabolic disorder which are precursors of cardiovascular disease, hypertension, insulin resistance, diabetes mellitus, dyslipidemia, polycystic ovary syndrome, hyperandrogenism, neoplasm but also a serious cause of adult overweight and obesity burden. Other than endocrine and cardiometabolic problems social and emotional impairment extending to adulthood may even be a cause of non physical disorders.[6-8]

Highlight

- Although BMI is the most frequently used parameter in diagnosis, in certain circumstances BMI may not distinguish FFM from the FM that is significantly associated with obesity-related complications.
- The use of BIA may help in distinguishing between both the fat mass and lean body mass that constitutes the body composition.
- Both in screening and clinical practice use of FMI and FFMI together with BMI would significantly contribute to detect and follow-up of adiposity rebound, puberty precious, delayed puberty, overweight and obesity.

The primary assesment tools for nutritional status can be listed as height, weight, mid uppper arm circumference, and skinfold thickness.[9] To diagnose the obesity-and overweight-related problems, body mass index (BMI) is still the fundamental method but not the competent measure, since BMI does not solely is a measure of body composition which discriminates fat and fat-free mass content.[10] Then, we need non-complicated and useful measures to detect the main risk factors for endocrine and cardiometabolic risk such as fat mass or fat mass distribution. Since both fat mass (FM) and fat-free mass (FFM) constitutes BMI the interchanging ratio of fat mass and fat-free mass as an indicator of health risk that BMI does not discriminate.[11,12] Failure of discriminating fat and lean mass for BMI lead to research of other methods like bioelectrical Impedance Analysis (BIA) and Dual-energy X-ray absorptiometry (DEXA).[13]

DEXA provides a precise assessment of FM (fat mass), FFM (fat free mass) and bone mineral density which are the three main body components. However, DEXA uses an X-ray source, which is not preferable for children and it is expensive and required specialized equipment. Thus it is not feasible for routine clinical practice (14). On the other hand, BIA method can also give valuable information about body composition.[15]

Although relatively small differences may exist between BIA and DEXA, these differences may be neglected since BIA is a practical, non-invasive and cheap method versus DEXA.[9,16]

The primary aim of this study is to produce the FM and FFM percentiles and fat mass and fat- free mass indexes (FMI, FFMI) in a quite competent sample in Turkish children and adolescents for the first time. This would provide the opportunity of both to detect fat and fat- free mass and also its variation for height. Calculated percentiles then may be used in evaluation of body composition for thinness, overweight and obesity resulted by body fat or muscle mass content and distribution.

Materials and Methods

The Ethical Committee of Erciyes University, Faculty of Medicine, approved this study (Approval date: 03.04.2019/304, number: 04-01/168).

This is the most recent (2007-2008) and the comprehensive cross-sectional study which uses the data of Determination of Anthropometric Measures of Turkish Children and Adolescents (DAMTCA II).[17] The study sample consists of 1776 male and 2252 female 6-17 years old children and adolescents.

In 6-17 years old children and adolescents age and gender specific FM, FMI, FFM and FFMI percentiles are produced by LMSP method (17). The device Tanita BC-418MA (Tanita Corporation, Tokyo, Japan) was used to calculate fat mass (FM), fat-free mass (FFM) fat. The mass index (FMI; FM/height^2), fat-free mass index (FFMI: FFM/Height^2) were then calculated.[16]

Age-related FFM, FFMI, FM and FMI z-score plots were examined and the discontinuities were checked. Further, liberal cut-off values, where the z-scores of data values outside[6,11], were used to detect outliers.[18] After outlier detection, remaining 4.028 observations (1.776 boys, 2.252 girls) were randomly split into training (70%) and validation (30%) sets. Training set was used for model building and validation set was used for model validation and model selection. GAMLSS models were used to fit the models.[19] For each anthropometric measure and each gender, three methods including LMS, LMST and LMSP methods were applied to data. Box-Cox normal (BCN), Box-Cox t (BCT) and Box-Cox power exponential (BCPE) distributions were used in GAMLSS models, respectively. Maximum penalized likelihood method was used, RS algorithm and Fisher scoring procedure was applied to estimate distribution parameters. As smoothing functions, cubic splines were used. Each gender was modeled separately. Analyses were conducted using GAMLSS package (version 4.3-1) of R 3.1.1 software (www.r-project.org).

Parameter Optimization

In order to apply LMSP method, we followed the three step optimization procedure of Rigby and Stasinopoulos[20] and generalized Akaike's information criteria with parameter #3 for model selection. Firstly, identity link functions were defined for μ and ν, log-link functions were defined for σ and τ. An initial age transformation was optimized

as x=ageλ after a grid search of λ between -2 to 2 in steps of 0.25. Next, initial degrees of freedom of all four parameters was set to 1 and df(μ), λ and df(σ) values were optimized respectively. For df(μ) and df(σ) we made a search between 1 to 20 in steps of 1 and for λ between -2 to 2 in steps of 0.05. After optimizing these three parameters, optimal df(ν) and df(τ) were searched ranging between 0 to 9 in steps of 1, respectively. In last step of procedure, fine tuning was used for the model with optimum parameters with changing values of df(σ), df(μ), df(ν), df(τ) and λ. Same procedure was followed for LMST and LMS methods, considering the absence of τ parameter in BCCG distribution of LMS method. Results from the **Table 1** demonstrates the best fit models for age-related FFM, FFMI, FM and FMI data for both boys and girls. The contribution of fat and fat free mass (FMI, FFMI) to BMI and fat% is shown in Hattori chart (**Figure 1**).[21]

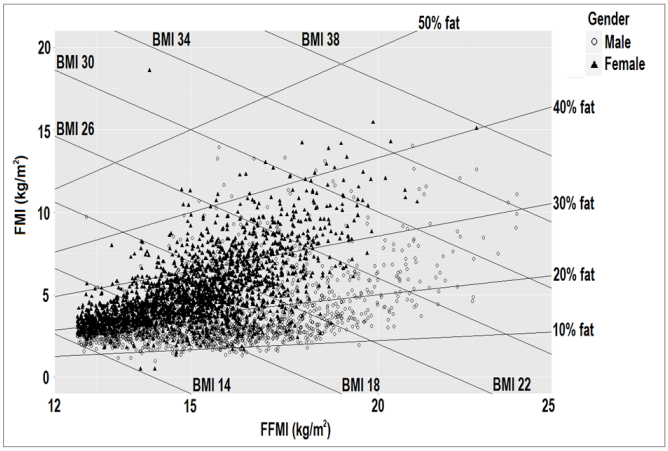

Figure 1. The contribution of fat and fat free mass (FMI, FFMI) to BMI and fat% inHattori chart. Lines in this chart represents BMI and Fat%. This configuration shows gender specific configuration of fat distribution in a certain BMI range. Empty dots represents males and filled triangels represents females.

Results

The LMSP method parameters used to produce FM, FFM, FMI and FFMI. Our initial observation for FMI and FM was female predominance through 6 to 17 years in which the predominance significantly increases after 9 years (**Table 1**). The gender differences in 6 years were 0.16 kg but in 17 years gender difference became 2.05 kg. Although FM increased gradually from 6 to 17 years in male gender, there was a peak of FM in 14 years of female which then relatively decreases (**Table 1**).

The differences in 3rd-97th percentiles of FM were 4.38 kg-19.65 kg respectively, for 6 and 17 years old males where this difference was 5.57-19.65 kg at 6-17 years old females (**Table 2**). The increase in FM through 6-17 years old was 2.54 kg and 2.94 kg for 3rd percentile and 17.81 and 17.02 for 97th percentiles respectively for males and females. The 50th percentile increases for 50th percentile through 6-17 years were 5.85 and 8.57 respectively for males and females (**Table 2**).

The differences in 3rd-97th percentiles of FMI were 3.15-6.44 kg/m² respectively for 6 and 17 years old male where this difference was 3.38-7.59 kg/m² at 6-17 years old females (**Table 3**). The increase in FMI through 6-17 years old was -0.49 kg/m² and 0.8 kg/m² for 3rd percentile and 2.8 kg/m² and 4.29 kg/m² for 97th percentile respectively for males and females. The 50th percentile increases for 50th percentile through 6-17 years were 0.17 and 2.84 kg/m² respectively, for males and females (**Table 3**). In **Table 4**, we found that the mean FFM was slightly higher than females, but significantly higher after 13 years.

The differences in 3rd-97th percentiles of FFM were 8.16 kg–27.06 kg respectively, for 6 and 17 years old males where this difference was 7.95-13.31 kg at 6-17 years old females (**Table 5**). The increase in FFM through 6-17 years old was 30.05 kg and 23.63 kg for 3rd percentile and 48.95 and 28.99 for 97th percentile respectively, for males and females. The 50th percentile increases for 50th percentile through 6-17 years were 34.77 and 25.83 respectively for males and females (**Table 5**).

The difference in 3rd-97th percentiles of FFMI were 4.06 kg/m² – 7.20 kg/m² respectively for 6 and 17 years old males, where this difference was 4.06-6.95 kg/m² at 6-17 years old females (**Table 6**). The increase in FFMI through 6-17 years old was 4.06 kg/m² and 4.06 kg/m² for 3rd percentile and 7.20 kg/m² and 6.95 kg/m² for 97th percentiles respectively, for males and females. The 50th percentile increases for 50th percentile through 6-17 years were 5.25 kg/m² and 4.67 kg/m² respectively, for males and females (**Table 6**).

Table 1
Descriptives of fat mass fat mass index and (kg) of Turkish children and adolescents 6-17 years old

Age (years)	Boys			Girls		
	n	Fat mass index Mean (SD)	Fat Mass Mean (SD)	n	Fat mass index Mean (SD)	Fat Mass Mean (SD)
6	119	3.26 (1.10)*	4.63 (1.68)	129	3.52 (0.97)	4.79 (1.44)
7	148	3.53 (1.30)	5.42 (2.12)	161	3.82 (1.36)	5.84 (2.15)
8	160	3.71 (1.56)	6.32 (2.83)	165	3.89 (1.48)	6.52 (2.85)
9	141	4.06 (2.13)	7.49 (4.11)	144	4.20 (1.61)	7.56 (3.15)
10	163	3.87 (1.83)*	7.71 (3.97)*	177	4.70 (1.92)	9.57 (4.27)
11	141	3.83 (1.92)*	8.08 (4.40)*	115	4.78 (1.90)	10.48 (4.57)
12	116	3.98 (2.18)*	9.09 (5.23)*	156	4.87 (1.69)	11.53 (4.32)
13	133	3.72 (1.90)*	9.31 (4.72)*	159	5.55 (2.39)	13.46 (5.66)
14	147	3.56 (2.04)*	9.92 (5.91)*	147	6.05 (2.17)	15.58 (6.03)
15	217	3.53 (1.73)*	10.48 (5.20)*	378	5.35 (2.04)	13.85 (5.42)
16	212	3.79 (2.05)*	11.47 (6.11)*	413	5.56 (2.27)	14.41 (5.98)
17	84	3.74 (1.72)*	11.44 (5.29)*	133	5.26 (1.96)	13.49 (4.96)

Age indicates whole age group (e.g. 7.00-7.99 years, etc.),*; p<0.05, SD; Standard Deviation

Table 2
Fat mass percentiles of Turkish children and adolescents

Age (years)	Percentiles										
	3rd	5th	10th	15th	25th	50th	75th	85th	90th	95th	97th
Boys											
6	2.64	2.75	2.93	3.07	3.30	3.82	4.54	5.07	5.51	6.33	7.02
7	2.95	3.09	3.33	3.51	3.82	4.59	5.71	6.53	7.20	8.46	9.51
8	3.16	3.32	3.60	3.83	4.22	5.27	6.86	8.01	8.97	10.72	12.17
9	3.30	3.48	3.81	4.08	4.56	5.87	7.93	9.43	10.65	12.88	14.70
10	3.44	3.65	4.02	4.32	4.88	6.42	8.88	10.64	12.08	14.66	16.72
11	3.62	3.84	4.26	4.60	5.21	6.94	9.68	11.64	13.22	16.03	18.25
12	3.83	4.08	4.53	4.90	5.57	7.43	10.38	12.48	14.16	17.16	19.52
13	4.09	4.36	4.84	5.24	5.95	7.92	11.00	13.20	14.96	18.10	20.58
14	4.37	4.66	5.18	5.59	6.34	8.38	11.56	13.83	15.66	18.93	21.52
15	4.66	4.96	5.51	5.95	6.73	8.83	12.09	14.43	16.34	19.78	22.53
16	4.93	5.25	5.82	6.28	7.10	9.26	12.61	15.04	17.04	20.70	23.67
17	5.18	5.52	6.12	6.60	7.45	9.67	13.10	15.63	17.74	21.63	24.83
Girls											
6	3.05	3.17	3.39	3.56	3.84	4.53	5.51	6.21	6.77	7.79	8.62
7	3.08	3.21	3.45	3.63	3.94	4.75	5.93	6.74	7.40	8.58	9.51
8	3.57	3.73	4.02	4.25	4.65	5.72	7.32	8.42	9.29	10.81	12.01
9	3.72	3.90	4.22	4.48	4.95	6.22	8.14	9.45	10.46	12.22	13.56
10	4.25	4.48	4.88	5.21	5.80	7.44	9.91	11.55	12.81	14.94	16.53
11	4.93	5.21	5.73	6.15	6.90	8.97	12.04	14.04	15.54	18.03	19.84
12	5.34	5.69	6.30	6.80	7.69	10.06	13.45	15.62	17.22	19.84	21.70
13	5.88	6.30	7.05	7.65	8.70	11.41	15.15	17.49	19.21	21.98	23.94
14	6.54	7.06	7.98	8.70	9.95	13.06	17.21	19.78	21.66	24.67	26.79
15	6.53	7.11	8.13	8.91	10.25	13.46	17.62	20.18	22.05	25.03	27.12
16	6.26	6.88	7.95	8.77	10.13	13.31	17.31	19.77	21.57	24.43	26.42
17	5.99	6.64	7.76	8.60	9.98	13.10	16.93	19.29	21.00	23.74	25.64

Table 3
Fat mass index percentiles of Turkish children and adolescents

Age (years)	Percentiles										
	3rd	5th	10th	15th	25th	50th	75th	85th	90th	95th	97th
Boys											
6	2.12	2.20	2.33	2.43	2.60	2.98	3.52	3.90	4.21	4.79	5.27
7	2.09	2.18	2.34	2.46	2.65	3.12	3.80	4.30	4.72	5.52	6.21
8	2.04	2.14	2.31	2.45	2.67	3.21	4.00	4.61	5.12	6.11	6.98
9	1.97	2.08	2.26	2.41	2.65	3.25	4.13	4.80	5.37	6.49	7.45
10	1.90	2.01	2.21	2.36	2.62	3.25	4.19	4.91	5.51	6.68	7.69
11	1.84	1.95	2.16	2.31	2.58	3.24	4.22	4.96	5.59	6.79	7.81
12	1.78	1.90	2.11	2.27	2.55	3.22	4.23	4.99	5.63	6.85	7.88
13	1.74	1.86	2.07	2.24	2.52	3.20	4.23	5.00	5.65	6.88	7.92
14	1.70	1.83	2.04	2.20	2.49	3.19	4.23	5.01	5.67	6.91	7.95
15	1.67	1.80	2.01	2.18	2.47	3.17	4.23	5.02	5.69	6.94	7.99
16	1.65	1.77	1.99	2.16	2.45	3.16	4.23	5.03	5.70	6.97	8.03
17	1.63	1.75	1.97	2.14	2.43	3.15	4.23	5.04	5.72	7.01	8.07
Girls											
6	2.35	2.42	2.55	2.66	2.83	3.28	3.92	4.34	4.68	5.27	5.73
7	2.33	2.41	2.56	2.68	2.88	3.39	4.13	4.63	5.02	5.70	6.23
8	2.32	2.42	2.58	2.71	2.93	3.53	4.38	4.95	5.40	6.17	6.76
9	2.32	2.42	2.60	2.74	2.99	3.66	4.63	5.28	5.77	6.61	7.24
10	2.39	2.50	2.71	2.87	3.16	3.93	5.04	5.76	6.31	7.22	7.89
11	2.48	2.61	2.85	3.03	3.36	4.24	5.49	6.29	6.88	7.86	8.56
12	2.56	2.71	2.97	3.18	3.55	4.53	5.90	6.75	7.38	8.40	9.12
13	2.63	2.80	3.09	3.33	3.74	4.81	6.27	7.18	7.84	8.90	9.64
14	2.66	2.85	3.18	3.44	3.90	5.05	6.58	7.52	8.20	9.29	10.05
15	2.62	2.82	3.19	3.47	3.95	5.14	6.70	7.65	8.34	9.42	10.18
16	2.53	2.75	3.13	3.43	3.93	5.15	6.70	7.64	8.32	9.39	10.13
17	2.43	2.66	3.06	3.37	3.89	5.12	6.66	7.58	8.25	9.30	10.02

