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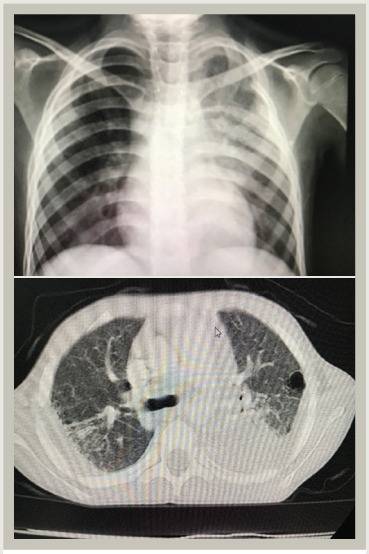

Figure1. Chest radiography and thorax CT of the patient
CT: Computed tomography

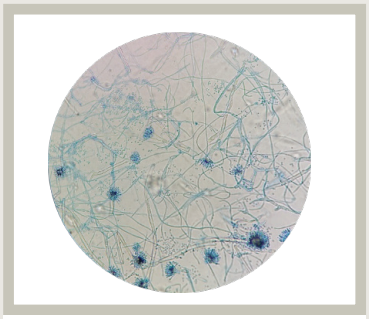

Figure 2. Aspergillus terreus
- The following culture growths were detected in the sampling made from the feather of the same patient, which he has fed at home.
- Domestic Bird Feather
- *Aspergillus terreus*

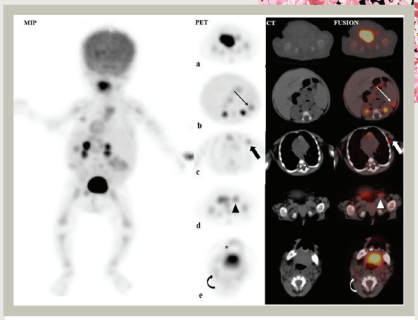

Figure 1. A four months-old girl infant presented with eczematous and squamates rash that began from the cranium and spread to the trunk in a day. Physical examination revealed disseminated erythematous, papules skin lesions.

CAM & SAKURA MEDICAL JOURNAL

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About Us

Journal History

Cam ve Sakura Medical Journal (CSMJ) is an international, scientific, open access periodical published journal. It has independent, unbiased, and double-blinded peer-review principles. The journal is the official publication of the Basaksehir Cam & Sakura City Hospital. It is published three times per year (April, August, December). A special supplement including interesting, novel and attractive theme has also been published every year. The publication language of the journal is English.

Title: Cam ve Sakura Medical Journal

Official abbreviation: CSMJ, Csmedj

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Aims and Scope

Cam ve Sakura Medical Journal (CSMJ) is an international, scientific, open access periodical published journal. It has independent, unbiased, and double-blinded peer-review principles. The journal is the official publication of the Basaksehir Cam & Sakura City Hospital. It is published three times per year (April, August, December). A special supplement including interesting, novel and attractive theme has also been published every year. The publication language of the journal is English.

Cam & Sakura Medical Journal publishes original experimental or clinical research, review articles, case reports, technical reports, diagnostic puzzle, clinical images, video article, novel insight, and letters to the editor in the field of general medicine. Review articles will be only prepared by expert academicians upon invitation. The journal's target audience includes academics and expert physicians working in all fields of general medicine.

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Peer Review, Publication Ethics and Malpractice Statement

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The Editorial Policies and General Guidelines for manuscript preparation specified below are based on "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" by the International Committee of Medical Journal Editors (2016, archived at http://www.icmje.org/).

Preparation of research articles, systematic reviews and meta-analyses must comply with study design guidelines:

CONSORT statement for randomized controlled trials (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 2001; 285:1987-91) (http://www.consort-statement.org/);

PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/);

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al., for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/);

STROBE statement, a checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/);

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

Manuscripts are accepted only online and can be submitted electronically through web site (http://csmedj.org) after creating an account. This system allows online submission and review. The ORCID (Open Researcher and Contributor ID) number of the correspondence author should be provided while sending the manuscript. A free registration can be done at http://orcid.org. The manuscripts gathered with this system are archived according to ICMJE-www.icmje.org, Index Medicus (Medline/PubMed) and Ulakbim-Turkish Medicine Index Rules. Rejected manuscripts, except artworks, are not returned.

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6. The ORCID (Open Researcher and Contributor ID) number of all authors should be provided while sending the manuscript. A free registration can be done at http://orcid.org

b. Abstract

The abstract should summarize the manuscript and should not exceed 300 words. The abstract of the original articles consists of subheadings including "Objective, Methods, Results, and Conclusion". Separate abstract sections are not used in the submission of the review articles, case reports, technical reports, diagnostic puzzles, clinical images, and novel articles. The use of abbreviations should be avoided. Any abbreviations used must be taken into consideration independently of the abbreviations used in the text.

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Instructions to Authors

c. Keywords

A list of minimum 4, but no more than 6 keywords must follow the abstract. Keywords in English should be consistent with "Medical Subject Headings (MESH)".

d. Original Article

The instructions in general guidelines should be followed. The main headings of the text should include "Introduction, Material and Methods, Results, Discussion, Study Limitations and Conclusion". The introduction should include the rationale and the background of the study. The results of the study should not be discussed in this part. "Materials and methods" section should be presented in sufficient details to permit the repetition of the work. The statistical methods used should be clearly indicated. Results should also be given in detail to allow the reproduction of the study. The Discussion section should provide a correct and thorough interpretation of the results with the relevant literature. The results should not be repeated in the Discussion Part. The references should be directly related to the findings of the authors. Study Limitation should be detailed in the section. The conclusion section should be highlighted and interpreted with the study's new and important findings.

The excessive use of abbreviations is to be avoided. All abbreviations should be defined when first used by placing them in brackets after the full term. Abbreviations made in the abstract and in the text are taken into consideration separately. Abbreviations of the full terms stated in the abstract must be re-abbreviated after the same full term in the text.

Original Articles should be no longer than 3500 words and include no more than 6 tables and 7 or a total of 15 figures and 40 references. The abstract word limit must be 250.

Introduction

The article should begin with a brief introduction stating why the study was undertaken within the context of previous reports.

Materials and Methods

These should be described and referenced in sufficient detail for other investigators to repeat the work. Ethical consent should be included, as stated above.
The name of the ethical committee, approval number should be stated. At the same time, the Ethics Committee Approval Form should be uploaded with the article.

Results

The Results section should briefly present the experimental data in text, tables, and/or figures. Do not compare your observations with that of others in the results section.

Discussion

The Discussion should focus on the interpretation and significance of the findings with concise and objective comments that describe their relation to other work in that area and contain study limitations.

Study Limitations

Limitations of the study should be detailed. In addition, an evaluation of the implications of the obtained findings/results for future research should be outlined.

Conclusion

The conclusion of the study should be highlighted.

e. References

The reference list should be typed on a separate page at the end of the manuscript. Both in-text citations and references must be prepared according to the Vancouver style. Accuracy of reference data is the author's responsibility. While citing publications, preference should be given to the latest, most up-to-date references. The DOI number should be provided for citation of ahead-of-print publication, Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/MEDLINE/PubMed. All authors should be listed in the presence of six or fewer authors. If there are seven or more authors, the first three authors should be listed, followed by "et al." References should be cited in text, tables, and figures should be cited as open source („„4) in parenthesis numbers in parentheses. References should be numbered consecutively according to the order in which they first appear in the text. The reference styles for different types of publications are presented as follows:

i) Standard Journal Article

Salminen P, Paajanen H, Rautio T, et al. Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis: the APPAC randomized clinical trial. JAMA 2015;313:2340-2348.8.

ii) Book

Getzen TE. Health economics: fundamentals of funds. New York: John Wiley & Sons; 1997.

iii) Chapter of a Book

Volpe JJ: Intracranial hemorrhage; in Volpe JJ (ed): Neurology of the Newborn, ed 5. Philadelphia, Saunders, 2008, pp 481-588.

Porter RJ, Meldrum BS. Antiepileptic drugs. In: Katzung BG, editor. Basic and clinical pharmacology. 6th ed. Norwalk, CN: Appleton and Lange; 1995. p. 361-380.

If more than one editor: editors.

iv) Conference Papers: Bengtsson S, Solheim BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Reinhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sep 6-10;Geneva, Switzerland: North-Holland; 1992. p. 1561-1565.

v) Journal on the Internet: Morse SS. Factors in the emergence of infectious disease. Emerg Infect Dis [serial online] 1995 1(1):[24 screens]. Available from:s URL:http://www/cdc/gov/ncidoc/EID/eid.htm. Accessed December 25, 1999.

vi) Thesis: Kaplan SI. Post-hospital home health care: the elderly access and utilization (thesis). St. Louis (MO): Washington Univ; 1995.

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f. Tables, Graphics, Figures, Pictures, Video:

All tables, graphics or figures should be numbered consecutively according to their place in the text and a brief descriptive caption should be given. Abbreviations used should be explained further in the figure's legend. The text of tables especially should be easily understandable and should not repeat the data of the main text. Illustrations already published are acceptable if supplied by permission of the authors for publication. Figures should be done professionally, and no grey colors should be used. Authors are responsible for obtaining permission to publish any figures or illustrations that are protected by copyright, including figures published elsewhere and pictures taken by professional photographers. The journal cannot publish images downloaded from the Internet without appropriate permission.
Figures or illustrations should be uploaded separately.

Special Sections

Reviews

Reviews will be prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors and subjects will be invited by the journal. All reviews within the scope of the journal will be taken into consideration by the editors; also, the editors may solicit a review related to the scope of the journal from any specialist and experienced authority in the field.

The entire text should not exceed 25 pages (A4, formatted as specified above).

Reviews should be no longer than 5000 words and include no more than 6 tables and 10 or a total of 20 figures and 80 references. The abstract word limit must be 250.