Table 4
FFM index and FFM (kg) of Turkish boys and girls

Age (years)	Boys			Girls		
	n	FFM index Mean (SD)	FFM Mean (SD)	n	FFM index Mean (SD)	FFM Mean (SD)
6	119	12.84 (1.09)*	18.20 (2.35)*	130	12.16 (1.01)	16.49 (2.24)
7	148	13.17 (1.13)*	20.18 (2.89)*	160	12.59 (1.23)	19.23 (2.65)
8	160	13.59 (1.29)*	22.99 (3.27)*	166	12.86 (1.2)	21.41 (3.29)
9	141	14.02 (1.32)*	25.72 (3.66)*	145	13.26 (1.23)	25.72 (3.66)
10	163	14.09 (1.42)	27.78 (4.40)	177	13.95 (1.55)	28.20 (4.99)
11	141	14.64 (1.56)*	30.62 (5.07)	115	14.22 (1.62)	30.95 (5.09)
12	118	15.22 (1.44)*	34.75 (5.52)	156	14.65 (1.65)	34.52 (5.32)
13	133	15.89 (1.66)*	39.89 (6.79)*	157	15.03 (1.78)	36.60 (4.89)
14	147	16.64 (1.86)*	46.46 (7.78)*	147	15.49 (1.68)	39.74 (5.49)
15	216	17.30 (1.83)*	51.56 (7.21)*	378	15.85 (1.34)	40.86 (3.79)
16	213	17.79 (1.99)*	54.06 (7.56)*	412	16.11 (1.26)	41.71 (3.56)
17	84	18.14 (1.72)*	55.59 (6.92)*	133	15.96 (1.26)	41.08 (3.82)

Age indicates whole age group (e.g. 7.00-7.99 years, etc.),*; p<0.05, SD; Standard Deviation

Table 5
Fat-free mass percentiles of Turkish children and adolescents

Age (years)	Percentiles										
	3rd	5th	10th	15th	25th	50th	75th	85th	90th	95th	97th
Boys											
6	13.43	13.82	14.44	14.87	15.53	16.79	18.21	19.10	19.76	20.83	21.59
7	15.06	15.49	16.19	16.68	17.43	18.94	20.65	21.69	22.45	23.68	24.55
8	16.90	17.38	18.17	18.73	19.60	21.41	23.48	24.71	25.61	27.03	28.01
9	18.72	19.25	20.13	20.76	21.77	23.91	26.40	27.85	28.89	30.51	31.63
10	20.47	21.05	22.02	22.73	23.87	26.39	29.32	31.01	32.21	34.05	35.31
11	22.19	22.82	23.89	24.68	25.98	28.88	32.29	34.23	35.60	37.69	39.10
12	24.45	25.17	26.37	27.27	28.75	32.10	36.04	38.27	39.83	42.21	43.81
13	27.60	28.44	29.84	30.89	32.60	36.45	40.96	43.51	45.28	47.99	49.81
14	31.94	32.94	34.59	35.81	37.78	42.11	47.13	49.98	51.97	55.02	57.08
15	36.86	38.00	39.88	41.24	43.40	48.01	53.29	56.33	58.47	61.78	64.03
16	40.72	41.93	43.91	45.33	47.54	52.13	57.33	60.39	62.56	65.97	68.31
17	43.48	44.71	46.71	48.12	50.30	54.71	59.68	62.65	64.80	68.19	70.54
Girls											
6	12.23	12.57	13.14	13.54	14.17	15.46	16.94	17.82	18.46	19.48	20.18
7	13.84	14.23	14.87	15.33	16.05	17.52	19.21	20.22	20.95	22.10	22.90
8	15.62	16.07	16.81	17.33	18.15	19.84	21.78	22.93	23.76	25.08	26.00
9	17.40	17.93	18.81	19.43	20.41	22.43	24.74	26.13	27.13	28.71	29.81
10	19.15	19.82	20.92	21.70	22.93	25.46	28.38	30.12	31.38	33.38	34.77
11	21.44	22.23	23.53	24.46	25.91	28.88	32.27	34.29	35.73	38.01	39.59
12	24.59	25.44	26.80	27.76	29.26	32.28	35.65	37.62	39.02	41.21	42.70
13	27.70	28.55	29.92	30.88	32.37	35.34	38.62	40.50	41.84	43.91	45.31
14	30.05	30.93	32.34	33.33	34.86	37.94	41.32	43.28	44.66	46.81	48.27
15	32.88	33.67	34.94	35.83	37.20	39.95	42.97	44.71	45.94	47.85	49.14
16	35.33	35.98	37.03	37.76	38.89	41.15	43.64	45.08	46.10	47.69	48.77
17	35.86	36.44	37.40	38.08	39.13	41.29	43.76	45.23	46.30	47.99	49.17

We checked the age-specific contribution of FMI, FFMI to BMI and fat% with Hattori chart (**Figure 1**). In interpretation of Hattori chart, we found that children with similar BMI may lie in different fat %.

Another finding was discrimination between males and females for fat % which was prominent in BMI higher than 26 kg/m². The 50th percentiles of FM, FMI, FFM and FFMI were compared in **Figure 2**. The prominent findings in **Figure 3** were the increase in FM from 9 years on and increase in FFM from 13 years on respectively, for females and males.

Discussion

The well-known determinant of body composition; the BMI is composed of both the body fat (FM) and fat-free mass (FFM). In this study, we produced both FM and FFM

Table 6
Fat-free mass index percentiles of Turkish children and adolescents

Age (years)	Percentiles										
	3rd	5th	10th	15th	25th	50th	75th	85th	90th	95th	97th
Boys											
6	11.02	11.18	11.44	11.63	11.92	12.55	13.29	13.75	14.10	14.67	15.08
7	11.27	11.44	11.72	11.91	12.23	12.89	13.68	14.17	14.53	15.13	15.56
8	11.52	11.70	12.00	12.21	12.54	13.24	14.08	14.59	14.98	15.60	16.05
9	11.75	11.94	12.26	12.48	12.84	13.58	14.46	15.00	15.41	16.06	16.53
10	11.97	12.18	12.51	12.75	13.13	13.92	14.85	15.42	15.84	16.52	17.00
11	12.24	12.46	12.81	13.07	13.47	14.31	15.28	15.88	16.32	17.02	17.52
12	12.60	12.83	13.21	13.49	13.91	14.80	15.83	16.46	16.92	17.65	18.17
13	13.07	13.32	13.72	14.02	14.47	15.41	16.50	17.16	17.65	18.42	18.96
14	13.60	13.87	14.30	14.60	15.08	16.08	17.24	17.93	18.44	19.26	19.84
15	14.13	14.40	14.85	15.17	15.68	16.73	17.94	18.68	19.22	20.09	20.70
16	14.60	14.89	15.35	15.68	16.21	17.30	18.57	19.35	19.92	20.84	21.50
17	15.05	15.35	15.83	16.17	16.71	17.84	19.17	19.98	20.59	21.56	22.25
Girls											
6	11.14	11.30	11.56	11.75	12.05	12.68	13.42	13.88	14.23	14.79	15.20
7	11.34	11.51	11.79	11.99	12.30	12.96	13.74	14.23	14.59	15.18	15.60
8	11.56	11.74	12.03	12.24	12.58	13.28	14.11	14.62	15.00	15.62	16.07
9	11.74	11.93	12.24	12.47	12.82	13.57	14.45	14.99	15.39	16.05	16.51
10	11.91	12.11	12.45	12.69	13.06	13.85	14.78	15.35	15.77	16.46	16.95
11	12.10	12.32	12.68	12.93	13.33	14.17	15.16	15.76	16.20	16.92	17.42
12	12.46	12.69	13.07	13.34	13.77	14.65	15.69	16.32	16.78	17.52	18.04
13	12.99	13.24	13.64	13.93	14.38	15.32	16.40	17.06	17.54	18.31	18.85
14	13.61	13.87	14.30	14.61	15.09	16.08	17.23	17.92	18.43	19.24	19.81
15	14.19	14.47	14.92	15.24	15.74	16.79	18.01	18.75	19.29	20.16	20.77
16	14.64	14.92	15.39	15.73	16.25	17.35	18.64	19.42	20.00	20.93	21.59
17	15.14	15.44	15.91	16.26	16.80	17.93	19.26	20.07	20.67	21.64	22.33

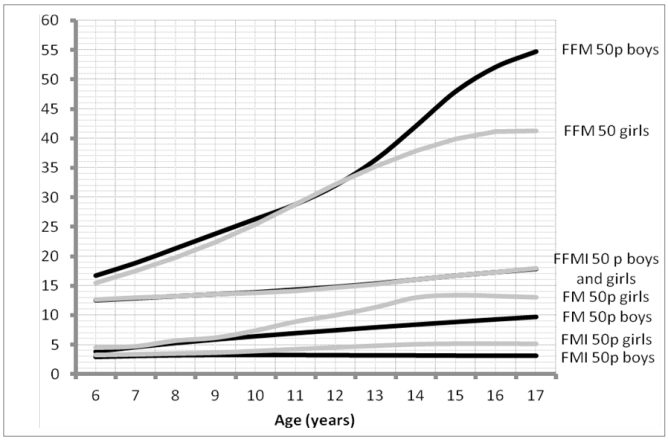

Figure 2. Gender comparison for FM, FFM, FMI and FFMI 50th percentiles.

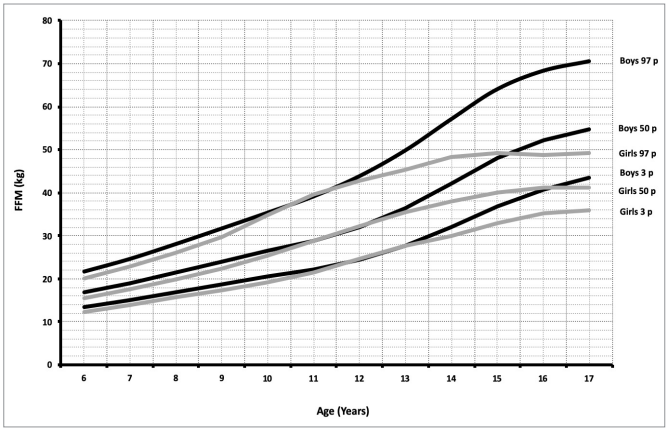

Figure 3. The comparison of 3rd, 50th anfd 97th percentiles of FFM.

references which are the two components of BMI; FMI and FFMI references of 6–17 years old Turkish children for the purpose of screen and compare these references with other references. We constructed Hattori chart in which FMI versus FFMI was classified according to both BMI and fat % (**Figure 1**). The use of FMI, FFMI other than BMI is the fact that similar BMI may have significantly different FMI (fat mass) and FFMI (lean) component.[22] In other words BMI may fail to discriminate children with overfat (fat mass) and overweight (fat mass and lean mass) both of which has discrete cardiometabolic end points.

Our findings also support the above statement by indicating that children with similar BMI may have significantly different fat content (**Figure 1**). Even in normal BMI range gender related splitting in favour of females for fat mass index can be observed. In the overweight children the discrimination between each gender becomes much more apparent. In overweight and obese children distraction between FMI and FFMI becomes much more clear where females are concentrated in 30-40% and males 20-30% range after the BMI value exceeds 18 (**Figure 1**). Then, we may conlude that not solely BMI but its components FMI and FFMI should be considered together in clinical assesment. Although BIA is not the gold standard it is stil may be considered as both the most practical and reliable method of screening and detection of overweight and obesity.

In comparison of our results with previous studies we detected that almost all previous studies were performed in relatively narrow age groups. Other than age group, it

is not easy to find studies performed in similar periods which may bias comparison. FM of Turkish children was higher than Japan (2003)[23] and Bengal (2013)[24] children which may be related with several factors such as geographic location, nutrition, ethnic origin, and e.t.c. Considering the findings of Eissa MA et al[25] in white USA children (n=678) FFM ve FFMI are similar with our findings. Inconsiderable differences between our data and Eissa MA data were detected in 8, 11 and 14th years of age in favor of USA male children and female Turkish children. This comprehensive similarity between USA and Turkish children may be an indicator of body composition change towards USA children. Comparison of our data with Bangladesh study supported our above statement indicating body composition of Turkish children is similar with Bangladesh data (n=200) in relatively young children (6 years) but extending towards USA children as they get older. This finding may show that increased fat mass may be caused by nutritional shift to western type.[26] Prins M et al[27] determined FFM values in 133 Gambian children aged between 5-16 years. We detected higher FFM values for Turkish children in all ages. This finding pointed out both ethnic and socio-economic differences. Similarly, in Nightingale CM et al. study conducted in London with Southeast Asian, African and English children aged between 8-10 years, found different FFM values and emphasized ethnicity as a determinant factor.[28] McCarthy HD et al[29] measured FFM and skeletal muscle mass with BIA in 1985 English children aged between 5-18 years. FFM values were similar to Turkish children both in males and females, whereas higher values were found in 17 years. These reflect the nutrition and physical activity difference in late adolescent period.

In another study performed with Tanita BC-418, no difference was detected between BIA-DEXA values in normal-weight children.[13] In another study, the correlation of BIA and DEXA methods is also shown by Wang L at al.[8]

In addition to determining BMI solely, information about the two components of BMI; FM and FFM is essential for pediatricians to decide about future cardiometabolic risk by body fat and its distribution.[29,30-32] Anormal body fat and its distribution lead hypertension, cardiovascular disease and type 2 diabetes mellitus and named incubation period during childhood and adolescents.[32] Besides a couple of childhood diseases (such as adiposity rebound, lipodystrophy, malignancy, cystic fibrosis, obesity, eating disorders) may also lead distinctive alterations in FM, FFM and bone mineral density.[10,30,33-36] Even short term existance of these disorders may cause long term effects in body composition in terms of fat and lean mass. Then determination of body composition may have significant use in progress of disorders such as obesity, eating disorders, undernutrition, FFM changes in hospital stay, growth monitoring of liver transplantation, HIV patients screening the effectiveness of therapy (insulin and etc.), change in body fat content (parenteral and gastrostomy nutrition), prediction of disorder related risks (obesity), regulation of nutrition (energy and liquid need), drug dose adjustment (dialysis, growth hormone and e.t.c).[31,33,34,37]

Another consideration is that FMI and FFMI may be significant indicator of pubertal variants, normal puberty, precocious or delayed puberty.[38,39] In girls with premature adrenarche, changes in body composition as increase total body fat, decrease FFM, muscle mass and total body water were observed by Cebeci AN et al.[39] Throughout male puberty, there is a progressive in total body bone mineral content, and lean body and a progressive decrease in body fat. In girls, increased in body fat content, lean body mass and body fat distribution occurs in the typical female contours.[38] In our study, the prominent increase in 50th percentile FM in females after 9.5 years and increase in 50th percentile FFM in males supports our consideration that fat to lean mass ratio significantly and inversly changes during adolescence (**Figure 2**).

The incorconcordence between fat mass and lean mass is classified by Shultz[40] as leanness (Low FFMI vs low BMI), obesity (Low FFMI vs high FMI), muscle hypertrophy (High FFMI vs low FMI), and combined excess (High FFMI vs high FMI).

In conclusion both in screening and clinical practice use of FMI and FFMI together with BMI would significantly contribute to detect and follow-up of adiposity rebound, puberty precous, delayed puberty, overweight and obesity. This study would contribute to literature as one of the most comprehensive one. Additionally future studies on the same subject in Turkish population can use our data as acomparison base.

Ethics Committee Approval: The Ethical Committee of Erciyes University, Faculty of Medicine, approved this study (Approval date: 03.04.2019/304, number: 04-01/168).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version

Conflict of Interest: The authors have no conflict of interest to declare.

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References

1. Lobstein T, Baur L, Uauy R. IASO International Obesity Task Force. Obesity in children and young people: a crisis in public health. *Obes Rev*. 2004; 5: 4-104. *[CrossRef]*
2. Han JC, Lawlor DA, Kimm SY. Childhood obesity. *Lancet.* 2010; 375: 1737-1748. *[CrossRef]*
3. Ernst MA, Gerver WJ, Simons MY, et al. Obesity in childhood: a secular trend or an epidemic disease? *J Child Health Care.* 2012; 17: 30-40. *[CrossRef]*
4. Johnson W, Chumlea WC, Czerwinski SA, et al. Secular trends in the fat and fat-free components of body mass index in children aged 8-18 years born 1958-1995. *Ann Hum Biol.* 2013; 40: 107-110. *[CrossRef]*
5. Sabin MA, Kao KT, Juonala M, et al. Viewpoint article: Childhood obesity - looking back over 50 years to begin to look forward. *J Paediatr Child Health.* 2015; 51: 82-86. *[CrossRef]*

6. Dietz WH. Health consequences of obesity in youth: childhood predictors of adult disease. *Pediatrics.* 1998; 101: 518-525. [CrossRef]
7. Melanson KJ, Mcinnis KJ, Rippe JM, et al. Obesity and cardiovascular disease risk: research update. *Cardiol Rev.* 2001; 9: 202-207. [CrossRef]
8. Wang L, Hui, SS, Wong SH. Validity of bioelectrical impedance measurement in predicting fat-free mass of Chinese children and adolescents. *Med Sci Monit.* 2014; 20: 2298-2310. [CrossRef]
9. Maynard LM, Wisemandle W, Roche AF, et al. Childhood body composition in relation to body mass index. *Pediatrics.* 2001; 107: 344-350. [CrossRef]
10. Prentice AM, Jebb SA. Beyond body mass index. *Obes Reviews.* 2001; 2: 141-147. [CrossRef]
11. Thibault R, Pichard C. The evaluation of body composition: a useful tool for clinical practice. *Ann Nutr Metab.* 2012; 60: 6-16. [CrossRef]
12. Aguirre CA, Salazar GD, Lopez de Romaña DV, et al. Evaluation of simple body composition methods: assessment of validity in prepubertal Chilean children. *Eur J Clin Nutr.* 2015; 69: 269-273. [CrossRef]
13. Meredith-Jones KA, Williams SM, Taylor RW. Bioelectrical impedance as a measure of change in body composition in young children. *Pediatr Obes.* 2015; 120: 252-259. [CrossRef]
14. Micklesfield LK, Goedecke JH, Punyanitya M, et al. Dual-energy X-ray performs as well as clinical computed tomography for the measurement of visceral fat. *Obesity (Silver Spring).* 2012; 20: 1109-1194. [CrossRef]
15. Achamrah N, Colange G, Delay J, et al. Comparison of body composition assessment by DXA and BIA according to the body mass index: A retrospective study on 3655 measures. *PLoS One.* 2018; 13(7): e0200465. [CrossRef]
16. Talma H, Chinapaw MJ, Bakker B, et al. Bioelectrical impedance analysis to estimate body composition in children and adolescents: a systematic review and evidence appraisal of validity, responsiveness, reliability and measurement error. *Obes Rev.* 2013; 14: 895-905. [CrossRef]
17. Kurtoglu S, Mazicioglu MM, Ozturk A, et al. Body fat reference curves for healthy Turkish children and adolescents. *Eur J Pediatr.* 2010; 169: 1329-1335. [CrossRef]
18. Van Buuren S, Hayes DJ, Stasinopoulos DM, et al. Estimating regional centile curves from mixed data sources and countries. *Stat Med.* 2009; 28: 2891-2911. [CrossRef]
19. Rigby RA, Stasinopoulos DM. Generalized additive models for location, scale and shape. *J Roy Stat Soc C Appl Stat.* 2005; 54: 507-554. [CrossRef]
20. Rigby RA, Stasinopoulos DM. Smooth centile curves for skew and kurtotic data modelled using the Box–Cox power exponential distribution. *Stat Med.* 2004; 23: 3053-3076. [CrossRef]
21. Hattori K, Tatsumi N, Tanaka S. Assessment of body composition by using a new chart method. *Am J Hum Biol.* 1997; 9: 573-578. [CrossRef]
22. Wells JCK. *The Evolutionary Biology of Human Body Fitness*. Cambridge: Cambridge University Press; 2010:16-48. [CrossRef]
23. Nakao T, Komiya S. Reference norms for a fat-free mass index and fat massindex in the Japanese child population. *J Physiol Anthropol Appl Hum Sci.* 2003; 22: 293-298. [CrossRef]
24. Sen J, Mondal N. Fat mass and fat-free mass as indicators of body composition among Bengalee Muslim children. *Ann Hum Biol.* 2013; 40: 286-293. [CrossRef]
25. Eissa MA, Dai S, Mihalopoulos NL, et al. Trajectories of fat mass index, fat free-mass index, and waist circumference in children: Project HeartBeat! *Am J Prev Med.* 2009; 37: 34-39. [CrossRef]
26. Khan AI, Hawkesworth S, Hawlader MD, et al. Body composition of Bangladeshi children: comparison and development of leg-to-leg bioelectrical impedance equation. *J Health Popul Nutr.* 2012; 30: 281-290. [CrossRef]
27. Prins M, Hawkesworth S, Wrigh A, et al. Use of bioelectrical impedance analysis to assess body composition in rural Gambian children. *Eur J Clin Nutr.* 2008; 62: 1065-1074. [CrossRef]
28. Nightingale CM, Rudnicka AR, Owen CG, et al. Are ethnic and gender specific equations needed to derive fat free mass from bioelectrical impedance in children of South asian, black-african Caribbean and white European origin? Results of the assessment of body composition in children study. *PloS One.* 2013; 8: e76426. [CrossRef]
29. McCarthy HD, Samani-Radia D, Jebb SA, et al. Skeletal muscle mass reference curves for children and adolescents. *Pediatr Obes.* 2014; 9: 249-259. [CrossRef]
30. Wells JC, Fewtrell MS. Is body composition important for paediatricians? *Arch Dis Child.* 2008; 93: 168-172. [CrossRef]
31. Wells JC. Toward body composition reference data for infants, children, and adolescents. Adv Nutr. 2014; 5: 320-329. [CrossRef]
32. Rose G. Incubation period of coronary heart disease. *Br Med J (Clin Res Ed).* 1982; 284: 1600-1601. [CrossRef]
33. Gaynor EP, Sullivan PB. Nutritional status and nutritional management in children with cancer. *Arch Dis Child.* 2015; 100: 1169-1172. [CrossRef]
34. Alicandro G, Battezzati A, Bianchi ML, et al. Estimating body composition from skinfold thicknesses and bioelectrical impedance analysis in cystic fibrosis patients. *J Cyst Fibros.* 2015; 14: 784-791. [CrossRef]
35. Plachta-Danielzik S, Bosy-Westphal A, Kehden B, et al. Adiposity rebound is misclassified by BMI rebound. *Eur J Clin Nutr.* 2013; 67: 984-989. [CrossRef]
36. Demerath EW, Schubert CM, Maynard LM, et al. Do changes in body mass index percentile reflect changes in body composition in children? Data from the Fels Longitudinal Study. *Pediatrics.* 2006; 117: 487-495. [CrossRef]
37. Thibault R, Genton L, Pichard C. Body composition: why, when and for who? *Clin Nutr.* 2012; 31: 435-447. [CrossRef]
38. Rico H, Revilla M, Villa LF, et al. Body composition in children and Tanner's stages: a study with dual-energy x-ray absorptiometry. *Metabolism.* 1993; 42: 967-970. [CrossRef]
39. Cebeci AN, Taş A. Higher body fat and lower fat-free mass in girls with premature adrenarche. *J Clin Res Pediatr Endocrinol.* 2015; 7: 45-48. [CrossRef]
40. Schutz Y, Kyle UU, Pichard C. Fat-free mass index and fat mass index percentiles in Caucasians aged 18-98 y. *Int J Obes Relat Metab Disord.* 2012; 26: 953-960. [CrossRef]

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One-Year Follow-Up Results of Patients With Prenatally Diagnosed Hydronephrosis and Evaluation of Renal Functions

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Abstract

Hydronephrosis is the most common urologic anomaly detected in the fetus. Obstructive uropathy can cause long-term mortality and morbidity by leading to renal damage and decreasing renal functions. We aimed to determine the etiological reasons and frequency of prenatal determined hydronephrosis, also to evaluate the association between some (clinical and laboratory) parameters and renal functions during study. 48 patients with antenatally detected hydronephrosis were followed prospectively. The ultrasonography scan and renal functioning tests were performed on day 3rd-7th of life and repeated on week 4th-6th, months 3rd, 6th and 12nd. The degree of hydronephrosis at the end of study was decreased significantly when compared to antenatal hydronephrosis severity ($p<0.05$). Transient hydronephrosis was diagnosed in 22 (28.9%) of 76 renal unit with prenatal hydronephrosis. Ureteropelvic junction obstruction was the most common cause of antenatal hydronephrosis. Positive correlations between the end study glomerular filtration rate (GFR) and tubular reabsorption of phosphate, blood urea nitrogen and creatinine levels were found at the end of the study. Some significant negative correlations between the end study GFR and fractional excretions of K^+ and Mg^{++} were found at several periods of the study. Transient hydronephrosis is one of the most important reasons of prenatally detected hydronephrosis. The patients with antenatal hydronephrosis must be followed-up closely. Tubular functioning test may be impaired in early stages. The episodic evaluation of tubular functions may predict renal damage before the development of renal failure.

Keywords: Prenatal hydronephosis, renal functions, renal ultrasonography

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Introduction

As a result of the increased use of ultrasonography in routine prenatal practice, most anomalies can be detected in the fetus. The presentation of urologic problems of the neonate has changed in this way. The most common organ system anomalies detected by maternal sonography are the genitourinary anomalies.[1] When these anomalies are detected by the prenatal ultrasound (US) and managed, pyelonephritis, hypertension, or even end-stage renal failure associated with these urologic abnormalities could be prevented.[2] Hydronephrosis is the most common detected urologic anomaly of the fetus. However, there is no specific guideline to evaluate these infants; how frequently and which to image or whether specific intervention is necessary. So that the postnatal approach to fetal renal pelvis dilatation remains controversial.[3]

In this prospective study we aimed to determine the etiological reasons and frequency of prenatal determined hydronephrosis, to evaluate the association between some (clinical and laboratory) parameters and renal functions during one year follow-up period.

Highlight

- Hydronephrosis is the most common detected urologic anomaly of the fetus.
- Patients with antenatal hydronephrosis should be evaluated in postnatal period.
- We suggest that a careful follow-up should include the evaluation of renal and tubular functioning tests in addition to other screening methods.

Materials and Methods

Informed consent information was obtained from all patients in the study and the research protocols were approved by the Ethics Committee at Erciyes University (Approval date: 2005, Approval number: 2005/304).

Fourty eight patients born during one year with antenatally detected hydronephrosis were followed prospectively in Erciyes University, Medical Faculty Pediatric Nephrology department. Hydronephrosis was classified into three degrees (mild, moderate, severe) according to antenatally sonographic measurement of fetal renal pelvic diameter and gestational age.[4]

Postnatally, all infants with prenatal hydronephrosis were given prophylactic amoxicilin- (10 mg/kg/day). If both two US findings and voiding cystouretrography (VCUG) were normal antibiotic prophylaxis was discontinued. All children were investigated according to a systematic procedure illustrated in **Figure 1**.

The US scan, renal functioning tests (BUN, creatinine, electrolytes), glomerular filtration rate (GFR) according to Schwartz formula and tubular functioning tests (TRP, FENa, FEK, FEMg, urine Ca/Cr, urine protein/cr) were performed on day 3-7 of life and repeated on weeks 4th-6th, months 3rd, 6th and 12nd. On admission and on every routine visit blood pressure, body weights and lengths were measured, urinalysis and urine culture tests were performed. Urinary tract infection were defined by the presence of 10^5 CFU/mL bacteria in bagged specimens. Infants with proven urinary tract infection were treated with suitable antibiotics.

A voiding cystourethogram was performed for infants whose renal US scan showed greater than 5 mm AP pelvic diameter on day 3rd-7th of life or week 4th-6th. If the VCUG showed the presence of vesicoureteral reflux (VUR), it was classified according to the report of the International Reflux Study Committee.[5]

Surgery was performed in cases with evidence of obstructive injury, which was defined as a reduction in differential renal function below 40%, ultrasonographic progression of hydronephrosis with renal cortical atrophy, and with posterior urethral valve (PUV).

Statistical analysis was performed in SPSS 11.0 programme. Chi-square and Pearson tests were used. A p value of less than 0.05 was considered to be significant.

Results

Demographic data and antenatal findings of patients are given in **Table 1**.

Degree of hydronephrosis at postnatal period and causes of hydronephrosis:

Of the 96 kidney units of 48 patients, 76 units were antenatally detected to be pathological. The degree of hydronephrosis in right units was more commonly severe. The ratio of the patients with severe hydronephrosis was decreased from 43.4% (33 of 76) to 7.8% (6 of 76) at the end of the study. The difference of severe hydronephrosis ratios between beginning and at the end of the study was significant ($p<0.05$).

Postnatal outcome of antenatally hydronephrotic kidney units in each of three degrees are seen on **Table 2**.

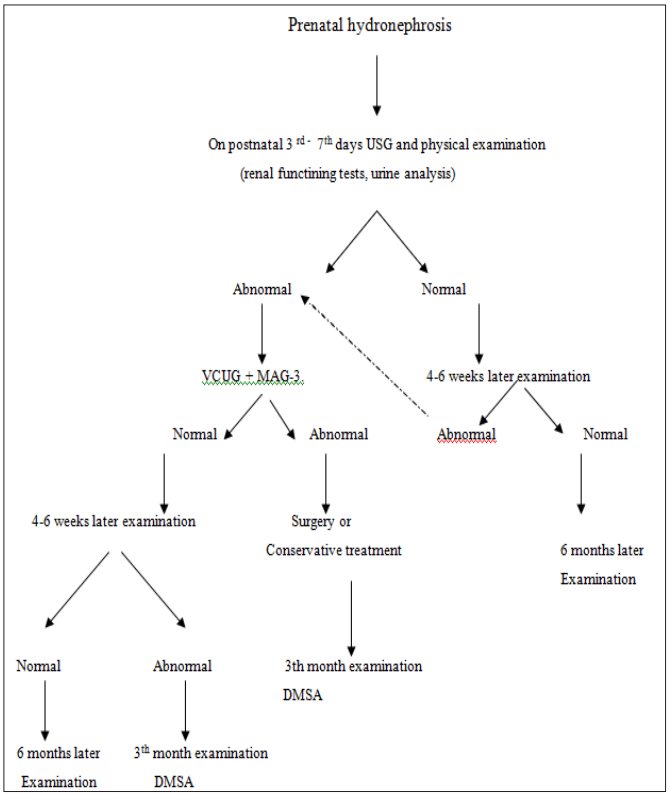

Figure 1. Investigation procedure

Table 1
Demographic data and antenatal findings

Patient number (N)	48
Follow up period (months) Mean ± SD	17.1±5.6
Female/Male	15/33
Antenatal detection time (weeks)	29.6±6.8
<24 weeks	15
≥25 weeks	33
Age of mother (Years)	27.0±5.0
Gestationel age (weeks)	38.6±2.2
The number of renal unit with antenatal detected hydronephrosis	
Right	10
Left	10
Bilateral	28
All	76
The degree of antenatal detected hydronephrosis (number of renal unit)	
Mild	25
Moderate	18
Severe	33

Table 2
Postnatal outcome of antenatally hydronephrotic kidney units

Degree of antenatal hydronephrosis	Postnatal evaluation				
	Not hydronephrosis at any postnatal period (Transient)	Hydronephrosis at the end of the study			
		No	Mild	Moderate	Severe
Mild (n=25)	14	5	6	-	-
Moderate (n=18)	3	7	2	4	2
Severe (n=33)	5	10	4	10	4
Total (n=76)	22	22	12	14	6

Transient hydronephrosis was diagnosed in 22 (28.9%) of 76 renal unit with antenatal hydronephrosis. Antenatal degree of patients with transient hydronephrosis was mild in 14 (63%) of 22, whereas moderate in 3 (14%) and severe in 5 (23%) of 22.

Transient hydronephrosis ratios were 56% (14 of 25) in mild group, 16% (3 of 18) in moderate group and 15% (5 of 33) in severe hydronephrotic kidney units.

Ureteropelvic junction obstruction (UPJO) was the most common cause of antenatal hydronephrosis. In children with UPJO (n=30) the degree of antenatal hydronephrosis was severe in 17 (56.7%), moderate in 9 (30%) and mild in 4 (13.3%). In children with VUR (n=10) the degree of antenatal hydronephrosis was severe in 4 (40%), moderate in 1(10%) and mild in 5 (50%). In children with UPJO the degree of antenatal hydronephrosis was more severe, but in children with VUR it was seemed to be variable.

Ureterovesical junction obstruction (n=5), PUV+VUR (n=9) were the other etiologic causes of antenatal hydronephrosis. Surgery was performed in 23 renal units.

Urinary tract infection:

Fourty eight urinary tract infection attacks were seen in 48 patients during study. In 16 patients there was no urinary tract infection. The most common underlying pathology in patients with urinary tract infection was PUV. Escherichia coli was the most common cause of urinary tract infection.

Evaluation of the association between some parameters and renal functions:

There was a negative correlation between end study GFR and fractional K^+ excretion at the 3rd month and 1st year ($p<0.05$).

There was a negative correlation between end study GFR and fractional Mg^{++} excretion at the 3rd and 6th months ($p<0.05$).

There was positive correlation between end study GFR and tubular reabsorption of phosphate at 1st year and negative correlation between end study GFR and serum BUN levels of 1st year.

Otherwise a negative correlation tendency between end study GFR and fractional Na^+ excretion of 1st year was determined ($p=0.056$).

Correlation results are seen on **Table 3**.

Table 3
Relationship with GFR and some parameters

Parameters	GFR at the end of the study (end study GFR)							
	4th-6th weeks		3rd month		6th month		First year	
	r	p	r	p	r	p	r	p
Weight	0.18		0.11		0.06		0.006	
Blood Pressure	0.05		-0.17		-0.12		-0.05	
BUN	-0.18		-0.03		-0.09		-0.49	0.001
FENa	-0.02		-0.19		-0.07		-0.30	0,056
TRP	0.36	0.02	0.30		-0.03		0.38	0.01
Ca/Cr	-0.26		-0.05		-0.16		0.13	
Protein/Cr	-0.06		0.29		-0.11		0.09	
FEK	-0.28		-0.34	0.02	-0.10		-0.44	0.003
FEMg	-0.26		-0.40	0.01	-0.29	0.04	0.03	

Significant p values are cited in the table, r: correlation coefficient FE: Fractional excretion

There were no correlations between end study GFR and other parameters (weight, height, blood pressure, Fe Na, Protein/creatinine and Calcium/creatinine ratios).