Case Reports

Case reports should present important and rare clinical experiences. It must provide novel and/or rare clinical data or new insights to the literature. Case reports should consist of an unstructured abstract (maximum 150 words) that summarizes the case. They should consist of the following parts: introduction, case report, discussion. Informed consent or signed releases from the patient or legal representative should be obtained and stated in the manuscript.
Reviews should be no longer than 1000 words and include no more than 200 tables and 10 or a total of 20 figures and 15 references. The abstract word limit must be 150.

Clinical Images

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. It can be signed by no more than 5 authors and can have no more than 5 references and 1 figure or table. 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.

Video Article

Video articles should include a brief introduction on case, surgery technique or a content of the video material. The main text should not exceed 500 words. References are welcomed and should not be more than 5. Along with the main document, video material and 3 images should be uploaded during submission. Video format must be mp4 and its size should not exceed 100 MB and be up to 10 minutes. Author should select 3 images, as highlights of the video, and provide them with appropriate explanations. Video and images must be cited within main text.

Technical reports

Technical reports are formal reports designed to convey technical information in a clear and easily accessible format. A technical report should describe the process, progress, or results of technical or scientific research or the state of a technical or scientific research problem. It might also include recommendations and conclusions of the research. Technical reports must include the following sections: abstract, introduction, technical report, discussion, conclusions, references. Technical reports should contain less than 20 references.

Diagnostic puzzle

Diagnostic puzzles report unusual cases that make an educational point. Since the aim of these articles is to stimulate the reader to think about the case, the title should be ambiguous and not give away the final diagnosis immediately. Diagnostic puzzles should include an introduction and answer part. The introduction part should include a brief clinical introduction to a case (maximum 250 words) followed by an image and a question designed to stimulate the reader to think about what the image shows. The legend should not indicate the diagnosis but should simply describe the nature of the image. Then, the answer part should appear later (maximum 250 words) outlines a brief description of the key diagnostic features of the image, the outcome, and a teaching point.
Diagnostic puzzles will not include more than 5 references. The quality of the image must be at least 300dpi and in TIFF, JPEG, GIF or EPS format. Videos are also welcome and should be in .mov, .avi, or .mpeg format.

Novel insight

This section will offer an opportunity for articles instead of the traditional category of Case Reports. Submissions to this section should contribute significant new insights into syndromological problems, molecular approach and real novelties on recognized or entirely new genetic syndromes or a new technique. The novel aspect(s) can be in the phenotype and/or genotype, the presentation, and the investigation. Submissions can be based around a single case or serial cases. Manuscripts for this section will go through the usual peer reviewing process. The manuscripts should contain abstract (maximum 150 words), a brief introduction, case report(s) and discussion.

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Instructions to Authors

Letters to the Editor

This section welcomes manuscripts that discuss important parts, overlooked aspects, or lacking parts of a previously published article in this journal. In addition, articles on subjects within the scope of the journal that might have an attraction including educative cases, may also be submitted in the form of a "Letter to the Editor." The manuscripts for this section should be written in an unstructured text including references. The editor may request responses to the letters. There are no separate sections in the text.

Letter to the editors should be no longer than 500 words.

Revision Process

During the submission of the revised version of a manuscript, the authors should submit a detailed "Response to the reviewers and editors" that states point by point how each issue raised by the reviewers and/or editors has been replied to and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts should be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be cancelled.

Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue.

LIMITATION TABLE

Type of Manuscript	Word Limit	Abstract Word Limit	Reference Limit	Table Limit	Figure Limit
Original Article	3500	250 (Structured)	40	6	7 or total of 15 images
Review	5000	250	60	6	10 or total of 20 images
Case Report	1000	150	20	200	10 or total of 20 images
Letter to the Editor	500	No Abstract		No tables	No media
Video Article	500		5		
Diagnostic Puzzle	250 (as a brief clinical introduction		5		
Clinical Images	500 (as a brief explanation)		5	1	1
Technical Reports			20		

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Editorial

Dear Colleagues,

We have just published the second issue of CSMJ in 2022. In this issue, you will read 1 invited review, 4 original articles, 1 case report, and 1 clinical image.

The review covers the recent data about the persistent neurocognitive problems related to COVID-19 in children and adolescents. The authors of this invited review evaluated all the original studies about this topic and it includes a systematic review of the literature. I believe this review will provide new insights about long COVID-19 in children and adolescents. The first original study in this issue is about the survival of children with acute lymphobalstic leukemia (ALL). In this retrospective study, the authors evaluated both the survival and acute toxicty rates of children with ALL. The second study in this issue was performed to evaluate the echocardiographic factors for prediction of balloon atrial septostomy in neonates with the transposition of great arteries. In another original study, different asepsis techniques prior to amniocentesis were compared. Furthermore, the correlation between radiological and histopathological findings of ultrasound guided breast biopsy was evaluated in the last original study of this issue. The importance of histopathological evaluation was reported as an important finding of this study. You can also read lovebird-induced Aspegillus infection in a child with immune-deficiency, chronic granulamatous disease, as a case report in this issue. Lastly, you will find the importance of fluoro-2-deoxyglucose positron emission tomography imaging in langerhans cell histiocytosis as a clinical image. I hope these manuscripts will provide valuable information for all readers.

CSMJ has been indexed in J-Gate and Turk Medline in a short publication period. We believe that it will be indexed in other national and international indexes with your support. Therefore, we are waiting your manuscripts for the future issues. We are exciting to publish the last issue of 2022 and meet you on this issue.

On behalf of Deputy Editors, Associate Editors and Editorial Secretary

Merih Cetinkaya

Editor in Chief

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Persistent Neurocognitive Problems Related to COVID-19 in Children and Adolescents

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ABSTRACT

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection has caused persistent multisystemic symptoms. Data on the long-term effects of coronavirus disease-2019 (COVID-19) in children and adolescents are scarce. Persistent neurocognitive symptoms are important for the functionality of children in daily life. This review assessed the literature regarding the frequency, pathology, risk factors, and prognosis of the long-term neurocognitive effects of COVID-19 in the pediatric population. This review demonstrated that children and adolescents had various persistent neurocognitive problems related to COVID-19. The heterogeneity of studies prevents from drawing firm conclusions, as there were differences between study populations and designs in terms of disease severity and time of assessment. Because the pandemic is a recent event, long-term follow-ups to establish how long cognitive impairment persists after COVID-19 recovery are still impossible.

Keywords: COVID-19, SARS-CoV-2, cognition, children, long-COVID

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Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a type of coronavirus that has caused a coronavirus disease-2019 (COVID-19) pandemic with significant morbidity and mortality via direct or indirect effects (1). The risks of acquiring and transmitting SARS-CoV-2 tend to increase with age (2). Clinical studies have defined COVID-19 as a multisystemic infection that can affect various systems, such as cardiovascular, hematologic, renal, gastrointestinal, neurologic and hepatobiliary, and endocrinologic (3). Children and/or adolescents tend to generally have a symptomatic but mild COVID-19 course with few requiring intensive care treatment and a very low rate of mortality (1,4,5,6). Most of the children and adolescents with COVID infection in early period of the pandemic were hospitalized and a significant number of them required intensive care unit (ICU) care (6). Despite these generally positive prognostic features of infection, multisystem inflammatory syndrome in children (MIS-C), which is a rare post-infectious hyperinflammatory disorder associated with SARS-CoV-2 and can result in severe organ dysfunction, seems to occur approximately 2-6 weeks after recovery from COVID-19 infection (7). Compared to acute COVID-19, MIS-C has a higher prevalence of neurological but lower prevalence of respiratory symptoms (8). However, it has not been sufficiently revealed what has temporary or permanent effects in children and adolescents when viewed longitudinally.

Clinical studies have shown that COVID-19 could cause several sequelae, including nervous system and neurocognitive impairments, mental health disorders, and fatigue (9,10). To describe post-COVID symptoms or long-term effects of COVID-19, there are many terms in use (such as "long-COVID", "long-haul COVID", "post-COVID-19 syndrome", "chronic COVID syndrome", "post-acute sequelae of COVID-19") (11). While there is no globally accepted terminology, definition, or duration for these terms, the National Institute for Health and Care Excellence defined long-COVID, which is widely used in terminology, as a syndrome including both ongoing symptomatic COVID-19 (signs and symptoms persisting 4-12 weeks from acute COVID-19) and post-COVID-19 syndrome (signs and symptoms persisting ≥12 weeks from acute COVID-19) (2020 COVID-19 rapid guideline: Managing the long-term effects of COVID-19) (12). The persistent various multisystemic symptoms characterize long-COVID. The literature on the long-term symptoms of COVID-19 in children and adolescents compared with adults is limited (13). The few studies conducted on children and adolescents demonstrated the same symptoms of long-COVID reported in the adult population (14). The prevalence of long-COVID in children and adolescents, as defined by the presence of one or more symptoms more than four weeks following a SARS-CoV-2 infection, was 25.24%, with a much lower prevalence in studies including the control group (15,16) and with lower frequency of persistent sequelae in children/adolescents than in adults (17,18). Also, persistent symptoms seem higher among children diagnosed with MIS-C, indicating the importance of the COVID severity (19). In a recent review study of Izquierdo-Pujol et al. (18), it has been reported that 94% children/adolescents are symptomatic (compared with 99% of adults) and that the SARS-CoV-2 infection is mild in 99% of cases in children/adolescents (compared with 81% in adults). Also, they reported that post-COVID-19 condition was seen in 1-30% children/adolescents and 10-61% adults (18). This difference between two groups may be due to the lower frequency of SARS-CoV-2 infection and to the lower impact of the infection itself in children and adolescents (18). In children and adolescents, recent review studies have reported fatigue (11-20%), lack of concentration, and muscle pain as the most common post-COVID-19 symptoms (18) and mood symptoms (16%), fatigue (10%), and sleep disorders (8%) as the most prevalent clinical manifestations of long-COVID (15).