Discussion

The present research investigated the follow-up results of patients with antenatally detected hydronephrosis and evaluated the association between some clinical-laboratory parameters of these patients and renal functions during study.

The relationship between the antenatal degree of hydronephrosis and its' clinical outcome have been evaluated in several prospective and retrospective studies. Otherwise still there is no consensus on both timing and necessity of surgery, using invasive technique and conservative follow-up.[3,4,6-9] Unknowns about

hydronephrosis and increasing frequency of admission to hospitals led us to perform this study and to investigate if there are any probable prognostic factors.

Of the patients with antenatal hydronephrosis, 35-50% will have normal postnatal scans and are diagnosed as transient hydronephrosis.[10] Meeta Mallik et al[9] reported 38% transient hydronephrosis, Nejat Aksu et al[7] reported 24.8%. In the present study we found the ratio as 29.3% and it was smilar to previous data.

Ureteropelvic junction obstruction was the most common etiologic reason as reported in literature. In our study VUR ratio seems to be higher than others. VCUG was performed for all infants with pelvic dilation at first and-or second postnatal US examination. Therefore we were able to diagnose patients even with low degree of VUR.

The third trimester sonogram is important having the highest positive predictive value (PPV) to predict further urologic abnormality. The PPV for an AP diameter >7mm in the third trimester is 69%.[11] In our study five patients, with severe antenatal hydronephrosis degree, were diagnosed as transient hydronephrosis. Furthermore three patients' postnatal US findings were pathological whereas antenatal US were normal. These findings confirm that antenatal degree of hydronephrosis does not always correlate with postnatal outcome. However in our study the ratio of transient hydronephrosis was highest in antenatally mild graded group than moderate and severe ones. The degree of antenatal hydronephrosis in children diagnosed as UPJO tended to be more severe compared with other patients. On the other hand the degree of antenatal hydronephrosis in the patients with VUR was variable. According to these findings of our study it may be thought that the antenatal US findings always may not consist with postnatal US findings.

There is a consensus about timing of the first postnatal ultrasound. It must be done at least 48-72 hours later to avoid the false negative results. Because at first hours the baby is relatively oliguric.[6,7,9,11-13] In addition a second scan at 6th weeks is suggested because initial scans might be normal and postnatal hydronephrosis cannot be recognised.[10] Poor correlation between prenatal and postnatal US findings and the presence of VUR has been documented previously and so in our study. Antenatal degree of hydronephrosis and postnatal US findings of renal units with reflux were variable. Jawson et al. suggests postnatal investigation when anteroposterior pelvic diameter (APPD) is above 5 mm.[3] Ismaili et al[14] suggests that when APPD is above 7 mm. Because intermittent renal pelvic dilation can be seen in VUR, even in the presence of normal US finding the work up for prenatal hydronephrosis should go on. Keeping in mind the future results of missing VUR, we continued further evaluation when there was a APPD > 5 mm.

Many different retrospective and prospective studies have been performed to evaluate clinical characteristics and postnatal outcome of fetal hydronephrosis. Despite much investigation much controversy still exists.[15] Renal functions are deteriorated in some children. Possible prognostic factors have been investigated to avoid unnecessary investigation and missing the diagnosis for underlying etiology. Therefore we evaluated renal functions, tubular functions and GFR at every period in our study. Only one patient diagnosed as PUV, was on chronic renal insufficiency period. In the past few decades, the mortality rates associated with PUV has declined from 50% than 5%. Despite all the advances, 24-33% of patients with PUV still have end-stage renal failure in childhood period. A common predictor of future renal function is the lowest creatinine concentration in the first year of life. Salam M.[16] suggests the lowest creatinine concentration in the first year of life as a highly predictive and appropriate outcome measure to evaluate the effects of antenatal intervention on renal function when compared with the most recent creatinine concentration. Long-term renal function is variable in patients with obstructive uropathy. The creatinine level at one year of age has been best correlated with long-term outcomes; there are better outcomes when the serum creatinine is <0.8 mg/dl by one year of age.[17] Smilarly, a negative correlation was determined between end study GFR and serum BUN levels of 1st year in our study. Also recently significantly increased risk for end stage renal disease was reported in those children who have structural abnormality in childhood, even if renal function was normal.[18]

More efficient predictors of the clinical course apart from serum creatinine and renal scans are required. Some urinary biomarkers like neutrophil gelatinase-associated lipocalin (NGAL) or kidney injury molecule-1 are investigated in patients with hydronephrosis recently.[19] Those are both associated with kidney injury and originated from the renal tubular system. Several abnormalities in tubular function may occur in obstructive nephropathy.[20] Electrolyte and fluid balance abnormalities are expected in infants with severe obstructive uropathy.[17] The value of tubular functions in predicting the future renal damage in patients with hydronephrosis has been evaluated. In the prospective study of Miklovicova et al. 62 pediatric patients who underwent surgery for obstructive uropathy were examined. Selected biochemical markers of glomerular and tubular function, proteinuria, and ultrasound findings were evaluated. With respect to tubular function, 26% of patients had decreased concentration ability.

Proteinuria was detected in 4.8% of patients. On US, 66.7% of kidneys after surgery had residual dilatation of the renal pelvis. In our study, a negative correlation between end study GFR and fractional K^+ excretion at the 3th month and 1st year was determined. Similarly a negative correlation between end study GFR and fractional Mg^{++} excretion at the 3th and 6th months was found. There was a positive correlation between end study GFR and tubular reabsorption of phosphate at 1st year. Otherwise a negative correlation tendency between GFR of at the end of study and fractional Na^+ excretion of 1st year was determined (p=0.056). These results reflect not only patients with obstructive uropathy but also all prenatal hydronephrosis patients.

These significant relationships shown in the study suggests that a careful follow-up should include the evaluation of renal and tubular functioning tests in addition to other screening methods. Abnormalities found in these tests may predict the degree of renal

damage and probable decrease in GFR in the future. However our study group was small and future studies are warranted to investigate prognostic factors for renal damage in prenatally detected hydronephrosis.

Ethics Committee Approval: The Ethical Committeeof Erciyes University, Faculty of Medicine, approved this study (date: 2005, number: 2005/304).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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References

1. Mesrobian HG. Urologic problems of the neonate: an update. *Clin Perinatol.* 2007; 34: 667-viii. *[CrossRef]*
2. Chevalier RL. Congenital urinary tract obstruction: the long view. *Adv Chronic Kidney Dis.* 2015; 22: 312-319. *[CrossRef]*
3. Jaswon MS, Dibble L, Puri S, et al. Prospective study of outcome in antenatally diagnosed renal pelvis dilatation. *Arch Dis Child Fetal Neonatal Ed*. 1999; 80: F135-F138. *[CrossRef]*
4. Estrada CR Jr. Prenatal hydronephrosis: early evaluation. *Curr Opin Urol.* 2008; 18: 401-403. *[CrossRef]*
5. Report of the International Reflux Study Committee. Medical versus surgical treatment of primary vesicoureteral reflux: report of the International Reflux Study Committee. *Pediatrics.* 1981; 67: 392-400. *[CrossRef]*
6. Lim DJ, Park JY, Kim JH, et al. Clinical characteristics and outcome of hydronephrosis detected by prenatal ultrasonography. *J Korean Med Sci.* 2003;18: 859-862. *[CrossRef]*
7. Aksu N, Yavaşcan O, Kangin M, et al. Postnatal management of infants with antenatally detected hydronephrosis. *Pediatr Nephrol.* 2005; 20: 1253-1259. *[CrossRef]*
8. Sairam S, Al-Habib A, Sasson S, et al. Natural history of fetal hydronephrosis diagnosed on mid-trimester ultrasound. *Ultrasound Obstet Gynecol.* 2001; 17: 191-196. *[CrossRef]*
9. Mallik M, Watson AR. Antenatally detected urinary tract abnormalities: more detection but less action. *Pediatr Nephrol.* 2008; 23: 897-904. *[CrossRef]*
10. Woodward, M. and Frank, D. Postnatal management of antenatal hydronephrosis. *BJU International*. 2002; 89: 149-156. *[CrossRef]*
11. Yiee J, Wilcox D. Management of fetal hydronephrosis. *Pediatr Nephrol.* 2008; 23: 347-353. *[CrossRef]*
12. Shokeir AA, Nijman RJ. Antenatal hydronephrosis: changing concepts in diagnosis and subsequent management. *BJU Int.* 2000; 85: 987-994. *[CrossRef]*
13. Ek S, Lidefeldt KJ, Varricio L. Fetal hydronephrosis; prevalence, natural history and postnatal consequences in an unselected population. *Acta Obstet Gynecol Scand.* 2007; 86: 1463-1466. *[CrossRef]*
14. Ismaili K, Avni FE, Hall M. Brussels Free University Perinatal Nephrology (BFUPN) Study Group. Results of systematic voiding cystourethrography in infants with antenatally diagnosed renal pelvis dilation. *J Pediatr.* 2002; 141: 21-24. *[CrossRef]*
15. Riccabona M. Assessment and management of newborn hydronephrosis. *World J Urol.* 2004; 22: 73-78. *[CrossRef]*
16. Salam MA. Posterior urethral valve: Outcome of antenatal intervention. *Int J Urol.* 2006; 13: 1317-1322. *[CrossRef]*
17. Becker A, Baum M. Obstructive uropathy. *Early Hum Dev.* 2006; 82: 15-22. *[CrossRef]*
18. Calderon-Margalit R, Golan E, Twig G, et al. History of Childhood Kidney Disease and Risk of Adult End-Stage Renal Disease. *N Engl J Med.* 2018; 378: 428-438. *[CrossRef]*
19. Noyan A, Parmaksiz G, Dursun H, et al. Urinary NGAL, KIM-1 and L-FABP concentrations in antenatal hydronephrosis. *J Pediatr Urol.* 2015; 11: 249.e1-249.e2496. *[CrossRef]*
20. Klahr S. Obstructive nephropathy. *Intern Med.* 2000; 39: 355-361. *[CrossRef]*

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Clinical and EEG Features, Treatment, and Outcome of Hot Water Epilepsy in Pediatric Patients

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Abstract

Hot water epilepsy is a type of reflex epilepsy which generally occurs with pouring water on the body during bath. The aim of this study is to evaluate the clinical and electrophysiological features, treatment, and outcome of the pediatric patients with diagnosis of hot water epilepsy. Patients were followed and treated at Erciyes University, between January 2010 and January 2016. There were 15 patients total, included 9 (60%) boys and 6 (40%) girls. The average age at diagnosis was 30 months (range: 13-60 months). The follow-up period was 16 months (range: 12-48 months). Seven patients (46.6%) had focal seizures with impaired consciousness, four (26.7%) had focal seizure and four (26.7%) had focal starting and generalized tonic-clonic continuing seizures. Seven patients (46.6%) had abnormal interictal EEG findings, ranged from unilateral slowing of the background activity to bilateral sharp wave. Intermittent clobazam treatment (0.8-1.2 mg/kg) was given to 13 patients (86.7%). Other epileptic treatments were used in 5 (33.3%) patients. Three patients (20.0%) developed nonreflex seizures during follow-up period. Intermittent clobazam prophylaxis prior to hot water bath, as well as changing bathing habits can be effective in pediatric patients with hot water epilepsy.

Keywords: Hot water epilepsy, electroencephalography, clobazam, reflex epilepsy

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Introduction

Reflex epilepsy is an epileptic event triggered exclusively by an external stimulus such as light, sound, eating, reading, and listening to music.[1,2] The rate of reflex epilepsies among all epileptic seizures is about 5-6%.[3] Hot water epilepsy (HWE) is a form of reflex epilepsy, requires a specific thermal cutaneous stimulus, triggered by bath with hot water, poured over the head. HWE described as water temperature higher then 37, is this necessary creteria.[4] It is more frequent in Southern India and Turkey, but rarely seen in European countries.[1,2,5,6] HWE is more frequent in childhood and male/female ratio is 2.6-3.6/1.0.[4,6] Seizures are generally focal with impaired consciousness type; however, they can also be focal starting and generalized tonic-clonic continuing type.[6,7]

In this study, we evaluated the clinical and EEG characteristics, treatments, and outcomes of children with HWE who were followed in our pediatric neurology clinic.

Highlight

- The patients with hot water epilepsy and their family should first be informed about staying away from hot water which causes seizure, using warm water while bathing and pouring water slowly instead of pouring water on the head and body fast.
- Intermittent clobazam prophylaxis prior to hot water bath, as well as changing bathing habits can be effective in pediatric patients with hot water epilepsy.
- Other antiepileptic drugs might require if they develop non-reflex seizure or cannot provide clobazam.

Materials and Methods

Informed consent information was obtained from all patients in the study and the research protocols were approved by the Ethics Committee at Erciyes University (date: 07.04.2017, number: 2017/210).

Subjects

The patients were examined in terms of age, gender, bathing habits, detailed physical examination findings, type of seizure, EEG findings, cranial magnetic resonance findings and the treatment given and its prognosis.

15 cases followed and treated with diagnosis of hot water epilepsy at Erciyes University, Faculty of Medicine, Pediatric Neurology Department between January 2010 and January 2016 were assessed retrospectively. The study protocol was approved by Local Ethics committee of Erciyes University. Informed consent was taken before the study from the parents or legal guardians of the all patients. All patients underwent detailed neurological examination, routine laboratory examinations, imaging techniques, detailed anamnesis were taken from the patients and their EEG records were taken. The patients were assessed in terms of age, gender, bathing habits and frequencies, type of seizure, response to treatment, period of follow-up and complications. The cases assessed as hot water epilepsy were those whose bathing water temperature was over 37 °C.

Statistical Analysis

The data uploaded to SPSS (SPSS Inc., Chicago, IL, USA) system, Shapiro-Wilk test was used to find out if the data were normally distributed. The data which were normally distributed were expressed as average ± standard deviation, while the data which were not normally distributed were expressed as median (min-max).

Results

Nine of the cases (60%) were male, while 6 were female (40%) and the average age was 30 months (distributed between 13 to 60 months). 14 (93.3%) cases were bathed in the bathtub by their families, while 1 (6.6%) case bathed alone while standing. 2 (13.3%) cases had a history of previous febrile convulsion. None of the cases had a history of hot water epilepsy in the family. The siblings of 2 (13.3%) cases had idiopathic epilepsy.

The follow-up period was 16 months (distributed between 12 to 48 months). It was learned that the cases bathed with water more than 37 degrees hot. 12 (80%) of the cases developed reflex epilepsy when hot water was poured down through the head, while 2 (13.3%) developed reflex epilepsy when hot water touched the neck and the face and 1 case (6.6%) developed reflex epilepsy when hot water touched anywhere in his body.

Seizure types were focal in 4 (26.6%) cases, focal with impaired consciousness in 7 (46.6%) cases and focal starting and generalized tonic-clonic continuing in 4 (26.6%) cases. Seizures disappeared completely in 2 (13.3%) cases when they changed bathing habits. In 8 (53.3%) cases, seizures were prevented with clobazam treatment given between 45 min to 60 min before bath. Carbamazepine was started to 1 (6.6%) case and topiramate was started to 1 (6.6%) case that could not provide clobazam. Of the 3 (20.0%) cases that developed non-reflex epilepsy during the treatment, 1 (6.6%) case benefited from clobazam + carbamazepine treatment, 2 (13.3%) cases benefited from phenobarbital + clobazam treatment (**Table 1**). The time between reflex and non-reflex seizures was 8.4 months (ranged: 7-12 months). All the medications except clobazam were taken continually like in epilepsy protocol, while clobazam was applied only 45 min-60 min before bath. No side effects of medication were seen in the patients.

In terms of EEG findings, during the interictal period, 8 patients (53.3%) had completely normal EEG findings, 2 patients (13.3%) had slowing at the base rhythm at unilateral temporoparietal areas, 1 patient (6.6%) had slowing at the base rhythm at bilateral temporoparietal areas, 2 patients (13.3%) had sharp wave activity at bilateral frontotemporal area while 2 patients (13.3%) had sharp wave activity unilateral at frontotemporal area. There was no obvious pathology in brain MRG's

Discussion

Hot water epilepsy was first defined by Allen in New Zealand in 1945. Studies are generally in the form of case reports and there are also a few large cohort studies in literature.[7-10] Our cohort has 15 pediatric cases from a reference center in Kayseri, an urban area in central

Table 1
Clinical characteristics of the patients with a hot water epilepsy

Patients	Age (months)	Gender	Bathing habits	Seizure type	Treatment	Follow-up (months)
1	18	F	Bathtub	Generalized	Clobazam	12
2	36	M	Bathtub	Complex partial	Clobazam	36
3	13	F	Bathtub	Generalized	Phenobarbital+clobazam	48
4	24	F	Bathtub	Simple partial	-	12
5	60	M	Bathtub	Complex partial	Clobazam Carbamezapine	36
6	18	M	Bathtub	Generalized	Clobazam	48
7	48	M	Bathtub	Simple partial	Clobazam	36
8	60	M	Bathtub	Simple partial	-	24
9	36	M	Bathtub	Complex partial	Clobazam	12
10	60	F	Bathtub	Complex partial	Topiramate	18
11	36	M	Shower	Complex partial	Clobazam	36
12	24	F	Bathtub	Simple partial	Carbamezapine+clobazam	24
13	18	M	Bathtub	Generalized	Phenobarbital + clobazam	20
14	26	F	Bathtub	Complex partial	Clobazam	14
15	45	M	Bathtub	Complex partial	Clobazam	17

Anatolia, and it is one of the largest cohort studies from Turkey.

The pathophysiology of the disease is not known completely; however, seizures are generally triggered by pouring down water from the head. The onset age of the disease, which is in the first decade, varies in literature and it is 2-3 times more frequent in men.[2,4,11] The disease has been reported in South India frequently and it makes up 3.6-3.9% of all epilepsy cases. This rate is 0.6% in our country.[3,10,12] This brings to mind that bathing habits are different in these areas. People living in these areas pour 40-50°C water down their heads successively in a fast way during bathing.[12,13] In our country, it is common in specific areas to pour down water with a cup by using tub, basin and/or boiler. 14 (93.3%) cases have habit of bathing in the tub with their families, while 1 (6.6%) case has habit of bathing alone while standing. The onset age of seizures was 2.5 years of age on average and it was found to be lower when compared with literature.

While febrile convulsion and head trauma can be seen in the backgrounds of hot water epilepsy cases, intracranial malformation is very rare.[4,14] 1 (6.6%) of our cases had history of head trauma. The rate of epilepsy in family has been reported as 18-22% and this rate supports the presence of genetic predisposition.[1,9,15] None of our cases' families had a history of hot water epilepsy, the siblings of 2 (13.3%) cases had idiopathic epilepsy. 2 (13.3%) of the cases have history of febrile convulsion. In addition, an autosomal recessive genetic predisposition of the disease has also been reported.[10,11]

Seizures are frequently focal with impaired consciousness.[12] In our study, the most frequent type was focal seizure with impaired consciousness with 7 cases (46.6%), which was in line with literature.

As for treatment, the patient and the family should first be informed about staying away from hot water which causes seizure, using warm water while bathing and pouring water slowly instead of pouring water on the head and body fast. Seizures of some patients have been prevented even with this method only.[2] 2 (13.3%) of our cases' seizures discontinued by changing bathing habits alone. Different antiepileptic drugs are used in the medical treatment of the disease. Clobazam is a novel option for preventing and seems to be an appropriate choice.[16-18]

Most reports of HWE are from India and Turkey, suggesting a genetic predisposition. A genetically aberrant thermoregulatory system or an anatomical abnormality of the temporo-insular and parietal networks has been suggested as a possible mechanism for epiloptogenesis.[19,20] HWE is caused by an X-linked gene—such as SYN1 —in a significant proportion of individuals.[21]

Conclusions: Intermittent clobazam prophylaxis prior to hot water bath, as well as changing bathing habits can be effective in pediatric patients with hot water epilepsy. Other anti-epileptics should be used in patients who do not benefit from changing bathing habits, in cases who cannot provide clobazam or who do not benefit from clobazam and in cases who have non-reflex epileptic seizures.

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Ethics Committee Approval: This study was approved by the Local Ethics Committee of Erciyes University (date: 07.04.2017, number: 2017/210).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: HP conceived the study. HP, SÇ, AKB, AA, MC, HG and SK were involved in patient care, including the process of procedure and routine clinical follow-up. HP, SÇ, AA and AKB performed the literature review and wrote the manuscript. SÇ, AKB also made statistical analysis. HP, HG and SK also made helpful suggestions to improve the manuscript.

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References

1. Meghana A, Sinha S, Sathyaprabha TN, et al. Hot water epilepsy clinical profile and treatment-a prospektive study. *Epilepsy Res*. 2012; 102: 160-166. *[CrossRef]*
2. Eroğlu E, Gökçil Z, Özdağ MF, et al. Hot water epilepsy. *Epilepsi* 1998; 4: 90-92. *[CrossRef]*
3. Incecik F, Herguner MO, Elkay M, et al. Hot water epilepsy -a report of three cases. *Indian Pediatr.* 2004; 41: 731-733. *[CrossRef]*
4. Satishchandra P. Hot water epilepsy. *Epilepsia*. 2003; 44: 29-32. *[CrossRef]*
5. Grosso S, Farnetani MA, Francione S, et al. Hot water epilepsy and focal malformation of the parietal cortex development. *Brain Dev.* 2004; 26: 490-493. *[CrossRef]*
6. Szymonowicz W, Meloff KL. Hot water epilepsy. *Can J Neurol Sci.* 1978; 5: 247-251. *[CrossRef]*
7. Yalçın AD, Toydemir HE, Forta H. Hot water epilepsy: clinical and electroencephalographic features of 25 cases. *Epilepsy Behav.* 2006; 9: 89-94. *[CrossRef]*
8. Allen IM. Observation on cases of reflex epilepsy. *N Z Med J.* 1945; 44: 135-142. *[CrossRef]*
9. Fukuda M, Morimoto T, Nagao H, et al. Clinical study of epilepsy with severe febrile seizures and seizures induced by hot water bath. *Brain Dev.* 1997; 19: 212-216. *[CrossRef]*
10. Bebek N, Gürses C, Gökyiğit A, et al. Hot water epilepsy: clinical and electrophysiologic findings based on 21 cases. *Epilepsia.* 2001; 42: 1180-1184. *[CrossRef]*
11. Auvin S, Lamblin MD, Pandit F, et al. Hot water epilepsy occurring at temperature below the core temperature. *Brain Dev.* 2006; 28: 265-268. *[CrossRef]*
12. Ritaccio AL. Reflex seizures. *Neurol Clin.* 1994; 12: 57-83. *[CrossRef]*
13. Roos RA, van Dijk JG. Reflex-epilepsy induced by immersion in hot water. Case report and review of literature. *Eur Neurol.* 1988; 28: 6-10. *[CrossRef]*
14. Tajima Y, Minami N, Sudo K, et al. Hot water epilepsy with pineal cyst and cavum septum pellucidi. J*pn J Psychiatry Neurol.* 1993; 47: 111-114. *[CrossRef]*
15. Grunanj G, Satishchandra P. Correlates of hot water epilepsy in rural Saouth India: a descriptive study. *Neuroepidemiogy.* 1992; 11: 173-179. *[CrossRef]*
16. Ekici A, Ozdemir O, Yimenicioglu S, et al. Hot water epilepsy successfully treated with daily clobazam. *Pediatr Emerg Care.* 2017; 33: e98-e99. *[CrossRef]*
17. Dhanaraj M, Jayavelu A. Prophylactic use of clobazam in hot water epilepsy. *J Assoc Physicians India.* 2003; 51: 43-44. *[CrossRef]*
18. Satishchandra P, Dilipkumar S, Subbakrishna DK, et al. Intermittent clobazam prophylaxis in hot water epilepsy is safe and effective: a prospective study. *Epilepsy Res.* 2014; 108: 1238-1242. *[CrossRef]*
19. Mosquera-Gorostidi A, Azcona-Ganuza G, Yoldi-Petri ME, et al. Ictal video-electroencephalography findings in bathing seizures: two new cases and review of the literature. *Pediatr Neurol.* 2019; 99: 76-81.*[CrossRef]*
20. Panda PK, Sharawat IK. Bathing and hot water epilepsy. *Pediatr Neurol.* 2020; 104: 72. *[CrossRef]*
21. Peron A, Baratang NV, Canevini MP, et al. Hot water epilepsy and SYN1 variants. *Epilepsia.* 2018; 59: 2162-2163. *[CrossRef]*

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Original Article

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The Effect of Thiaminepyrophosphate Levels on Mortality and Morbidity in Patients with Stress Hyperglycemia

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Abstract

The aim of this study is to evaluate the thiamine pyrophosphate deficiency and effects on critical illness hyperglycemia in pediatric intensive care. 126 critically ill children included to the study which applied to Erciyes University Faculty of Medicine, Department of Pediatric Intensive Care Unit (ICU). Age, sex, diagnosis and presence of malnutrition in admission to ICU; Pediatric risk of Mortality III (PRISM III) and Pediatric Logistic Organ Dysfunction (PELOD) scores; mechanical ventilation and length of stay in ICU was evaluated. Blood glucose, thiamine pyrophosphate, cortisol, insulin, C-peptide, HbA1c level, serum lactate in blood gas were analyzed at the time of application. The patients grouped based on blood glucose levels, the group whose glucose level in blood is more than 150 mg/dl (n:75); PRISM and PELOD scores were high, mechanical ventilation and length of stay in intensive care were longer, thiamine pyrophosphate levels were lower ($p<0.001$, $p=0.005$, $p=0.008$, $p<0.001$, $p<0.01$). In case of blood glucose >150 mg/dl (n:51) and thiamine pyrophosphate <180 nmol/l is together; mortality increases 3.342-fold and the case was statistically significant ($p=0.014$). The group whose glucose level in blood is more than 150 mg/dl respectively, insulin, c-peptide and cortisol levels found high and the findings were statistically significant ($p<0.001$, $p=0.005$, $p=0.040$). Stress hyperglycemia is a common situation seen in critically ill patients as a cause of worse clinical outcomes. Identification of stress hyperglycemia due to thiamine deficiency is difficult but it will shed light on the treatment of critically ill children.

Keywords: Critically ill child, morbidity, mortality, stress hyperglycemia, thiamine pyrophosphate

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Introduction

Hyperglycemia is a common pathology in critically ill patients and prevalence is high in pediatric intensive care units.[1] It is known that increasing blood glucose level above 150 mg / dl in the first 24 hours of hospitalization is associated with higher mortality rates.[2-4] Insulin resistance, insulin deficiency, cytokine-associated epinephrine and increased anti-insulin hormones as well as glucagon have been suggested in etiology.[5] The level and duration of hyperglycemia increases mortality and morbidity as a result of multiple organ insufficiency in both adults and children.[1] It has been shown that hyperglycemia, which develops as a result of insulin deficiency or resistance in diabetic patients increases endothelial damage and associated organ damage. However, in diabetic patients with thiamine deficiency, it is known that the regulation of blood glucose is more difficult and the related organ damage is much more severe.[6]

Highlight

- The risk of mortality is increased with low blood thiamine levels.
- Hyperglycemia is not a negative predictive factor for mortality and morbidity alone, clinical results were found to be worse in patients with thiamine deficiency.

In general, thiamine deficiency in children is 7.5% and in critically ill children is about 28%.[7,8] Lactic acidosis which develops in the presence of thiamine deficiency accompanied by liver dysfunction is more severe in patients with sepsis and is associated with mortality due to multiple organ dysfunction. Theoretically, increased metabolic stress due to catabolism is associated with low thiamin levels.[9] From this point on, the effect of thiamine pyrophosphate level on mortality and morbidity in patients with hyperglycemia at the time of application in pediatric intensive care is more important. We investigate whether thiamin can be hypothesised as a low cost, practical, easy-to-reach effective treatment to reduce mortality and morbidity by using in pediatric intensive care units with hyperglycemic children.

We aimed to evaluate the thiamine pyrophosphate deficiency and effects on critical illness hyperglycemia in pediatric intensive care.

Materials and Methods

126 critically ill children included to the study which applied to University Hospital. The study was approved by the "Medical Research Local Ethics Committee" of Erciyes University. (approval date: 2013, approval number of 2013-319). We took informed consents from all the parents of the patients. Patients with a history of diabetes mellitus, steroid and β2 agonist use were excluded from the study. Age, sex, diagnosis and presence of malnutrition in admission to pediatric intensive care unit; PRISM and PELOD scores; mechanical ventilation and length of stay in ICU was evaluated. Blood glucose, thiamine pyrophosphate, cortisol, insulin, C-peptide, HbA1c level, serum lactate in blood gas were analyzed at the time of application. Patients were divided into two groups according to their blood glucose values: <150 mg/dL as group 1 (n:51) and > 150 mg/dL as group 2 (n:75). 4-6 mg/kg/minute glucose infusion rate was given to patient as a glucose supply.

Venous blood glucose levels were performed in the laboratory. Lactate measurements were performed in Siemens Rapidlab-1265 device.Other laboratory analyses were carried out in the Central Laboratory.

HbA1c level was evaluated by immunoassay method in Roche COAS-6000 0.5 ml whole blood sample.

3 mL of blood for insulin, cortisol and C-peptide levels were taken into a flat tube and studied with immunoassay method in Roche COAS-8000-2 device.

Thiamine pyrophosphate level was analyzed using HPLC in 2 ml of Agilent HPLC 1100 in EDTA. The level of thiamine pyrophosphate <180 nmol/L was considered to be deficiency.[10]

In order to evaluate the mortality risk and morbidity of patients, Pediatric risk of Mortality III (PRISM III) and Pediatric Logistic Organ Dysfunction (PELOD) scores were used.

Statistical analysis

All statistical analyses were performed in the statistical package Statistical Package for the Social Sciences (SPSS) 22.0. Shapiro-Wilk test was applied to all variables and it was determined whether there was normal or abnormal distribution. The comparison between groups for data with a normal distribution (Insulin, C-peptide, HbA1c) was performed using Student's t-test, and the comparison between groups for data that did not show a normal distribution (Thiamine pyrophosphate, lactate) was performed using the Mann–Whitney U test. Categorical variables were compared by means of a chi-square test. ROC analysis was used to determine the predictive power. $p<0.05$ was considered statistically significant.

Results

126 patients who were admitted to pediatric intensive care unit at our hospital with different diagnoses under the age of 18 years were included in this study. Eighty-one (64.3%) of the patients were male and 45 (35.7%) were female. When groups of patients are evaluated according to their blood glucose level, blood glucose ≤150 mg/dL (Group 1) in the group of 51 patients (14 female, 37 male), >150 mg/dL (Group 2) in the group of 75 patients (31 girls and 44 boys) were detected. The median age of the Group 1 was 26 and Group 2 was 24 months, respectively, and there was no statistically significant difference between the groups.

Statistically significant difference was found between the groups according to PRISM and PELOD scores at the time of hospitalization according to blood glucose levels. (**Table 1**)

Insulin, c-peptide and cortisol values were detected statistically significant increase in group 2 and there was no statistically significant difference between the groups in terms of HbA1c values. Lactate levels were significantly higher and thiamine pyrophosphate levels were significantly lower in patients with blood glucose >150 mg / dl. (**Table 2**)

Table 1
Demographic features, PRISM and PELOD scores according to blood glucose levels

Variables	Blood glucose (mg/dl)		p
	Group 1 n (%)	Group 2 n (%)	
	51 (%40.4)	75 (%59.6)	
Age (month)	26 (12-72)	24 (7.5-50)	0.05
Gender			
female (n:45)	14	31	0.89
male (n:81)	37	44	
PRISM	10.27 (2-13)	14 (8-22)	<0.001
PELOD	10 (1-17)	13 (10-22)	0.01
Mechanical ventilation (day)	10 (1-17)	13 (10-22)	0.01
Length of PICU stay (day)	3 (1-7)	6 (3-9)	<0.001
Admission Diagnosis			
Respiratory n (%)	14 (27.4)	10 (13.3)	0,78
Cardiology n (%)	9 (17.6)	5 (6.7)	0,67
Trauma n (%)	10 (19.6)	7 (9.3)	0,54
Neurological n (%)	26 (50.9)	4 (5.3)	<0.001
Infection n (%)	16 (31.3)	9 (12)	0,37
Other n (%)	12 (23.5)	4 (5.3)	0,45

*PRISM: Pediatric Risk of Mortality
*PELOD: Pediatric Logistic Organ Dysfunction

Table 2
Hormone, lactate and thiamine pyrophosphate according to blood glucose levels

Variables	Blood glucose (mg/dl)		p
	Group 1 n (%)	Group 2 n (%)	
	51 (%40.4)	75 (%59.6)	
Insulin (IU/ml)	5 (2.6-9.5)	2.2 (0.98-3.46)	<0.001
C-peptide (pmol/ml)	9,5 (6.41-23)	3.07 (1.49-5.5)	0.005
HbA1c (%)	5.1 (4.8-5.3)	5.1 (4.7-5.4)	0.832
Cortisol (mg/dl)	35 (15.2-53.98)	43.31 (29.9-63)	0.040
Thiamine pyrophosphate (nmol/l)	206.74±31.26	180.47±37.13	<0.01
Lactate (mmol/l)	2.09±0.35	3.85± 0.399	<0.01

38 patients (30.2%) had thiamine pyrophosphate levels below 180 nmol / L. When the patient data were evaluated in terms of the relationship between blood glucose level and thiamine pyrophosphate, a negative and moderate correlation was found.(p=0,001, rho:0.51) The relationship between thiamine pyrophosphate and blood glucose is shown in **Figure 1**.

When the blood glucose and thiamine pyrophosphate values of the patients were evaluated to determine the predictive power by ROC analysis, the blood glucose level above 272 mg / dl and thiamine pyrophosphate below 177 nmol/l was determined. ROC analysis of the values presented in **Table 3** and **Figure 2**.