Cognitive function is consequential for children's functionality at school and at home. Cognitive abilities are substantial to children's learning capacity. The fundamental knowledge and skills acquired during early childhood set the course for learning in the following decades, if not for the whole life. Both social skills and academic performance predict children's possibility of being gainfully employed later in life (20). In children and adolescents, the data on the neurocognitive effects of COVID-19 are scarce, while a recent review has exhibited cognitive (memory, attention, and executive functions) impairments in adults with previous COVID-19 infection (21). This review investigates the literature about the neurocognitive effects of COVID-19 in the pediatric population. Also, possible neuropathological mechanisms and risk factors related to neurocognitive symptoms are discussed.

Neurocognitive Problems Related to COVID-19 in Children and Adolescents

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) defines six key domains of neurocognitive function, and each of these has subdomains: Complex attention (sustained attention, divided attention, selective attention, processing speed), executive function (planning decision-making, working memory, responding to feedback inhibition, flexibility), learning and memory (free recall, cued recall recognition, memory, semantic and

autobiographical long-term memory, implicit learning), language (object naming, word ending fluency, grammar, syntax receptive language), perceptual-motor function (visual perception, visuoconstructional reasoning, perceptual-motor coordination), and social cognition (recognition of emotions theory of mind insight) (22). For this part of this review article, literature published in English between January 2020 and May 2022 was searched on May 30, 2021 in PubMed and Google Scholar databases by two reviewers. Children and adolescents aged ≤18 who were diagnosed with COVID-19 with real-time polymerase chain reaction (RT-PCR) were included. We included patients with neurocognitive symptoms defined in DSM-5 following COVID-19. During scanning, the following keywords were used: (Coronavirus or COVID-19 or SARS-CoV-2 or long-COVID) and (infant or kids or young or children or adolescent or pediatric) and (cognition or neurocognition or cognitive or neurocognitive or cognitive decline or cognitive deficit or cognitive impairment or concentration or attention or attention deficit or processing speed or learning or memory or memory impairment or executive function or language or verbal fluency or perception or perceptual or visuospatial or orientation or confusion or delirium). We also scanned references of found articles. The studies found were categorized as author's name, study year, country of study, a type of article, collection mode, age range/mean age, sex, disease severity, time of assessment, neurocognitive test, and results. We assessed the cases according to the types of neurocognitive symptoms. The review and/or meta-analysis studies were also used for the content of this manuscript. We also examined symptoms affecting cognitive functions, for instance, sleep issues, fatigue, dizziness, and headache.

Nineteen studies were included in this part of the review. Most of the studies consisted of data obtained via online or electronic surveys or questionnaires. The time of assessment after diagnosis of COVID-19 was varying approximately 28-324 days. No evaluation based on neurocognitive tests was found in these studies. Characteristics of the included studies are demonstrated in Table 1.

Cognition/Neurocognition

Studies investigating cognitive/neurocognitive difficulties have reported different results, with a wide frequency range. Cognitive difficulties were found to be 10% in the evaluation made 1-3 months after the onset of the disease in children aged 8-15 years with a diagnosis of COVID-19 who were hospitalized (23). Another study, including children aged 0-18 who were hospitalized but evaluated longer than four months after the hospitalization, reported the frequency of cognitive difficulties as 5.4% (24). Similarly, in two meta-analyses conducted on children and adolescents, cognitive difficulties were reported as 6.3% and 3%, respectively (11,15). In another meta-analysis including pediatric COVID-19 patients with MIS-C, neurocognitive symptoms such as headache, irritability, lethargy, or visual change were reported in 31.8% (25). These differences suggest that higher frequency may be associated with shorter follow-up time, disease severity, and possibly narrow age range, as symptoms may resolve over time and symptom persistence may increase with age. Lower prevalence of cognitive symptoms was associated with higher study quality and longer follow-up duration (11). Moreover, Blankenburg et al. (26) did not reveal any significant differences between seropositive and seronegative students regarding the prevalence of any neurocognitive symptom. Conversely, when compared with the controls, cognitive sequelae were significantly associated with the SARS-CoV-2 infection (27). The prevalence of persistent cognitive complaints seems to increase considerably with age (27).

Attention, Concentration and Executive Functions

In this review, Roge et al. (27) reported impaired attention in 16.9% of the patients who had no MIS-C and were evaluated 1-6 months after acute COVID-19. Also, they stated that inability to focus their attention (24.1%) was one of the most reported persistent symptoms in adolescents. Additionally, from the same country, attention problems were declared less frequent in hospitalized children evaluated 1-3 months after the onset of the disease (23). Limited results of these two studies suggest that attention problems may be seen or noticed in older children later during post-COVID period. However, it is seen that most of the studies have found concentration difficulties ranging between 0.4-80% (13,16,27,28,29,30,31,32,33,34,35). Compared to SARS-CoV-2 positive peers, children and adolescents in the control group may experience more concentration difficulties, as reported by Borch et al. (16). Independent of the disease, compared to pre-pandemic, poorer concentration, attention, task engagement and persistence, and greater impulsivity during the pandemic were found, with evidence of possible mild impacts (36). Interestingly, children with ADHD had no notable changes in their ability to pay attention pre-pandemic to pandemic (36). We did not find any study investigating the impact of SARS-CoV-2 infection on executive function in children and adolescents.

Language Functions

The effect of COVID infection on language problems within neurocognitive functions in children and adolescents has been less studied. Parents of children and adolescents

with SARS-CoV-2 infection reported different language/speech dysfunctions including word repetition (12.1%) (32), trouble finding the right words (32), speech disturbances (1.3%) (27), and trouble forming words (0.4%) (37). In line with these findings, in a meta-analysis study, speech disturbances were declared as 0.4% in children and adolescents with SARS-CoV-2 infection (15). Also, Buonsenso et al. (32) showed that the word repetition was seen most in 3-6 months after SARS-CoV-2 infection and unassociated with age and sex.

Memory and Learning

In one of the first published studies, a five-patient case series evaluated 6-8 months after clinical diagnosis of COVID-19 identified that three of five children displayed memory loss (13). In other studies, memory problems after infection were considerably investigated in children and adolescents, showing memory loss (13%) (30), memory impairment (18%, 10%) (27,33), short-term memory issues (32.7%) (32) and loss (0.6%) (37), difficulty remembering information (45.9%) (32), difficulty in doing everyday tasks (40%) (32), difficulty processing information (32.7%) (32), and forgetfulness (1.5%) (37). Despite no further analysis, and when characteristics of these studies have been considered, these results related to memory dysfunctions seem to present mainly in older ages and every phase of post-COVID period, leading more cases with these problems to accumulate. Despite the absence of studies investigating learning deficits after SARS-CoV-2 infections, both acute and chronic attention and memory impairments related to hippocampal and cortical damage and neuroinflammation in brain areas essential for fine motor function, memory and learning may indicate some learning deficits in both children and adults (38,39).

Perceptual-motor Function and Social Cognition

Generally, studies have not reported any perceptual-motor and social cognitive difficulties directly related to SARS-CoV-2 infection in children and adolescents. However, brain areas having roles in perception, motor function, and social cognition may be damaged, as reported in adult studies (38), suggesting difficulties in these neurocognitive domains after infection in the pediatric population.

Other Neurocognitive Symptoms (Confusion, Orientation, Delirium, Hallucination)

In this review, some studies investigated these variables rarely seen in children and adolescents. Confusion was reported in 4% of children aged 0-16 at 1 month (37), 7.3% of adolescents at least 3 months (40), and 0.41% of children and adolescents at least 5 months (28) after SARS-CoV-2 infection confirmed with the test, suggesting increased risk with older age and in early phase of the post-COVID period. Also, Stephenson et al. (40) found that 7.3% of adolescents with positive test for SARS-CoV-2 reported disorientation at least 3 months after infection. Delirium, which is manifested by cognitive findings, is a rarely reported neurological condition due to COVID-19 infection in children and adolescents (41). Its development is closely related to the severity of the disease (41). The observation that cases with delirium secondary to an acute COVID-19 infection showed improvement after several weeks may lead to thinking of this problem as a long-COVID symptom (42). Also, it is claimed that delirium may be associated with long-term cognitive complications (43). Similar to very low frequencies of other neurocognitive symptoms, only one study by Zavala et al. (37) found that hallucination was reported as frequent as 0.2% among the 472 laboratory-confirmed SARS-CoV-2 RT-PCR-positive patients aged 0-16.

Pathological Mechanisms of Neurocognitive Problems

Despite clear evidence that post-COVID-19 condition is pathological in both children and adults, the pathological mechanisms of this disease remain unknown. The one or multiple organ/tissue damage, medical interventions, exacerbated immune response, viral persistence in certain tissues, olfactory neuroepithelium/sensory neurons infection, autoantibodies (particularly being generated according to the severity of the disease), re-activation of neurotrophic pathogens such as herpes viruses under conditions of COVID-19 immune dysregulation, SARS-CoV-2 interactions with host microbiome/virome communities, clotting/coagulation issues, dysfunctional brainstem/vagus nerve signaling, and ongoing activity of primed immune cells have been suggested as potential pathophysiological mechanisms of post-COVID-19 or long-COVID-19 symptoms (18,44). The exacerbated immune response may lead to delay or defects in the resolution of inflammation, which may explain the persistence of symptoms (45). The resolution of inflammation seems to be delayed, particularly in symptomatic cases and persistent symptoms decrease around 6 months post-infection (45). However, early postmortem studies revealed no evidence of CNS damage directly caused by COVID-19 (38,46). When examining genetic susceptibility to the symptoms of post-COVID-19 until March 2022, no studies were found that explored the potential link among them (18). A recent study conducted on seropositive adult patients with asymptomatic/mild disease reported that rs11385942 polymorphism of the leucine zipper transcription factor like 1 gene (coding a protein involved in the primary cilia function and the immunological synapse between T-cells and antigen-presenting cells) was

associated with disease severity but not with long-term symptoms (47). Moreover, Blankenburg et al. (48) reported no significant differences between the symptoms of the SARS-CoV-2- seropositive and seronegative children, suggesting that most of the symptoms are due to lockdown syndrome rather than viral infection. However, a review study by Behnood et al. (11) found more common persistent symptoms in PCR-positive children than in PCR-negative children. Although difficult, there seems to be a need to distinguish between long-term symptoms caused by SARS-CoV-2 infection and pandemic-related symptoms (49,50).

When evaluated in terms of neurocognitive symptoms associated with COVID-19, pathological mechanisms are still unclear. Crivelli et al. (10) expressed these possible mechanisms as the direct effects of cellular damage due to viral invasion, secondary inflammatory responses, decreased angiotensin-converting enzyme 2 (ACE2) activity that regulates neuroprotective and neuro-immunomodulatory functions, oxidative stress, hypoxia, sepsis, and/or multi-organ damage related to severe COVID-19. Also, they stated a possible association of the post-COVID-19 neurocognitive impairment with poorer pulmonary function and vascular pathology (elevated D-dimer levels) (10).

According to our current knowledge based on data from adult studies, neurocognitive impairment is unlikely to be due to COVID-19-related delirium (10). Recently, a potential pathomechanism was described based on structural similarities between the N-methyl-d-aspartic acid receptor (NMDAR) synonym NR1 (GluN1) and synonym NR2a (GluN2a) subunits and the SARS-CoV-2 non-structural proteins 8 and 9 , respectively, indicating an immune-mediated cross-reactivity to the NMDAR (51,52). Considering the roles of NMDAR in memory, learning, synaptic plasticity, this mechanism may be a explanation of neurocognitive impairments.

When evaluated in terms of post-COVID-19 or long-COVID neurocognitive symptoms, several factors, including hypoxemia, cerebral thrombotic/inflammatory endothelial damage, disruption of the blood-brain barrier (leading to parenchymal translocation of pro-inflammatory molecules, cytokines, and cytotoxic T-lymphocytes), microglial activation and astrogliosis are suggested as pathological mechanisms found generally in adult studies (53).

Studies generally conducted on adult patients found that SARS-CoV-2 was detected in brains from severely infected patients (54). There is no clarity yet on how the virus enters the brain and how it spreads in the brain (54). Possible mechanisms/routes of SARS-CoV-2 entry to the brain seem to be retrograde transport via sensory (olfactory, trigeminal, autonomic nervous system) nerve endings within nasal and buccal cavities, neuroinvasion via gastrointestinal tract, the virus associated with leukocytes entering the brain via receptors, interaction of virus entering blood from the infected lungs with the cerebrovasculature and/or at the blood-cerebrospinal fluid barrier, and the choroid plexus (54). Although there are no data to support any mechanism for the spread of SARS-CoV-2 in the brain, it can be argued that SARS-CoV-2 may interact with and spread through the ACE2, other facilitator receptors, or by adsorptive uptake by cells (54). Moreover, a meta-analysis study of neuroimaging findings revealed acute to subacute infarcts (24.0%), cerebral microhemorrhages (6.9%), acute spontaneous intracerebral hemorrhages (5.4%) and encephalitis/encephalopathy (3.3%) in adult patients with COVID-19 (55).

Risk Factors of Neurocognitive Problems

Although there is no study directly evaluating the risk factors of neurocognitive problems in children and adolescents, the results from the long-COVID studies give an idea about this issue. In a review study, risk factors associated with long-COVID in children and adolescents were stated as older age, female gender, severe COVID-19, overweight/obesity, comorbid-allergic diseases, other long-term comorbidities, and poorer physical and mental health before COVID-19 (11,15,28,56,57). Also, Asadi-Pooya et al. (17) reported older age, muscle pain at hospital admission, and admission to the ICU during acute infection as the predictors of post-COVID-19 condition in children and adolescents. Moreover, Blankenburg et al. (48) stated the associations of neurocognitive and pain symptoms with female gender and higher age. Conversely, in a meta-analysis study, persistent cognitive difficulties were associated with higher age but not with gender (11). This study also revealed that higher study quality was associated with lower prevalence of all symptoms, except the loss of smell and cognitive symptoms (11). However, fewer comorbidities, strong innate immune responses, reduced expression of ACE2 receptors, active thymic function, vaccines, past infections, nutrition, and/or the gut microbiome were stated as protective factors against severity and duration of COVID-19 and possibly long-COVID (15).

Prognosis of Neurocognitive Problems

Knowing the duration of long-COVID symptoms seems important to address the implications for the children and families. Since the disease is still very young, information about its course is limited. Although there is no study has directly examined the prognosis of neurocognitive problems, some pediatric studies revealed that most children recover within

2 weeks-5 months (16,31,58,59), indicating a need for future studies to draw a conclusion. This wide range of recovery time may be due to improvement of symptoms at different times (28). A possible steady decline in the prevalence of fatigue and smell disturbance over time was declared, whereas the prevalence of symptoms such as headache and sleep problems declined slower. This finding should be carefully interpreted because of recalling the symptom onset and duration at the single follow-up interview. However, Borch et al. (16) found that children in the control group had significantly more concentration difficulties, headache, muscle and joint pain, cough, nausea, diarrhea, and fever than SARS-CoV-2 infected, suggesting that these may be related to other factors (for example restrictions, lockdown of the pandemic, etc.) than SARS-CoV-2 infection.

Conclusion

Clinical studies are still exploring the long-term effects of COVID-19. The reports are conflicting regarding its prevalence, duration, and impact on daily life (14). Childhood is a critical period of life for acquiring social, behavioral, and educational development (31). Parents need to be informed about the cognitive effects of COVID-19. It is significant that teachers, psychiatrists, and pediatricians collaborate on cognitive impairments. Pediatric cases with neurocognitive signs raise concerns about the potential for health sequelae to affect child and family functioning over many life years (60). Early diagnosis is a substantial point for long-COVID in children. After COVID-19, children and adolescents may be followed up by outpatient services for a while. Doctors may assess the neurocognitive complaints. A multidisciplinary approach will be beneficial in this issue. More knowledge on long-term sequelae of COVID-19 in children and adolescents needs to be collected. Further studies are required to provide greater insight into the neurocognitive effects of COVID-19 on developing brain.

Table 1. Characteristics of the included studies: Methodological summary and main results

Author, year, country (reference)	Type of article and collection mode	Age range or mean age (year), sex (F %)	COVID-19 cases (n severity)	Time of assessment (neurocognitive test)	Results Associated with Neurocognitive Symptoms
Ludvigsson 2021, Sweden (13)	Case report and systematic review, internet-based social media forum (parental reports)	9-15, 80%	n= 5 Mild, hospitalized	6-8 months after clinical diagnosis of COVID-19 (-)	All children in this study reported fatigue and pain. Four of the five children complained of headaches, difficulties concentrating, and dizziness. The parents reported that three of the children experienced memory loss and depression
Buonsenso et al. 2021, Italy (31)	Cross-sectional study, phone or inpatient (questionnaire)	11±4.4, 48%	n= 129 26% symptomatic, 74% symptomatic, 5% hospitalised, 2% PICU	163±114 days after microbiological diagnosis (-)	129 children diagnosed with COVID-19 complained of insomnia (18.6%), fatigue (10.8%), concentration difficulties (10.1%), headache (10.1%)
Brackel et al. 2021, Netherlands (30)	Cross-sectional study, online questionnaire	9-15, NR	n= 89 52.8% had a positive PCR test, 34.8% positive serology tests, and 38.2% diagnosed clinically 18% hospitalised	≥12 weeks after diagnosis of COVID-19 (-)	89 children attended this study. Fatigue was the most common long-term complaint (87%). Many patients reported some degree of cognitive dysfunction, with 45% suffering concentration difficulties, 13% reporting memory loss, and 2% describing brain fog. 38% of children complained of headaches
Buonsenso et al. 2022, UK and USA (32)	Cross-sectional (preprint), online survey (parental reports)	10.3±3.8, 56%	n= 510 12% symptomatic, 74% managed at home, 4% hospitalised, 9% attended hospital (not admitted)	>4 weeks after symptom onset (-)	Several parents reported a lack of concentration (60.6%), difficulty remembering information (45.9%), difficulty in doing everyday tasks (40%), difficulty processing information (32.7%), short-term memory issues (32.7%), word repetition (12.1%) in their children

Sterky et al. 2021, Sweden (24)	Brief report, phone questionnaire	0-18, 42%	n= 55 All severities, hospitalized	219 days (123-324) after hospital admission (-)	Of 55 patients, 3 were suffering from cognitive difficulties (5.4%)
Ashkenazi-Hoffnung et al. 2021, Israel (33)	Brief reports, clinical	Mean age: 12±5, 41%	n= 90 all severities, mild n= 82 (91.1%) moderate n= 6 (6.7%) severe n= 2 (2.2%)	Median of 112 days (range: 33-410) after COVID-19 diagnosis (-)	Following the disease, they reported some symptoms such as memory impairment (17.8%) and difficulty in concentration (8.9%)
Roge et al. 2021, Latvia (27)	Ambidirectional cohort study, phone (questionnaire)	Mean age: 10.0, 44.5%	n= 236 86.9% outpatients with mild disease, 13.1% moderate/severe disease requiring hospitalization, no MIS-C	1-6 months after acute COVID-19 (-)	They complained of cognitive sequelae [including difficulties to concentrate (16.9%), impaired attention (16.9%), impaired memory (10.2%)], speech disturbances (1,3%). After the 12-week cut-off point, 105 (44.5%) COVID patients had persistent symptoms. No statistical differences were seen among most reported persisting symptoms before and after the 12-week cut-off point. Cognitive sequelae were significantly associated with the COVID-19 experience compared to the controls. In older children, one of the most prevalent persistent symptoms was cognitive disturbances, as well as neurological sequelae. The prevalence of persistent cognitive complaints increased considerably according to the study's age groups, with the highest rates seen among teenagers. In adolescents, cognitive disturbances including difficulty in concentrating (27.8%) and an inability to focus their attention (24.1%) were the most reported persistent symptoms
Miller et al. 2021, UK (56)	Cohort study, electronic (weekly survey)	Age groups: <2, 2-11, 12-17, 41%	NR	≥28 days after symptom onset (-)	4,504 participants attended this study. 175 patients were COVID-19 positive. 22.2% of patients had neurological (including cognitive impairment/"brain fog") symptoms
Fink et al. 2021, Brazil (34)	Prospective cohort study, outpatient and inpatients validated instruments and clinic	8-18, 58%	n= 53 Mild [16/23 (70%)], moderate/ severe/critical pediatric COVID-19 [7/23 (30%)]	4.4 months (0.8-10.7) after COVID-19 diagnosis (-)	In 53 patients with symptomatic pediatric COVID-19, one of the most frequently reported symptoms is difficulty concentrating (4%)
Borch et al. 2022, Denmark (16)	Retrospective cohort study, electronic (questionnaire)	0-17, NR	n= 15,041 Asymptomatic, mild	Symptoms lasting >1 month (-)	One of the most common symptoms was concentration difficulties. Children in the control group aged 0-5 years experienced significantly more concentration difficulties than children in the SARS-CoV-2 group. Correspondently, 6-17-year-old controls were more prone to concentration difficulties than their SARS-CoV-2 positive peers