When the factors affecting mortality in patients included in the study were evaluated, the mortality for blood glucose >150 mg / dl increased 1.875 times but was not statistically significant. In the case of thiamine pyrophosphate <180 nmol / l, the mortality was 3.025 times higher and was statistically significant. In the present study, the risk of death was found to be 3.342 times higher if both cases were present at the same time and it was statistically significant. (**Table 4**)

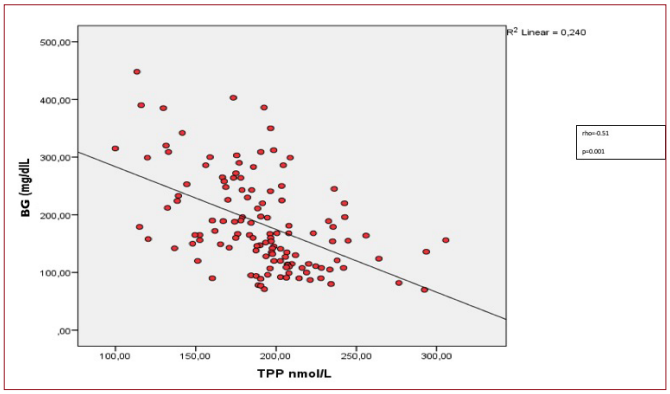

Figure I. The relationship between the level of blood glucose level and thiaminepyrophosphate graph
BG: Blood glucose, TPP: Thiaminepyrophosphate

Table 3
Results of ROC analysis of thiamine pyrophosphate and blood glucose values

Variables	AUC	p
Blood glucose	0.616	0.046
Thiaminepyrophosphate	0.675	0.03

AUC: Area under the curve

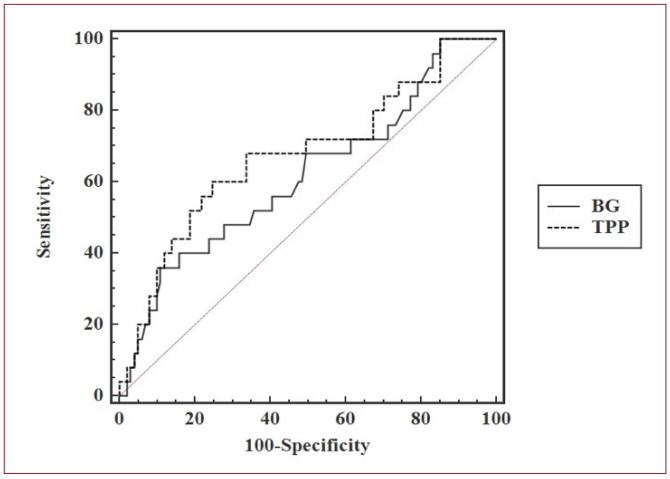

Figure II. ROC analysis of the mortality-related values of thiaminepyrophosphate and blood glucose values

Table 4
Evaluation of The Effect of Blood Glucose Level And Thiamine Pyrophosphate Values On Mortality

Variables	OR (CI %95)	p
Blood glucose >150 mg/dl	1.875 (0.67-5.21)	0.228
TPP <180 nmol/l	3.025 (1.159-7.896)	0.024
Blood glucose >150 mg/dl, TPP <180 nmol/l	3.342 (1.274-8.766)	0.014

Discussion

Although the information about the definition of stress hyperglycemia is not clear, different values are taken as limit in the literature and the data are calculated on these values. In our study, we obtained the limit of stress hyperglycemia as 150 mg/dL, which has the strongest relationship between mortality and morbidity. In the study of 1616 pediatric intensive care patients, the hyperglycemia limit was determined as 200 mg/dL

and it was found that the PRISM score was significantly higher in both the deceased and survived patient groups when the blood glucose level was high (>200 mg/dl).[11] Hirshberg et al[12] reported a linear relationship between PRISM score and blood glucose level. In a study involving 19 pediatric intensive care patients, the PELOD score of the hyperglycemic group was expressed to be significantly higher.[13] In our study PRISM and PELOD scores at the admission were evaluated and a statistically significant difference was found between the hyperglycemic and normoglycemic groups and these findings were consistent with the literature.

Ballestero et al[14] found that the relationship between hyperglycemia and C-peptide was generally linear, but not associated with hyperglycemia. Preissig et al.[13] reported C-peptide levels were found to be significantly low in the hyperglycemic group with respiratory and/ or cardiovascular insufficiency. In a study of 29 postoperative pediatric patients, they found there was no relationship between hyperglycemia and cortisol but cortisol levels were higher in the dying patient group.[14] In our study, insulin, c-peptide and cortisol values were detected statistically significant increase in group 2 and there was no statistically significant difference between the groups in terms of HbA1c values. According to obtained data, cortisol values were higher in the group with high blood glucose as expected in stress hyperglycemia. In our study, insulin and C peptide levels were measured in parallel with hyperglycemia. This can be explained by the expected insulin resistance in stress hyperglycemia.

The first study on thiamine deficiency in critically ill children was performed by Seear et al[15] the thiamine deficiency in 80 well-nourished children was found to be 12.5%. In a study involving 202 patients, thiamine deficiency was reported in 28% of critically ill children in Brazil. Severe sepsis or septic shock with thiamine deficiency has been reported to be higher in mortality.[17] In different studies where thiamin levels were evaluated in adult patients with trauma, burns, myocardial infarction, cardiac surgery, renal failure, and refractory syndrome, it has shown that mortality and morbidity increase in different groups of patients with thiamine deficiency.[14] In the present study 38 patients (30.2%) had thiamine pyrophosphate levels below 180 nmol / L.

Lactate levels were significantly higher and thiamine pyrophosphate levels were significantly lower in patients with blood glucose >150 mg / dl. When thiamine levels are insufficient, pyruvate is unable to be converted to acetyl coenzyme A (by pyruvate dehydrogenase), resulting in impaired aerobic respiration and a compulsory shift to the anaerobic pathway, resulting in elevated serum lactate levels. There are two types of lactic acidosis. Type A is more common in patients with impaired tissue perfusion, with or without hypoxia. Type B lactic acidosis is caused by some drugs, chemicals, toxic compounds or genetic disorders that can cause lactate accumulation.[16] It is very difficult to say whether the increasing lactate levels in PICU patients is due to thiamine deficiency (type B) or to impaired organ perfusion (type A).

When the blood glucose and thiamine pyrophosphate values of the patients were evaluated to determine the predictive power by ROC analysis, the blood glucose level above 272 mg / dl and thiamine pyrophosphate below 177 nmol/l was determined. In the present study, it was found that the risk of mortality increased by 1.875 fold for blood glucose and 3.025 fold for TPP and 3.342 fold for mortality if both cases were present at the same time. This suggests that the blood glucose alone may not be sufficient to estimate mortality; especially when it is associated with thiamine deficiency, the mortality is significantly increased.

There are some limitations in our study. Long-term follow up is needed to see if there will be any impairments due to stress hyperglycemia and also the duration of stress hyperglycemia was not considered.

Stress hyperglycemia is a common situation seen in critically ill patients as a cause of worse clinical outcomes. Identification of stress hyperglycemia and causative factors of stress hyperglycemia, it will shed light on the treatment of critically ill children. Although hyperglycemia was not a negative predictive factor for mortality and morbidity alone, clinical results were found to be worse in patients with thiamine deficiency. We demonstrated thiamine deficiency in critically ill children with hyperglycemia. But there is no information about the replacement of thiamine is helpful for the treatment of stress hyperglycemia or not. Further studies are needed to obtain clearer results regarding the results of thiamine supplementation.

Ethics Committee Approval: The study was approved by the “Medical Research Local Ethics Committee” of Erciyes University. (approval date: 2013, approval number of 2013-319).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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References

1. Van Herpe T, Vanhonsebrouck K, Mesotten D, et al. Glycemic control in the pediatric intensive care unit of Leuven: two years of experience. *J Diabetes Sci Technol* 2012; 6: 15-21. *[CrossRef]*
2. Kliegman RM, Stanton B, Game J, et al. *Nelson textbook of pediatrics.*(20th ed) Saunders Elsevier, New York, 2016: 375-376.
3. Donahey E, Folse S, Jacobi J. Management of Hyperglycemia in Critically Ill Patients. *Pharm Prac News* 2013; 48: 126-135. *[CrossRef]*
4. Verhoeven JJ, Brand JB, van de Polder MM, et al. Management of hyperglycemia in the pediatric intensive care unit; implementation of a glucose control protocol. *Ped Crit Care Med* 2009; 10: 648-652. *[CrossRef]*
5. Santos L. Stress response in critical illness. *Curr Probl Pediatr Adolesc Health Care* 2013; 43: 264-272. *[CrossRef]*
6. Luong KVQ, Nguyen LTH. The impact of thiamine treatment in the diabetes mellitus. *J Clin Med Res.* 2012; 4: 153-155. *[CrossRef]*

7. Lima LFP, Leite HP, de Taddei JACA. Low blood thiamine concentrations in children upon admission to the intensive care unit: risk factors and prognostic significance. *Am J Clin Nutr.* 2011; 93: 57-61. *[CrossRef]*
8. Shaw NS, Wang JL, Pan WH, et al. Thiamin and riboflavin status of Taiwanese elementary schoolchildren. *Asia Pac J Clin Nutr* 2007; 16: 564-571. *[CrossRef]*
9. Donnino MW, Carney E, Cocchi MN, et al. Thiamine deficiency in critically ill patients with sepsis. *J Crit Care*. 2010; 25: 576-581. *[CrossRef]*
10. Mancinelli R, Ceccanti M, Guiducci MS, et al. Simultaneous liquid chromatographic assessment of thiamine, thiamine monophosphate and thiamine diphosphate in human erythrocytes: a study on alcoholics. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2003; 789: 355-363. *[CrossRef]*
11. Klein GW, Hojsak JM, Schmeidler J, et al. Hyperglycemia and outcome in the pediatric intensive care unit. *J Pediatr* 2008; 153: 379-384. *[CrossRef]*
12. Hirshberg E, Larsen G, Van Duker H. Alterations in glucose homeostasis in the pediatric intensive care unit: Hyperglycemia and glucose variability are associated with increased mortality and morbidity*. *Pediatr Crit Care Med.* 2008; 9: 361-366. *[CrossRef]*
13. Preissig CM, Rigby MR. Pediatric critical illness hyperglycemia: risk factors associated with development and severity of hyperglycemia in critically ill children. *J Pediatr.* 2009; 155: 734-739. *[CrossRef]*
14. Ballestero Y, López-Herce J, González R, et al. Relationship between hyperglycemia, hormone disturbances, and clinical evolution in severely hyperglycemic post surgery critically ill children: an observational study. *BMC Endocr Disord.* 2014; 14: 25-28. *[CrossRef]*
15. Manzanares W, Hardy G. Thiamine supplementation in the critically ill. *Curr Opin Clin Nutr Metab Care.* 2011;14: 610-617. *[CrossRef]*
16. Luft FC. Lactic acidosis update for critical care clinicians. *J Am Soc Nephrol.* 2001; 12: 15-19. *[CrossRef]*

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Case Report

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Wernicke Encephalopathy Due to Prolonged Total Parenteral Nutrition in A Child with Signet Ring Cell Gastric Carcinoma

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Abstract

Signet ring cell gastric carcinoma is extremely rare during childhood. One of the most important problems in these patients is nutritional difficulty and impairment, and these patients are often supported by total parenteral nutrition. Herein, the authors report a case of Wernicke encephalopathy due to prolonged total parenteral nutrition in a 13-year-old girl with diffuse gastric cancer with signet ring cell.

Keywords: Gastric carcinoma, signet ring cell, Wernicke encephalopathy, total parenteral nutrition

Introduction

Wernicke's encephalopathy caused by thiamin deficiency is seen frequently absorption problems such as malnutrition and hyperemesis, increased metabolism such as sepsis and malignancy, and increased carbohydrate intake such as administration of intravenous dextrose. Its clinical manifestations are altered mental state including confusion and encephalopathy, ocular abnormalities including nystagmus and ophtalmoplegia, and cerebellar dysfunction including gait disturbance and ataxia.[1-3] The disorder results from a defi ciency invitamin B1 (thiamine), which in its biologically active form, thiamine pyrophosphate, is an essential coenzyme in several biochemical pathways in the brain. It has been reported in different childhood cancers including leukemia, central nervous system, neuroblastoma and osteosarcoma.[4-15]

Childhood gastric tumors are very rare and a significant proportion of them are lymphoma and sarcomas. Presenting symptoms are pain located at epigastric region, feeling of fullness, belching, nausea, vomiting, weight loss, and

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loss of appetite.[16,17] The most important problems in these patients are nutritional difficulty and impairment at follow-up. Generally, this problem is solved by total parenteral nutrition (TPN). Herein, the authors report a case of Wernicke encephalopathy due to prolonged total parenteral nutrition in a 13-year-old girl with diffuse gastric cancer with signet ring cell.

Case

A 13-year-old girl admitted in a local hospital presenting with complaints of dysphagia for five years, odynophagia for 2 years, weight loss (>10 kg over 2 years), regurgitation for 6 months, chest pain and heartburn. On barium swallow, the esophagus was dilated and contrast material passed slowly into stomach as the lower esophageal sphincter was opening intermittently and the distal esophagus was narrow and was described as resembling a bird's beak. Endoscopic examination and biopsy ruled out cancer of gastroesophageal junction or fundus. The patient was referred to another center with initial diagnosis for achalasia. Laparoscopic cardiomyotomy was planned for achalasia. However, gastric linitis plastica, peritoneal carcinomatosis and ascites were detected during operation. So, the patient was considered as unresectable gastric carcinoma. Only biopsy could be performed. Signet ring cell gastric carcinoma was diagnosed. After that, she referred to our hospital for chemotherapy.

She was presented to our clinic with complaints of severe abdominal and back pain, abdominal distension, nausea and vomiting and weight loss. Also, she could not eat or drink anything. Physical examination revealed cachexia, pale, abdominal discomfort and abdominal distension.

The patient was started on systemic 5-fluorouracil and oxaliplatin (FOLFOX)[18]. Also, TPN without multivitamins was initiated. There was a decrease in the pain and distention of the patient in the days following chemotherapy. However, there was no significant improvement in oral intake and so, TPN was continued. On the 40th day of TPN, complaints of hallucination and confusion had begun. Physical examination revealed ataxia, ophthalmoplegia, nistagmus, areflexia and encephalopathy. Biochemistry was normal. On magnetic resonance imaging, the axial fluid attenuated inversion recovery weighted imaging showed that abnormal high signal intensity in both periventricular areas, medial and dorsomedial thalamus and caudate nucleus, suggesting the diagnosis of Wernicke encephalopathy (**Figure 1a** and **Figure 1b**). The patient was instituted thiamine 500 mg intravenously once a day for Wernicke Encephalopathy. At the third day of the thiamine, the symptoms and findings improved. However, the patient died of primary disease.

Discussion

Wernicke's encephalopathy, an acute and neuropsychiatric syndrome, is characterized by nistagmus and ophtalmoplegia, mental-status changes, and unsteadiness of stance and gait.[1,3,19] However, these findings are only seen in a small proportion of patients. Clinical statuses related to Wernicke's encephalopathy are staple diet of polished rice, chronic alcohol abuse and malnutrition, gastrointestinal surgical procedures, recurrent vomiting or chronic diarrhea, cancer and chemotherapeutic treatments, systemic diseases, magnesium depletion, use of chemical compounds and drugs, and unbalanced nutrition.[3,19]

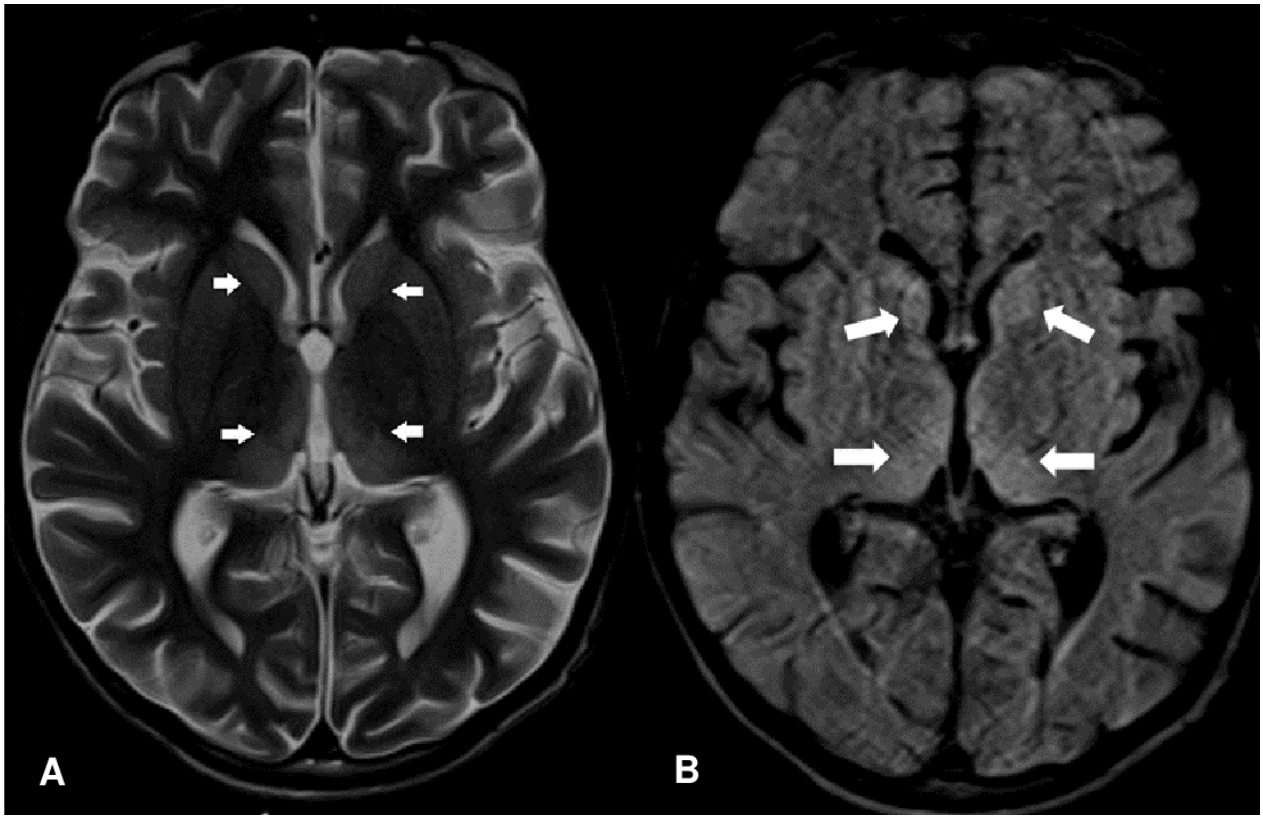

Figure 1. (**a**) The axial T2 and (**b**) FLAIR weighted imaging showed that abnormal high signal intensity in bilateral and symmetrical hyperintense lesions in pulvinar and dorsomedial thalami

The most common known symptoms and signs of the Wernicke encephalopathy are alteration of sensorium, oculomotor dysfunction with ophtalmoplegia and gait ataxia. However, all of these well-known clinical features cannot be seen completely in all of the patients with Wernicke encephalopathy. Also, some uncommon and non-specific symptoms and sings including hypotension, tachycardia, hypothermia, bilateral visual disturbances, papilledema, sluggish pupillary reaction, anisocoria, mydriasis, hypotonia, absence of deep tendon reflexes, tremor, seizures including status epilepticus, hearing loss, hallucinations and behavioral disturbances; n later periods, hyperthermia, hypertonia, paresis, dyskinesia, coma and death can be seen.[1-3] In our patient, hallucination, confusion, ataxia, ophthalmoplegia, nistagmus, areflexia and encephalopathy were determined.

In addition to clinical features, magnetic resonance imaging is also helpful in the diagnosis of Wernicke encephalopathy. The most common magnetic resonance imaging findings of Wernicke encephalopathy are an increased T2 signal, bilaterally symmetrical, in the paraventricular regions of the thalamus, the hypothalamus, mamillary bodies, the periaqueductal region, the floor of the fourth ventricle and midline cerebellum.[2,3,9] In our patient, magnetic resonance imaging show that the axial fluid attenuated inversion recovery weighted imaging showed that abnormal high signal intensity in both bilateral thalamus and caudate nucleus.

Up to now, Wernicke encephalopathy has been reported in some childhood cancers including leukemias (acute or chronic), non-Hodgkin lymphoma, central nervous system tumors (primitive neuroectodermal tumor, medullolastoma, germ cell tumor and pontine glioma), osteosarcoma, and rhabdomyosarcoma. Wernicke's encephalopathy developing in children with cancer in the English literature which full text can be reached are summarized in **Table 1**. Factors that facilitate the development of Wernicke's encephalopathy in children with cancer are rapidly proliferating and growing cancer cells, increased catabolism, some chemotherapeutic agents interacting with thiamine, vomiting, poor intake, and prolonged TPN.[4-17]

In conclusion, Wernicke encephalopathy should be kept in mind in pediatric patients with cancer especially with rapidly proliferating and growing cancer cells such as leukemia, non-Hodgkin lymphoma and some central nervous system tumors and who need to be fed with prolonged TPN.

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Table 1
Summary of previous published Wernicke's encephalopathy developing in children with cancer

No	Age / Gender	Diagnosis	Risk Factors				Treatment	Reference
			Vomiting	TPN (days) with / without MVs	Poor intake	SCT		
OP	13/F	Gastric carcinoma (signet ring cell)	+	+ (40), w/o MVs	+	-	Thiamine	
1	12/M	ALL (with ASD)	+	-	+	-	Thiamine	4
2	13/F	ALL	+	+ (8), w/o MVs	+	-	Thiamine	5
3	10/M	ALL (Down syndrome)	+	+ (5), w/o MVs	+	-	Thiamine	6
4	5/F	Neuroblastoma	-	+ (?), with MVs	+	+	Thiamine	7
5	6/M	Pontine glioma	-	-	-	-	Thiamine	8
6	12/M	CNS PNET	-	+ (?), unknown	+	+	Thiamine	8
7	5/F	Medulloblastoma	+	+ (?), w/o MVs	+	-	Thiamine	9
8	9/F	Osteosarcoma	-	-	+	-	Thiamine	9
9	19/F	AML	+	+ (60), w/o MVs	+	-	Thiamine	9
10	4/F	Rhabdomyosarcoma	-	+ (14), with MVs	+	-	Thiamine	9
11	6/M	Medulloblastoma	+	-	+	+	Thiamine	9
12	10/F	Osteosarcoma	+	-	+	-	Thiamine	10
13	6/M	Germ cell tumor	-	+ (?), unknown	-	-	Thiamine	10
14	12/F	AML	-	+ (?), unknown	-	-	Thiamine	10
15	12/M	AML (CNS positive)	+	+ (30), w/o MVs	+	-	Thiamine	11
16	16/M	ALL (panceatitis)	+	+ (14), w/o MVs	+	-	Thiamine	12
17	12/M	AMLL	+	+ (?), w/o MVs	+	-	Thiamine	13
18	17/F	Osteosarcoma	+	+ (?), unknown	-	-	?	14
19	9/M	ALL	-	-	-	-	Thiamine	15

OP: Our patient, F: Female, M: Male, TPN: total parenteral nutrition, w/o: with out, MVs: multivitamins, ALL: acute lymphoblastic leukemia, ASD: autism spectrum disorder SCT: Stem Cell Transplant, CNS PNET: Central nervous system primitive neuroectodermal tumor, AML: acute myeloid leukemia, AMLL: acute mixed lineage leukemia

References

1. Gregory S, Day C, del Campo M. Wernicke encephalopathy: a medical emergency. *CMAJ.* 2014; 186: E295. *[CrossRef]*
2. Lallas M, Desai J. Wernicke encephalopathy in children and adolescents. *World J Pediatr.* 2014; 10: 293-8. *[CrossRef]*
3. Sechi G, Serra A. Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management. *Lancet Neurol.* 2007; 6: 442-55. *[CrossRef]*
4. Cefalo MG, De Ioris MA, Cacchione A, et al. Wernicke encephalopathy in pediatric neuro-oncology: presentation of 2 cases and review of literature. *J Child Neurol.* 2014; 29: NP181-5. *[CrossRef]*
5. Darlington WS, Pinto N, Hecktman HM, et al. Stem cell transplant-associated Wernicke encephalopathy in a patient with high-risk neuroblastoma. *Pediatr Blood Cancer.* 2015; 62: 2232-4. *[CrossRef]*
6. Kálmánchey R, Koós R, Majtényi K et al. Wernicke-encephalopathy in children with cancer. *Med Pediatr Oncol.* 1994; 22: 133-6. *[CrossRef]*
7. Kızılocak H, Özdemir G, Dikme G, et al. Wernicke's encephalopathy in a child with acute lymphoblastic leukemia. *Turk J Haematol* 2017; 34: 99-100. *[CrossRef]*
8. La Spina M, Catania R, Lo Nigro L, et al. Neurological complications during treatment of childhood cancer: mind Wernicke encephalopathy. *Pediatr Hematol Oncol.* 2010 ; 27: 320-3. *[CrossRef]*
9. Lim Y-J, Kim H-J, Lee Y-J, et al. Clinical features of encephalopathy in children with cancer requiring cranial magnetic resonance imaging. *Pediatr Neurol.* 2011; 44: 433-8. *[CrossRef]*
10. Miyajima Y, Fukuda M, Kojima S, et al. Wernicke's encephalopathy in a child with acute lymphoblastic leukemia. *Am J Pediatr Hematol Oncol.* 1993; 15: 331-4. *[CrossRef]*
11. Muwakkit S, Al-Aridi C, Saab R, et al. Wernicke's encephalopathy during total parenteral nutrition in a child with acute lymphoblastic leukemia and acute pancreatitis. *Neuropediatrics.* 2009; 40: 249-251. *[CrossRef]*
12. Onodera N, Nakahata T, Tanaka H, et al. Successful treatment of Wernicke's encephalopathy in a boy with acute mixed lineage leukemia. *Acta Paediatr Jpn.*1998; 40: 271-274. *[CrossRef]*
13. Perko R, Harreld JH, Helton KJ, et al. What goes around comes around? Wernicke encephalopathy and the nationwide shortage of intravenous multivitamins revisited. *J Clin Oncol.* 2012; 30: e318–e320. *[CrossRef]*
14. Yıldırım AT, Bilgili G, Akman B, et al. Wernicke's encephalopathy in a child with Down syndrome, undergoing treatment for acute lymphoblastic leukemia. *Pediatr Int.* 2016; 58: 757-759. *[CrossRef]*
15. Zensho K, Ishida H, Nagai H, et al. A Wernicke's encephalopathy in a child with autism during chemotherapy for T-cell acute leukemia. *Pediatr Int.* 2018; 60: 757-758. *[CrossRef]*
16. Aydoğan A, Corapçioğlu F, Elemen EL, et al. A case report: gastric adenocarcinoma in childhood. *Turk J Pediatr.* 2009; 51: 489-492. *[CrossRef]*
17. Patiroglu T, Eke Gungor H, Arslan D, et al. Gastric signet ring carcinoma in a patient with ataxia-telangiectasia: a case report and review of the literature. *J Pediatr Hematol Oncol.* 2013; 35: e341-3. *[CrossRef]*
18. Peixoto RDA, de Sousa TT, Silva PAIA, et al. Complete Response for More than 4 Years following Neoadjuvant FOLFOX and Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy for a Patient with Advanced Gastric Cancer with Extensive Peritoneal Carcinomatosis. *Case Rep Oncol*. 2018; 11: 305 *[CrossRef]*
19. Tozzo P, Caenazzo L, Rodriguez D, et al. Delayed diagnosis of Wernicke encephalopathy with irreversible neural damage after subtotal gastrectomy for gastric cancer: A case of medical liability? *Int J Surg Case Rep.* 2017; 30: 76–80. *[CrossRef]*

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Case Report

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Glioblastoma and Colorectal Adenocarcinoma in an Adolescent Girl with Constitutional Mismatch Repair Deficiency Syndrome Mimicking Neurofibromatosis Type-I

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Abstract

Children with constitutional mismatch repair deficiency syndrome (CMMRDS) are prone to different types of cancers. A 16-year-old girl who was misdiagnosed with neurofibromatosis Type-I (NF-I) for 1 years had experienced glioblastoma and colonic adenocarcinoma. After operation, chemotherapy and radiotherapy were started for adenocarcinoma. Genetic analysis from the patient, effected brother, and mother showed heterozygote (c.479 + 36A> G) mutation in the intron 4 region of NF-1 gene. Initially, it was thought that this genetic variant was causative. Furthermore, next generation sequencing showed that the index patient and his brother have homozygote (c.1444 C>T) mutations in the MSH6 gene which are associated with CMMRDS both died because of colonic adenocarcinoma, and T cell non-Hodgkin lymphoma, respectively. Patients with CMMRDS may resemble NF-I. The physicians must not be confused with the previous diagnosis. Increased awareness of CMMRDS, and prompt evaluation for an underlying genetic background is advised if there are unexpected cancer in patients with NF-I.

Keywords: : Adenocarcinoma, adolescent, DNA mismatch repair, neurofibromatosis type 1

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Introduction

Neurofibromatosis type 1 (NF-I) is an autosomal dominant disorder with multiple system involvement, and characterized by increased incidence of both benign and malignant tumors. NF-I occurs with an estimated incidence of 1 in 2500 to 3000 individuals independent of ethnicity, race, and gender.[1] Although cancer can develop at any age, the type of tumors varies in adults and children. NF-I is common in children with optic nerve glioma, and brain tumors.[2] The constitutional mismatch repair deficiency syndrome (CMMRDS) is a rare condition characterized by hematologic malignancies, brain tumors and cancers associated with Lynch syndrome in childhood.[3] Many patients with CMMRDS have café au lait spots (CLS) and similiar features of NF-I such as cancers.[3]

Colorectal cancers are very rare in childhood and are usually associated with cancer susceptibility syndromes.[4-6]

Here we present a case with CMMRDS mutation detected by genetic tests after the development of colon adenocarcinoma and glioblastoma in an adolescent girl followed with the misdiagnosis of NF-I. We discuss her clinical and genetic features based on the reported case series.

Case

A 16-year-old girl with no previous disease was admitted to the pediatric emergency of Erciyes University Hospital with seizure. The patient's parents are first-degree cousins. There was neither significant feature in the patient's medical history, nor a familial history of cancer. She has 4 siblings, and her 12-year-old brother has about 15 CLS. But her brother does not have any disease history.

She had more than 15 CLS in different parts of her body on physical examination. Ophthalmologic examination was negative for Lisch's nodules. Pathological features were not seen in other system examinations. Computerized tomography was performed because of head trauma to the patient. The mass in the right frontoparietal region of the patient (**Figure 1a, 1b**) was operated. The pathology examination was consistent with glioblastoma **Figure 1c, 1d, 1e**). She received radiotherapy for 1 month and then received temozolomide at a dose of 200 mg/m². Anti-epileptic drugs (clobazam, levetiracetam and phenytoin) were also started because of refractory convulsions.

In the follow-up period, the patient was admitted to the emergency department with severe abdominal pain one year later. The radiological images showed stenotic colonic segment with wall thickening (**Figure 2a**). She was operated because of colon perforation. During this operation, stricture of colonic segment is observed. In colonoscopy, two polyps, approximately 4x3 cm in size, were observed in the rectum and a 3x2 cm polyp was observed at approximately 20 cm from the anal verge. Mucosa of the rest of the colon was normal. The pathology report of the patient was relevant with the adenocarcinoma (**Figure 2b**). The patient was re-operated and a large portion of the colon was removed and colostomy was opened. The genetic examination from patient, and the family (mother, father, and 3-years-old brother) were done. It was also noticed that her mother and her brother had CLS. Genetic examination revealed a heterozygous (c.479 + 36A > G) mutation in the intron 4 region of the NF-1 gene (dbSNP: rs1370379787). Her mother and brother also had the same mutation.

NF1 findings and synchronous tumors at different sites suggested CMMRDS. We applied clinical exome sequencing and Sanger sequencing for the patient. Genomic DNAs were extracted from peripheral venous blood using the QIAamp® DNA Mini Kit (QIAGEN, Ankara, Turkey). The Clinical Exome Solution (SOPHiA GENETICS, Switzerland) was used to exome enrichment. All procedures were carried out according to the manufacturer's protocols. It is a capture-based target enrichment kit and covers 4,493 genes with known inherited disease causing mutations. Paired-end sequencing was performed on an Illumina NextSeq 500 system (Illumina, San Diego, California, USA) with a read length of 150 x 2. Base calling and image analysis were conducted using Illumina's Real-Time Analysis (Integrated to NextSeq 500 system) software. The BCL (base calls) binary is converted into FASTQ utilizing Illumina package bcl2fastq. All bioinformatics analysis performed on Sophia DDMTM platform (SOPHiA GENETICS SA., Switzerland), which includes algorithms for alignment and calling single nucleotide polymorphisms (SNPs) and small indels (Pepper, SOPHiA GENETICS' patented algorithm), calling copy number variations (Muskat, SOPHiA GENETICS' patented algorithm) and functional annotation (Moka, SOPHiA GENETICS' patented algorithm). Raw reads were aligned to the human reference genome (GRCh37/hg19). Variant filtering and interpretation performed on Sophia DDMTM. Integrative Genomics Viewer (IGV) was used to bam file visualization (7). Next generation sequencing (NGS) showed a homozygous nonsense mutation, c.1444C>T, p.(Arg482*) in MSH6 (NM_000179) gene. The mutation was confirmed by the Sanger sequencing. Sanger sequencing was also applied to relatives of the patient. The mutation was homozygous for the patient and patient's younger brother, while heterozygous for other family members (**Figure 3**).

The patient was given a chemotherapy course containing oxaliplatin, 5 fluorouracil, and calcium leucovorin (folinic acid) for adenocarcinoma in the colon. In the continuation of the treatment radiotherapy was started. After radiotherapy. The general condition of the patient was improved with these treatments. But just after three months, adenocarcinoma recurred in the colostomy site, so nivolumab treatment was started. The patient was re-operated but the tumor could not be completely resected. The tumor continued to grow at the site of colostomy. She died after two months of the diagnosis of adenocarcinoma.