Kikkenborg Berg et al. 2022, Denmark (35)	Cross sectional study, case-control, electronic (survey)	15-18, 57.6%	n=6630 all severities	≥8 weeks after the positive SARS-CoV-2 test (-)	3,013 matched controls were excluded because of suspected SARS-CoV-2 infection. 6,630 (27.3%) responded in the case group and 21 640 (22.3%) responded and were eligible to participate in the control group. One of the most frequent symptoms in the long COVID group was trouble remembering or concentrating. Cases are included in the specified time periods if they had sufficient follow-up time since a positive SARS-CoV-2 test. For at least two months (5.6%), for at least three months (5.9%), for at least six months (5.2%), for at least nine months (4.9%), for at least twelve months (3.3%) patients reported often or almost always troubled to remember or to concentrate
Kikkenborg Berg et al. 2022, Denmark (61)	Cross sectional study, case-control, electronic (survey)	0-14, 10.2, 48.2%	n= 10997	≥8 weeks after the positive SARS-CoV-2 test (-)	Cases had higher odds of reporting at least one symptom lasting more than 2 months than did controls in the 0-3 years age group (40·0% vs. 27·2%), 4-11 years age group (38.1% vs. 33.7%), and 12-14 years age group (46.0% vs. 41.3%). Differences in Children's Somatic Symptoms Inventory-24 symptom scores between cases and controls were statistically significant but not clinically relevant. Among those aged 4-11 years, trouble remembering or concentrating was one of the most common; and among those aged 12-14 years, trouble remembering or concentrating was one of the most common. The prevalence of symptoms lasting at least 2, 3, 6, 9, and 12 months are presented. With increasing duration of symptoms, the proportion of children with those symptoms tended to decrease. In cases aged 12-14, more girls than boys had at least one symptom lasting more than 2 months (52.7% vs. 39.6%), and a similar pattern was seen in the control group. In the younger age groups, sex differences were only found for controls aged 4-11 years
Radtke et al. 2021, Switzerland (29)	Prospective cohort study, online (questionnaire)	6-16, 54%	n= 109 Asymptomatic and mild	>3 months after serologic testing (-)	4 of 109 seropositive children (4%) and 28 of 1246 seronegative ones (2%) reported at least 1 symptom lasting beyond 12 weeks. One of the most frequently reported symptoms lasting more than 12 weeks among seropositive children was difficulty concentrating (2%)
Blankenburg et al. 2022, Germany (26)	Cross sectional study, schools (12-question long-COVID-19 survey)	14-16, 55%	NR	>3 months after acute infection (-)	1,365 (88%) students were seronegative, and 188 (12%) were seropositive. Fisher's Exact test did not reveal any significant differences between seropositive and seronegative students regarding the prevalence of any neurocognitive symptoms reported. More than one-third of adolescents reported the presence of at least one neurocognitive, pain, or mood symptom, with tenseness, listlessness, and difficulties concentrating reported most commonly

Smane et al. 2021, Latvia (23)	Retrospective cohort study, clinical	8-15, 39%	n= 92 Hospitalized	1-3 months after COVID-19 onset (-)	Among the 92 patients, 47 (51%) reported persistence of at least one symptom. Persistent cognitive disturbances (memory, attention, and information processing problems) were present in 9 (10%)
Zavala et al. 2021, U.K. (37)	Retrospective cohort study, paper questionnaire	0-16, 49%	n= 387 All severities Among the positive cases, 32.2% were asymptomatic at the time of the RT-PCR test	At 1 month (-)	A total of 2456 children were invited, and 35.0% (859/2456) completed the questionnaire, including 38.0% (472/1242) laboratory-confirmed SARS-CoV-2 RT-PCR–positive cases and 32% (387/1214) SARS-CoV-2 RT-PCR–negative controls. Differences in neurological symptoms included confusion, which was only reported for symptomatic cases (5.6%). Most elicited symptoms were as common among symptomatic cases as among symptomatic controls. Among the 472 laboratory-confirmed SARS-CoV-2 RT-PCR–positive patients reported cognitive symptoms: Confusion (19/472), forgetfulness (7/472), short-term memory loss (3/472), trouble forming words (2/472), hallucinations (1/472). Of the 65 ongoing symptoms solicited, 3 clusters were significantly more common, albeit at low prevalence, among symptomatic cases (3-7%) than symptomatic controls (0-3%): neurological, sensory, and emotional and behavioral well-being.
Stephenson et al. 2021, England (57)	Cohort (preprint), paper questionnaire	11-17, 63%	n= 3065 non-hospitalized	14.9 weeks (13.1-18.9) after testing (-)	6804 adolescents (3065 who tested positive and 3739 who tested negative) completed the questionnaire (response rate of 13.4%). Among 3065 participants who tested positive for SARS-CoV-2 reported symptoms such as confusion, disorientation, or drowsiness (7.3%).
Osmanov et al. 2022, multinational (28)	Prospective cohort, telephone interview	≤18, 52%	n= 518 hospitalized	Median 256 (223-271) days (≥5 months) since hospital discharge (-)	At the time of the follow-up interview, parents of 24.7% of children reported at least one persistent symptom. Confusion/ lack of concentration (0.4%), Tingling feeling/"pins and needles" (0.4%), problems speaking or communicating (0.2%).

MIS-C: Multisystem inflammatory syndrome in children, COVID-19: Coronavirus disease-2019, RT-PCR: Real-time polymerase chain reaction, SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: C.M., E.R.T., Design: C.M., E.R.T., Data Collection or Processing: C.M., E.R.T., Analysis or Interpretation: C.M., E.R.T., Literature Search: C.M., E.R.T., Writing C.M., E.R.T.

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ORIGINAL ARTICLE

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Overall and Event-free Survival in Children with Acute Lymphoblastic Leukemia and Evaluation of Treatment Related Acute Toxicity

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What is known on this subject?

Although childhood cancers can be treated with chemotherapy today, deaths and recurrences caused by the disease itself and the drugs used are seen at certain rates.

What this study adds?

It is an important study because it has the first results of the Pediatric Hematology Oncology Clinic of Kanuni Sultan Suleyman Hospital, which has the highest bed capacity in its field in Istanbul at the time of the study.

ABSTRACT

Objective: The study aimed to evaluate the acute toxicity, overall survival (OS) and event-free survival (EFS) of children with acute lymphoblastic leukemia (ALL).

Material and Methods: This study included retrospective analysis of the medical records of 129 pediatric ALL patients aged 1 to 18 years old. Gender, risk group, central nervous system involvement at diagnosis, relapse and mortality status of patients, OS and EFS was evaluated. The Kaplan-Meier method was used to estimate survival rates. The survival difference of two groups was compared using the log-rank test.

Results: Eighty-six (66%) patients were boys and forty-three (33%) were girls. The mean age at diagnosis was 6.9±4.46 and 5.6±4.01 in male and female, respectively. Seventeen (13%) patients were classified as standard risk, 76 (58%) were intermediate risk, and 36 (27%) were high risk. Three patients (2.3%) died from acute toxicity during induction therapy. The median duration of follow-up was 25 months (range 1-65 months). The estimated 5-year OS and EFS was 88±4.6% and 78±4.1%, respectively. The estimated 5-year OS for the standard, intermediate and high-risk groups were 94±5.7%, 93±3.1%, and 59±13%, respectively, and EFS was 94±5.7%, 86.6±4.2%, and 49.9±10%, respectively.

Conclusion: The OS and EFS for standard-risk and intermediate-risk groups were good and comparable to the literature. However, the current study's results should be confirmed in a larger patient population and a longer follow-up period.

Keywords: Children, acute lymphoblastic leukemia, event-free survival, overall survival

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Introduction

Cancer is the 4th most common cause of death in children aged 1 to 15 years old the following infections, heart diseases and accidents in our country (1). Childhood cancer is rare and its incidence is reported as 1/7,000 in children 15 years and younger. Although solid tumors are predominant in adults, hematologic malignancies such as leukemia and lymphoma comprise approximately 40% of childhood cancers (2). Acute leukemia constitutes 97% of all childhood leukemias, and 75-80% of these are acute lymphoblastic leukemia (ALL) (3).

Despite the increase in the prevalence of childhood malignancies, the 5-year survival rate in children with ALL has approached 90% in recent reports because of advances in chemotherapy and supportive care (4). Randomized controlled clinical trials, intensive chemotherapy combinations, central nervous system (CNS) prophylaxis, determining risk groups, and adjusting treatment intensity, and determining residual leukemia cells in the body called minimal residual disease (MRD) showed a significant increase in patients' life expectancy (5,6).

In our study, ALL patients who were diagnosed and treated between 2012 and 2017 in the Pediatric Hematology Oncology Clinic of Sultan Suleyman Training and Research Hospital, in Istanbul, were retrospectively screened. Demographic data, ALL cell type, the risk groups, CNS involvement, acute toxicity related to ALL induction treatment, bone marrow transplantation (BMT) status, relapse/mortality rates and overall survival (OS) and event-free survival (EFS) rates were evaluated.

Material and Methods

A total of 130 ALL patients diagnosed and treated between 2012 and 2016 at the Pediatric Hematology Oncology Clinic of Kanuni Sultan Suleyman Training and Research Hospital, Istanbul, were retrospectively examined. Patient data were obtained from the Turkish Pediatric Oncology Group records and electronic hospital medical records. One case with infant leukemia was excluded from the study and 129 ALL cases aged 1 to 17 years were evaluated. Patients with 25% or higher blast percentage in bone marrow aspiration were diagnosed with acute leukemia and immunophenotyping was used to define the ALL subtype. Bone marrow samples were painted with May Grünwald-Giemsa and were evaluated according to the FAB criteria. The CNS involvement was defined as ≥5 lymphoblasts/mm^3 in cerebrospinal fluid (CSF), and the presence of >10/mm^3 erythrocytes in CSF was considered traumatic lumbar puncture (LP). At the beginning of treatment, the patient was divided into risk groups according to age, leukocyte counts, absolute blast count in the peripheral blood on day 8, MRD level in bone marrow on day 15, t(4;11) and, t(9;22) at the time of diagnosis.

Standard Risk Group (SRG)

Patients aged ≥1 to <6 years at the time of diagnosis, an initial leukocyte count of <20,000/mm^3, patients with <1,000/mm^3 blasts in the peripheral blood on day 8, M1/M2 bone marrow in the bone marrow aspiration on day 15, MRD level <0.1% (complete remission) on day 15, without Ph+ (BCR/ABL+), and t(4;11) (MLL/AF4+) were classified in to the SRG.

High Risk Group (HRG)

Patients with absolute blast count of ≥1,000/mm^3 in the peripheral blood on day 8, or M3 bone marrow with ≥25% blasts on day 15, or FC MRD level more than 10% on day 15, or those with M2/M3 bone marrow on day 33, and, irrespective of treatment response, patients with Ph+ (BCR/ABL+), or t(4;11) (MLL/AF4+) or hypodiploidy (<45 chromosomes) classified in to the HRG.

Medium Risk Group (MRG)

All patients who were not stratified to the standard and HRG were classified in to intermediate risk patients (7).

Relapse Criteria

More than 25% blasts in the bone marrow after the achievement of remission with initial leukemia treatment, and extramedullary leukemia involvement in any site was considered a relapse. Relapse can be isolated bone marrow, CNS and testicular, and ≥2 sites of involvement defined as combined relapse. Relapse 18 months after initial diagnosis defined as very early relapse; defined as early relapse if relapse occurred ≥18 months after initial diagnosis and <6 months after the completion of initial treatment, and defined as late relapse if relapse occurred ≥6 months after the completion of initial treatment. Conditions such as encephalopathy and shock that developed unexpectedly during induction chemotherapy were considered acute toxicity. Overall survival was defined as the time from the date of diagnosis to death from any cause or last follow-up period, EFS was defined as the time from remission until the date of failure (induction failure, relapse or death) and last follow-up time.

Statistical Analysis

Kolmogorov-Smirnov and Lilliefors test was used to determine the distribution of data, and analysis of independent groups was performed by t-test and chi-square test. One sample t-test was used for the comparison of the

literature and the current study's data; OS and EFS were estimated using Kaplan-Meier method and compared with log-rank (Mantel-Cox) test. IBM SPSS 22.0 was used to analyze the study's data. The results are presented as mean ± standard deviation, median and range, and the level of statistical significance was set at $p<0.05$.

Results

There were 86 boys (67%), and 43 girls (33%) and the male/female ratio was 1/2. Three (3%) of male ALL patients and 2 (4%) of ALL female patients had Down syndrome (Trisomy 21). The median follow-up period was 25 months (range: 1-65 months). Mean age of the patients at the time of diagnosis was 6.5±4.3 years (range: 1-17 years). Although the mean age of the diagnosis was higher compared to the literature, no significant difference was found (comparison p=0.105 for 5.9). The mean age of male ALL patients and female ALL patients was 6.9±4.5, and 5.6±4.0, respectively, and there was no significant difference between gender (p=0.97). When evaluated according to risk groups, the highest mean age was found to be in HRG patients (8.3 years) (p=0.014).

According to FAB classification, 106 (82%) patients were B-cell ALL, 22 (17%) patients were T-cell ALL and 1 patient was mix type ALL. After the stratification of ALL patients according to risk groups; there were 76 patients (58%) in MRG, 36 patients (27%) in HRG, and 17 patients (13%) SRG. In the HRG ALL patients, there were 31 (36%) male ALL patients, and 5 female (11%) ALL patients (p=0.014) (Table 1).

While there was no difference between SRG and MRG patients when comparing the risk groups by age (p=0.07), there was a significant difference between HRG patients and both MRG and SRG patients (p=0.01 and p=0.04, respectively). There were no patients with CNS involvement in the CSF examination at the time of diagnosis. Four of the female patients and 3 of the male patients' LP were traumatic. Traumatic LPs were not found to differ by gender (p=0.68). Eight patients underwent BMT, 6 patients were male (75%), and 2 patients were female (p=0.71). Acute toxicity developed during induction therapy in 3 (2%) of 129 patients, including 1 patient with hepatic encephalopathy, 1 with septic shock, and 1 patient was admitted to the intensive care unit due to pulmonary hemorrhage, and all 3 patients eventually died.

Table 1. The distribution of cases by risk groups

	Standard risk	Medium risk	High risk	Total
Male	10	45	31	86
Female	7	31	5	43
Total	17	76	36	129

Three (2.3%) of the cases did not achieve remission during induction, only 1 out 3 patients entered remission after high-risk-1 blocks. Six patients (4%) relapsed. All of these patients relapsed in the first 18 months after diagnosis and were classified as very early relapses. One case relapsed from B-ALL, 1 switched from B-cell ALL to T-cell ALL, and the other one switched from T-cell ALL to B-cell ALL. One patient had CNS+ bone marrow relapse and the others had isolated bone marrow relapse. None of the relapsed patients had testicular involvement. Two patients who developed relapse died of the disease and 4 patients continued to be followed without disease. Two patients underwent BMT and were followed up without disease. AML was not seen in any of our cases as a secondary leukemia. Twelve patients (9.3%) died without disease, 5 (3%) of whom died from septic shock, 1 due to macrophage activation syndrome and 2 due to hepatic encephalopathy. One patient with hepatic encephalopathy had axonal neuropathy leading to permanent sequelae. Four patients died of leukemia and non-treatment causes. Three (2%) patients died of the disease, 2 (1.5%) of these patients died during post-relapse chemotherapy due to septic shock and one due to liver failure. In one of our patients, vincristine was discontinued during reinduction treatment because of severe toxicity.

The median follow-up period was 24 months (range: 1-65 months). Five-year estimated overall OS was 88±4.6%, and EFS was 78±4.1% (Figures 1, 2, 3, 4).

Estimated 5-year OS by gender was found as 93% in female patients, and 86% in male patients (Figure 3). Event free survival by gender was found as 84% in female patients, and 80% in male patients (Figure 4). There was no statistically significant difference between male and female cases in terms of 5-year estimated OS and EFS (p=0.21 and p=0.49, respectively).

Five-year estimated OS according to the risk group was 94%±5.7% in the SRG, 92.9±3.1% in the MRG and 59.3%±3.1 in the HRG patients, respectively (Figure 5). A statistically significant difference was found in the HRG patients for OS compared with SRG and MRG patients (p=0.01).

Estimated 5-year EFS was found to be 94%±5.7% in the SRG, 86.6% in the MRG and ±49.9% in the HRG (Figure 6). The EFS comparison between the risk groups was found to be statistically significant (p<0.001).

The overall OS and EFS rates of 7 patients with traumatic LP (Table 2) were both lower compared to patients without traumatic LP and the difference was significant for EFS comparison (p=0.203, p=0.039, respectively) (Figures 7, 8). In

Table 2. CNS involvement/traumatic LP status according to risk classification

	No CNS involvement	Traumatic LP	Total
Standard risk	17	0	17
Medium risk	73	3	76
High risk	32	4	36
	122	7	129

CNS: Central nervous system, LP: Lumbar puncture

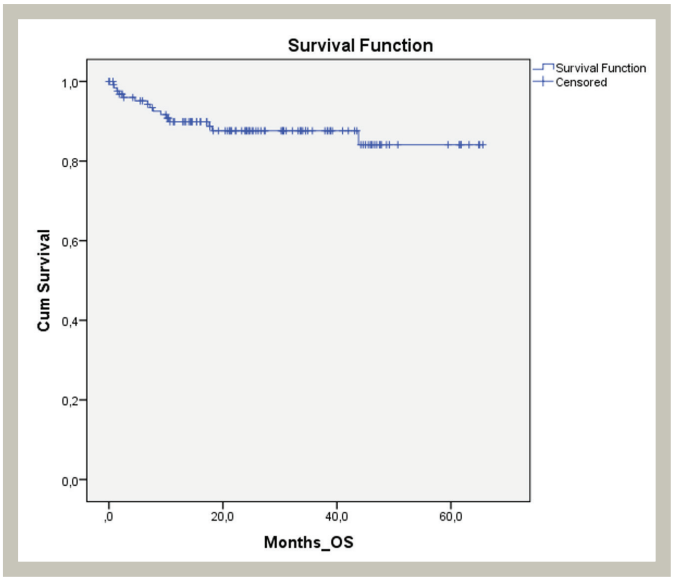

Figure 1. Kaplan-Meier curves of overall survival (OS) of all studied patient (n=129)