After the detection of mutation at the MSH6 gene, sibling with the homozygous mutation was also examined. Brain magnetic resonance imaging revealed a mass in the frontal region. Colonoscopy revealed polyps with tubulovillous adenoma. Nivolumab treatment was advised but the family refused. Two months later, the

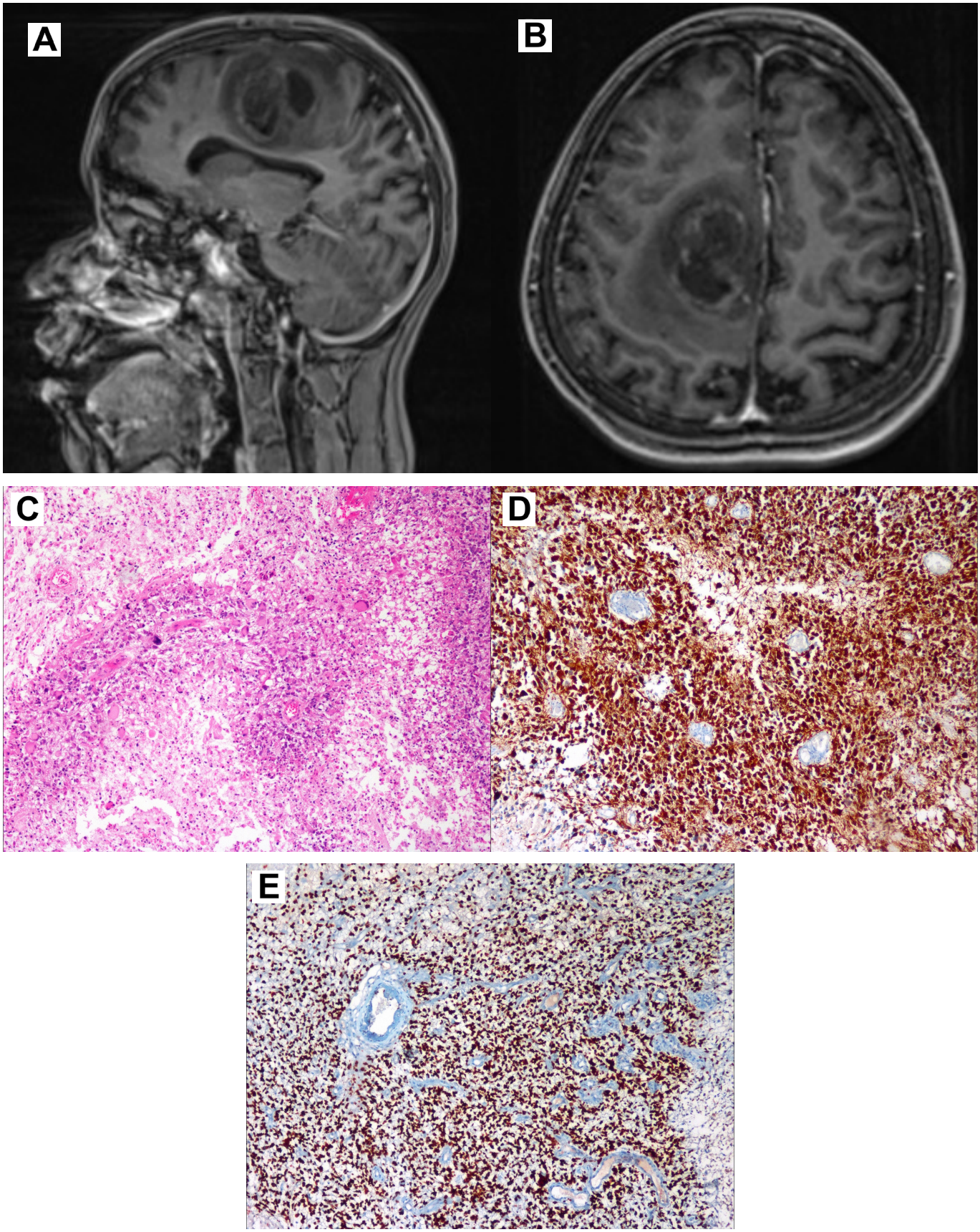

Figure 1. A heterogeneous cystic-necrotic mass is seen at right cerebral hemisphere vertex on sagittal (a), and axial (b) T1 Weighted MRI, with gadolinium contrast. Peripheral contrast enhancement is seen. Light microscopic image showed pleomorphic tumor cells with palisaded necrosis (Hematoxylin & Eosin, x100) (c), Tumor cells displayed glial fibrillary acidic protein positivity (x100) (d), p53 positivity (x100) (e).

male patient presented with respiratory distress. The mass in the mediastinum was compressing the trachea. The patient was intubated and hospitalized in pediatric intensive care unit. The pathology result of the biopsy was reported as T cell non Hodgkin lymphoma. Steroid treatment was started but his condition worsened and he died within a month.

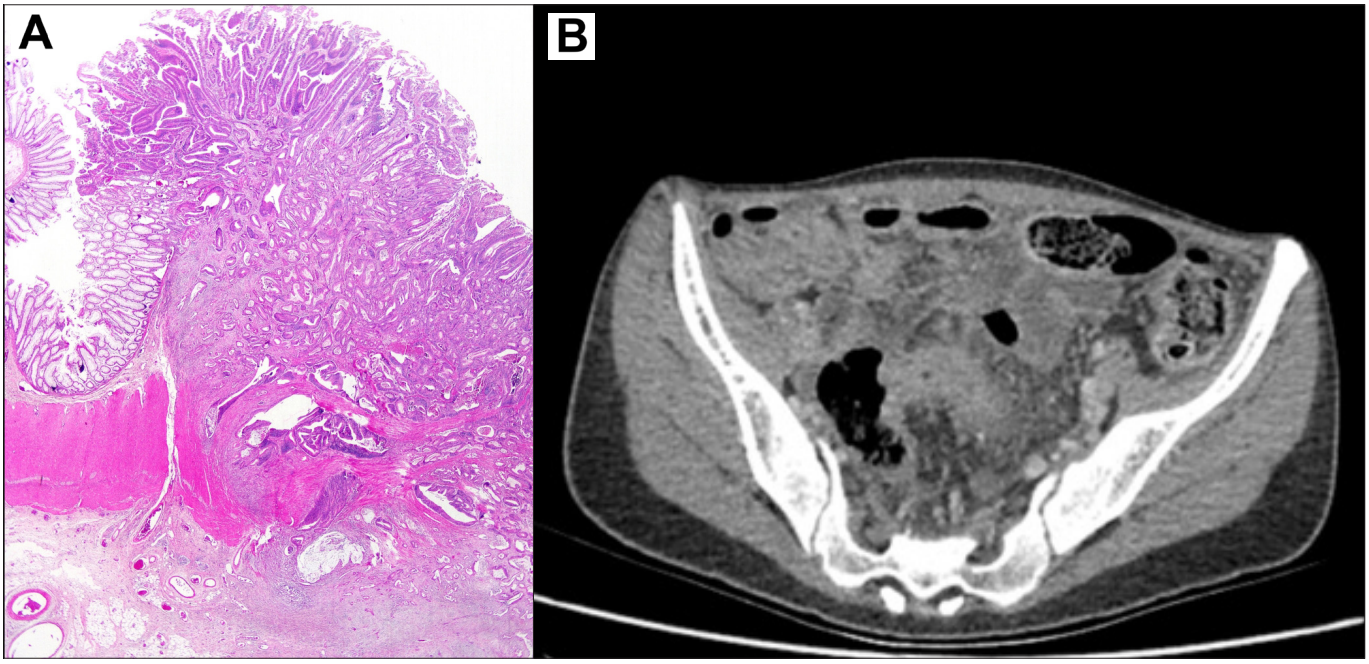

Figure 2. Sections form the colonic tumor showed neoplastic glands infiltrating the colonic wall through the serosa (Hematoxylin & Eosin x100) (a). Stenotic colonic segment with wall thickening is seen in sigmoid on axial image of pelvic contrast enhanced computed tomography (b).

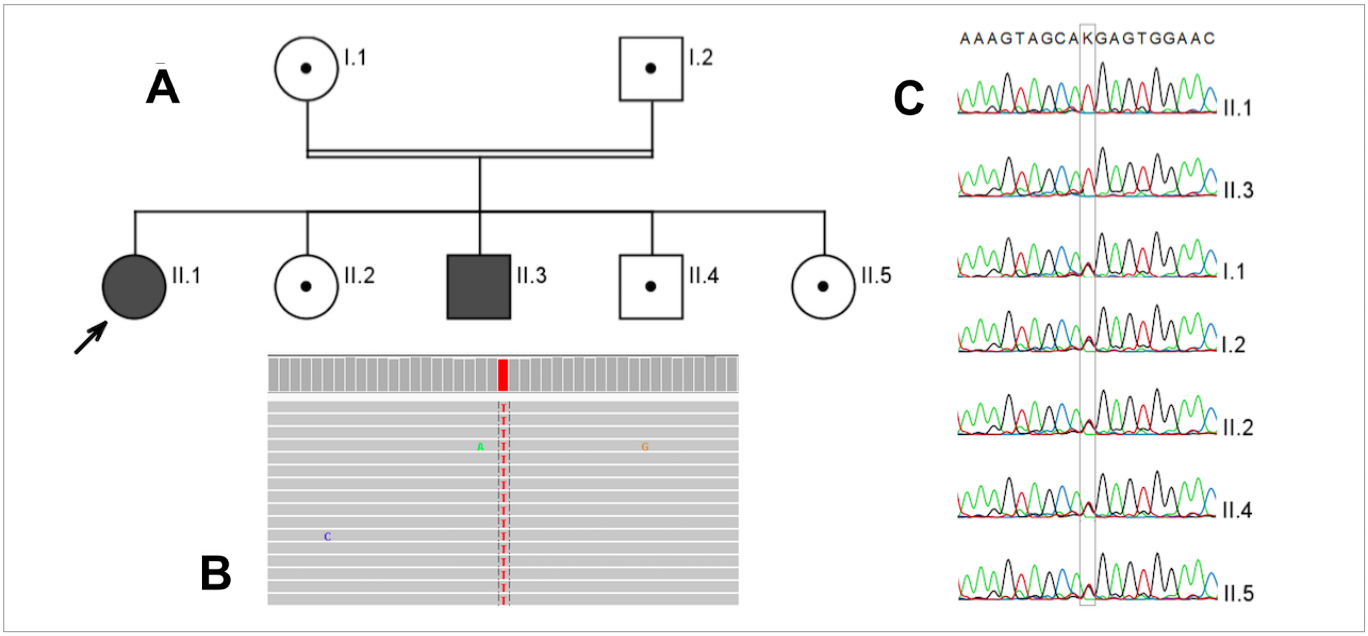

Figure 3. Pedigree of the family showing the identified MSH6 mutation (c.1444C>T, p.Arg482*). The arrow indicates the proband. Black symbols indicate the affected individuals. The proband, and II.3 are homozygous; I.1, I.2, II.2, II.4, and II.5 are heterozygous for the mutation (a). Excerpt of next-generation sequencing data visualized using Integrative Genomics Viewer (b). Results of DNA sequencing. A nonsense germline mutation, c.1444C>T, p.Arg482* in MSH6 (NM_000179) gene of the family (indicated by grey frame) (c).

Discussion

Constitutional mismatch repair (MMR) deficiency syndrome is a childhood cancer predisposition syndrome resulting from biallelic germline mutations in one of the four MMR genes (MLH1, MSH2, MSH6, or PMS2). The mostly encountered mutations in children with CMMRDS are PMS2 are MSH6 genes.[8] Although both parents are compulsory carriers, family history may not always be observed. Therefore, it is not uncommon for affected children to have unaffected parents.[9] In addition to the cancer predisposition, immune deficiencies and autoimmunity can be observed in children with CMMRDS.[3,10] Our patients did not show any features of autoimmunity or immunodeficiency. The mortality rate among patients with CMMRDS is high and 29% of patients die of primary tumor. The median survival from the diagnosis of the first tumor in these patients is 27 months.[11]

Colorectal carcinomas are rare in the pediatric population and very few cases with NF-I have been reported.[3,6,12,13] Changes in bowel habits and hematocesia are more common in left colon and rectum cancers. Iron deficiency anemia and tenesis can be seen in rectal tumors. Constipation and abdominal pain may be seen in all localization of colon cancer.[5,13]

Trilling, and Faucheron[14] performed a systematic review of the literature on acute intestinal obstruction due to

NF-I by searching the major electronic data bases. They have identified 25 articles from 1972 to 2013 reporting 25 patients with NF-I who underwent laparotomy for acute intestinal obstruction. The acute intestinal obstruction in this study were classified as intrinsic obstruction, extrinsic obstruction, and intussusception. The underlying reasons were mainly due to neurofibroma, gastrointestinal stromal tumor, and adenocarcinoma. Only the histological examination of 4 of these 25 showed adenocarcinoma; none of the 4 reported cases of adenocarcinoma with NF-I in this study were in pediatric age group.[14] Our patient was presented with abdominal pain and then bowel perforation. Because gastrointestinal carcinomas are documented in children with NF-I, the diagnosis, rapid evaluation of malignancy is necessary in the presence of gastrointestinal symptoms in these children. Different types of synchronous or meta-synchronous malignancies can be seen in children with CMMRS.[3] Our patient had different types of malignancy that occurred synchronously.

Consanguineous marriage rate varies by countries. Homozygous cases of CMMRDS are more observed in countries such as Turkey. Whereas CMMRDS are generally associated with a combined heterozygous mutation in non-consanguineous families especially in Europe.[15] The parents of our patient were relatives, but neither of them had cancer although both of them have heterozygous mutations. Only two of the five children had a homozygous mutation. One is our patient and the other is her brother, who has CLS on his body.

In conclusion, when rare malignancies associated with NF-I are detected, CMMRDS and other malignancy-related genetic diseases should be excluded in children who have previously been misdiagnosed with NF-I. These children and their families should be closely monitored for malignancies, and genetic counseling must be considered.

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References

1. Varan A, Şen H, Aydın B, et al. Neurofibromatosis type 1 and malignancy in childhood. *Clin Genet.* 2016; 89: 341–345. *[CrossRef]*
2. Peltonen S, Kallionpää RA, Rantanen M, et al. Pediatric malignancies in neurofibromatosis type 1: A population-based cohort study. *Int J Cancer.* 2019; 145: 2926–2932. *[CrossRef]*
3. Wimmer K, Etzler J. Constitutional mismatch repair-deficiency syndrome: have we so far seen only the tip of an iceberg? *Hum Genet.* 2008; 124: 105–122. *[CrossRef]*
4. Urganci N, Genc DB, Kose G, et al. Colorectal Cancer due to Constitutional Mismatch Repair Deficiency Mimicking Neurofibromatosis I. *Pediatrics.* 2015; 136: e1047–1050. *[CrossRef]*
5. Kim SE, Heo EP, Yoon TJ, et al. Segmentally distributed neurofibromatosis associated with adenocarcinoma of the colon. *J Dermatol.* 2002; 29: 350–353. *[CrossRef]*
6. Ladd AP, Grosfeld JL. Gastrointestinal tumors in children and adolescents. *Semin Pediatr Surg.* 2006; 15: 37–47. *[CrossRef]*
7. Robinson JT, Thorvaldsdóttir H, Winckler W, et al. Integrative genomics viewer. *Nat Biotechnol.* 2011; 29: 24–26. *[CrossRef]*
8. Wimmer K, Kratz CP, Vasen HF, et al. Diagnostic criteria for constitutional mismatch repair deficiency syndrome: suggestions of the European consortium 'care for CMMRD' (C4CMMRD). *J Med Genet.* 2014; 51: 355–365. *[CrossRef]*
9. Tabori U, Hansford JR, Achatz MI, et al. Clinical management and tumor surveillance recommendations of inherited mismatch repair deficiency in childhood. *Clin Cancer Res.* 2017;23:e32–e37. *[CrossRef]*
10. Tesch VK, IJspeert H, Raicht A, et al. No Overt Clinical Immunodeficiency Despite Immune Biological Abnormalities in Patients With Constitutional Mismatch Repair Deficiency. *Front Immunol.* 2018; 9: 1506. *[CrossRef]*
11. Lavoine N, Colas C, Muleris M, et al. Constitutional mismatch repair deficiency syndrome: clinical description in a French cohort. *J Med Genet.* 2015; 52: 770–778. *[CrossRef]*
12. Wimmer K, Rosenbaum T, Messiaen L. Connections between constitutional mismatch repair deficiency syndrome and neurofibromatosis type 1. *Clin Genet.* 2017; 91: 507–519. *[CrossRef]*
13. Ozaydın S, Atas E, Tanriseven M, et al. Colorectal Cancer in Patients 30 Years Old and Younger: A 17-Year Experience. *Erciyes Med J.* 2019; 41: 62-68. *[CrossRef]*
14. Trilling B, Faucheron JL. Intestinal obstruction in von Recklinghausen's disease. *Colorectal Dis.* 2014; 16: 762–768. *[CrossRef]*
15. Vasen HF, Ghorbanoghli Z, Bourdeaut F, et al. EU-Consortium Care for CMMR-D (C4CMMR-D). Guidelines for surveillance of individuals with constitutional mismatch repair-deficiency proposed by the European Consortium "Care for CMMR-D" (C4CMMR-D). *J Med Genet.* 2014; 51: 283–293. *[CrossRef]*

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