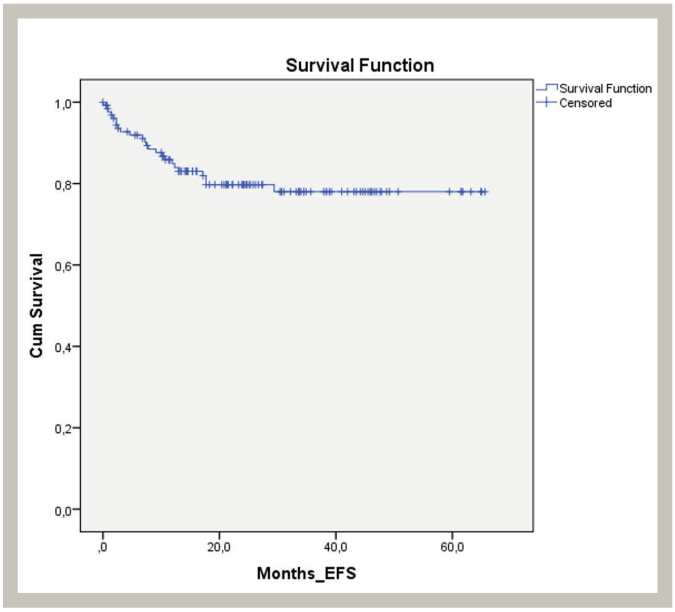

Figure 2. Kaplan-Meier curves of event-free survival (EFS) of all studied patients (n=129)

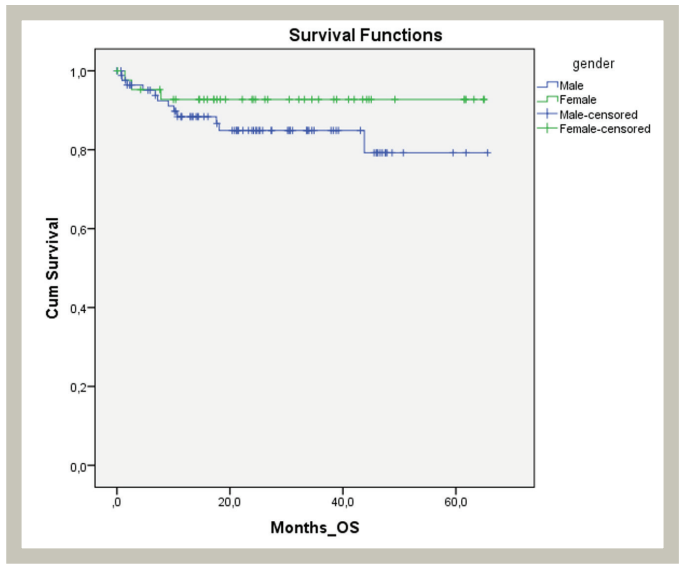

Figure 3. Overall survival (OS) of gender of male (n=86) and female (n=43) patients

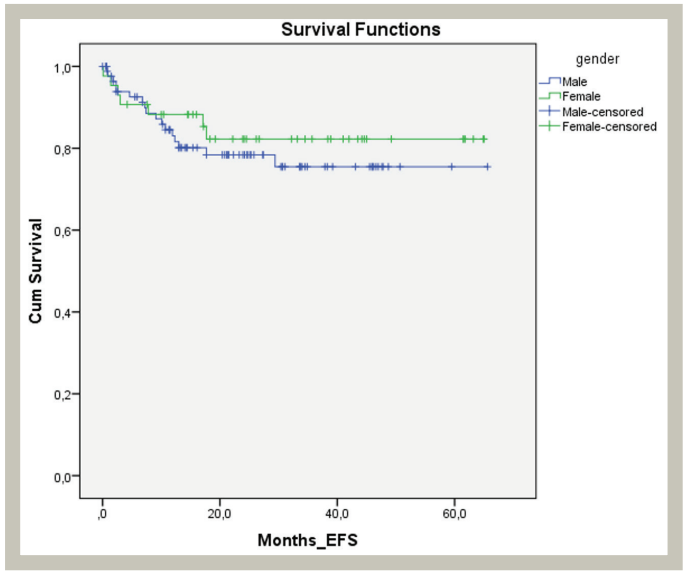

Figure 4. Event-free survival (EFS) of male (n=86) and female (n=43) patients

3 of these patients, 1 developed CNS relapse and 1 with T-cell ALL relapsed, 1 patient died disease-free and 1 patient died of the disease. There were more patients with traumatic LP in HRG patients, so the contribution of variables was compared with the Omnibus test and CNS involvement was found to be significantly higher in HRG patients ($p<0.05$). The main reason for the low survival of patients with traumatic LP was likely due to a high-risk group.

The 5-year estimated OS for B-cell ALL patients in our study was 83%, compared with 88% in patients with T-cell ALL ($p=0.631$) (Figure 9).

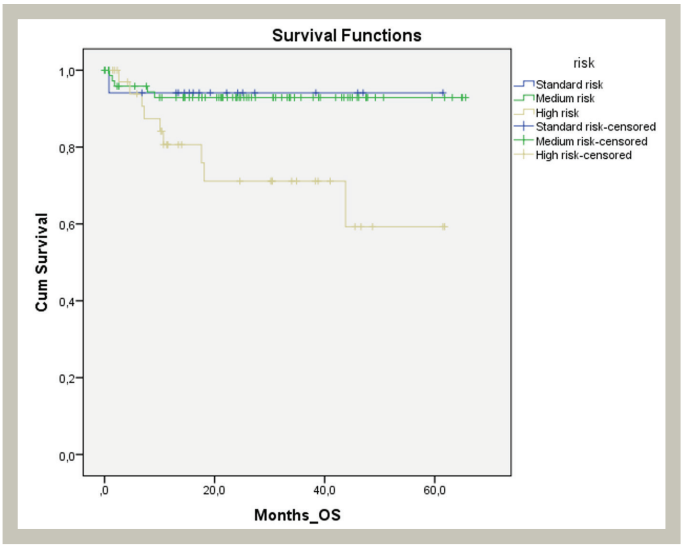

Figure 5. Kaplan-Meier curves of overall survival (OS) for the SRG (n=17), MRG (n=76), and HRG patients (n=36)
SRG: Standard risk group, MRG: Medium risk group, HRG: High risk group

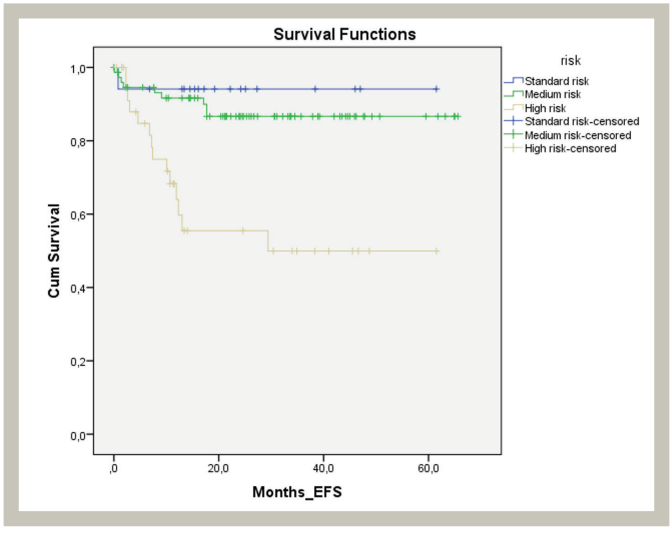

Figure 6. Kaplan-Meier curves of event-free survival (EFS) for SRG (n=17), MRG (n=76), and HRG patients (n=36)
SRG: Standard risk group, MRG: Medium risk group, HRG: High risk group

The 5-year estimated EFS for B-cell ALL patients in our study was 83%, while the EFS for T-cell ALL patients was 57% (Figure 10). Although the p value was close to 0.05, there was no statistically significant difference between the two groups (p=0.06).

Discussion

Leukemia is one of the most common malign diseases in children and accounts for 30% of all childhood cancers (8). Although it varies depending on genetic and environmental factors, ALL comprises 75% of newly diagnosed leukemias and

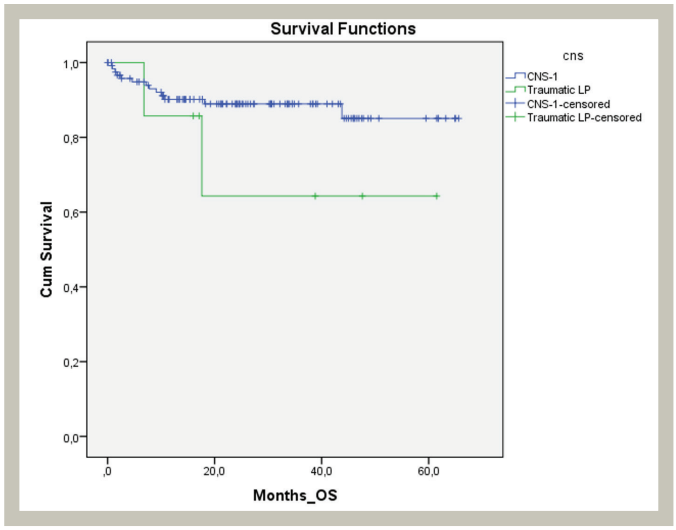

Figure 7. Overall survival (OS) curves of patients without CNS involvement and traumatic LP
CNS: Central nervous system, LP: Lumbar puncture

80% of acute leukemias (9). The incidence of acute leukemias in the United States is 3.4/100,000, while the annual incidence in Turkey is 3/100,000 (10). The incidence rate of ALL in Whites is higher (11). ALL usually develops as the first cancer, rarely developing in the form of secondary cancer (12).

The male/female ratio for ALL is generally reported to be around 1.2-2, and this ratio rises to 4 in T-cell ALL (13,14,15). In the study by Dujua and Hernandez (16) from the Philippines, the rate of male ALL cases was found to be 61.5%. In some studies conducted in our country, ALL was reported to be more common in male, while in some studies, it was reported to be more common in female (17,18). In our study, 86 of the 129 patients (66%) were male, 43 (33%) were girls and the male/female ratio was 2/1. In a study by Koc et al. (17), they reported a male/female ratio of 8/3 in T-ALL. In this study, 16 of 22 patients with T-cell ALL were boys and 6 were girls, and the male/female ratio was found to be 8/3, which was consistent with the literature.

Jabeen et al. (19) reported a mean age of 7.6±0.29 of 255 ALL patients who received BFM protocol. In a study from Turkey by Hazar et al. (18), the mean age of 142 ALL patients who received the TR ALL-2000 protocol was 5.9±4. In our study, the mean age of the ALL-patients was 6.5±4.3, which was higher compared to literature, however the difference was not statistically significant (p=0.105).

B-precursor cells account for 86% of ALL cases, and patients with this immunophenotpe generally enter a standard or intermediate risk group, with a better prognosis. T-cell ALL accounted for 13% of ALL cases. This subtype is associated with older age at presentation, high initial white cell count,

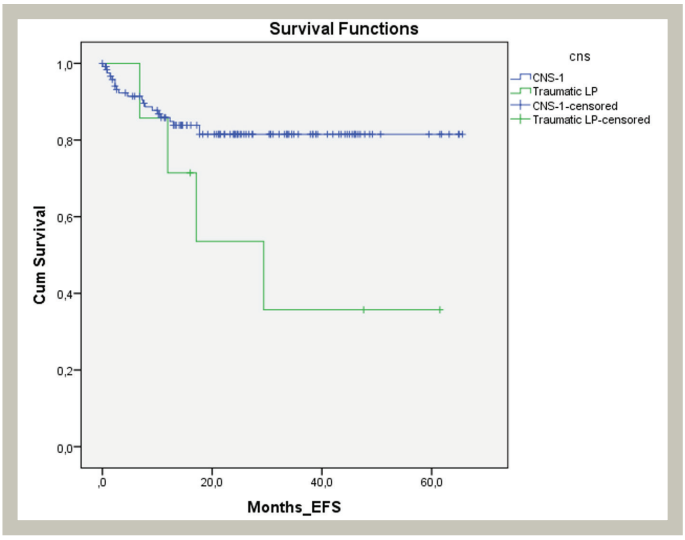

Figure 8. Event-free survival (EFS) curves of patients without CNS involvement and traumatic LP
CNS: Central nervous system, LP: Lumbar puncture

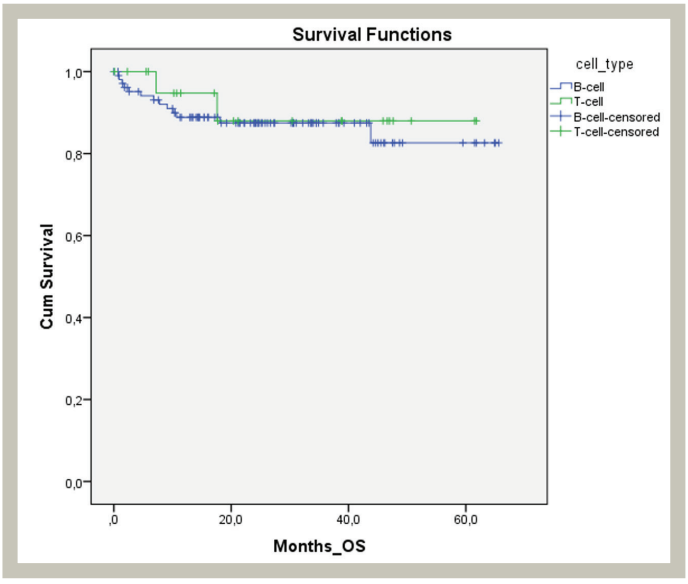

Figure 9. Overall survival (OS) curves of patients according to cell type

CNS involvement, mediastinal mass, and traditionally poor prognosis.

In a multicenter BFM study by Möricke et al. (20), immunphenotypic distribution of 2,169 ALL patients was reported as precursor B-cell ALL in 86.5% of the cases, and was reported as T-cell ALL in 13.3% of the cases. Jabeen et al. (19), reported a rate of 73%, 47%, 3%, and 17% for precursor B-cell ALL, T-cell ALL, mixed type ALL, and unidentified ALL, respectively. In the study by Hazar et al. (18) in Turkey, 78.9% of the cases were precursor B-ALL, 16.2% of were T-cell ALL, and 4.9% could not be defined. In another study from Turkey

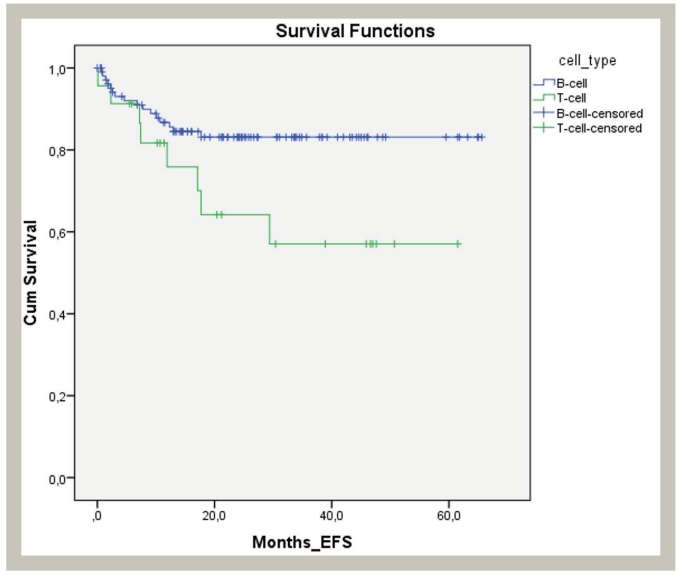

Figure 10. Event-free survival (EFS) curves of patients according to cell type

by Dogru (21), precursor B-cell ALL was found in 89.6% and T-cell ALL in 9.4% of the cases, and 1% was defined as bi-phenotypic. There were 106 cases (82%) of B-cell ALL, 22 (17%) of T-cell ALL, and 1 case (0.7%) of bi-phenotypic ALL in this study, which was consistent with the literature.

In the multicenter BFM study by Möricke et al. (20), 35% of patients were reported as SRG, 53% as MRG and 12% as HRG. In the studies of Hazar et al. (18), 38% of patients reported as SRG, 43.7% as MRG and 18.3% as HRG. In the study by Canbolat Ayhan et al. (22), 32% of ALL patients were in SRG, 45% were in MRG, and 22% were in HRG. In similar studies, 28%-36% of patients reported as SRG, 50%-61% as MRG, and 10%-14% as HRG (23,24). When our patients were evaluated according to risk groups, 13% of the patients in our study group entered SRG, 58% into MRG and 27% into HRG. Compared to the literature, in the current study, HRG patient rate was higher. We think that it was due to the higher mean age of the current study's patient group, as well as treatment response which were evaluated by blast count in the peripheral blood on day 8 and MRD analysis on the 15th day, was also worse.

Schmiegelow et al. (25) defined 14 severe acute toxic effects for childhood lymphoblastic leukemia treatment, which may occur at a frequency of ≤5%-10% during the leukemia treatment. However, they did not report the frequency of deaths that could be related to treatment toxicity (25). Koc et al. (17) reported a frequency of 12.5% acute toxicity, and that was 2% in our study. The low frequency of acute toxicity in the current study might be due to the use of antimicrobial prophylaxis and the supportive care given to the patients during the leukemia treatment. Since there is no detailed

information about the frequency of infections in the literature, a solid conclusion cannot be made in this regard. In this study, acute toxicity related to leukemia treatment was observed in 3 ALL cases (2%), which included hepatic encephalopathy, septic shock and pulmonary hemorrhage, and eventually led to death in all cases.

In a multicenter study by Schrappe et al. (26), induction failure was defined in 1,041 of 44,017 newly diagnosed ALL patients (2.4%). In our country, Orhaner (27), and Degirmenci (28) reported a frequency of 10%, and 3.1% induction failure, respectively. In our study, 3 (2.3%) of 129 patients had induction failure.

In various multicenter studies, the relapse rate in childhood lymphoblastic leukemia was reported to be between 14%-17.5% (16,20,29). In the studies from Turkey, childhood ALL relapse rate was reported to be between 11.5%-19.5% in patients treated with ALL BFM protocol, while Koc et al. (17) reported a 9% relapse rate in patients treated with St. Jude ALL protocol (28,30). In our study, very early recurrence developed in 6 patients (4%). The main reason for our lower relapse rates compared with the literature was the short follow-up period, especially for late relapses.

After the 1960s, the 5-year OS rate for childhood ALL has greatly increased over time (6). Pui et al. (31) reported a 5-year OS of 71.8% in 2000. Following this study, Hussein et al. (29) reported a 5-year OS of 75% in 154 pediatric cases with ALL in 2004, Schmiegelow et al. (32) reported a 5-year OS of 89% in 2007, and Liu et al.'s (33) reported a 5-year OS of 90.6% in 2014. In the results of the BFM-95 multicenter BFM-95 study conducted in our country between 1995 and 2006, the 5-year OS rate was reported as 80% (3). Koc et al. (17) reported a 5-year OS of 77.4% in 2013 from Turkey. In another study, 5-year OS for 256 pediatric ALL patients was reported as 77.4% (28). In our study, 5-year estimated OS was found to be 88%, which was higher than the literature. The possible reason for this might be the shorter follow-up period or the development in supportive treatments.

In addition to improvement in 5-year OS in childhood ALL over time, it was observed in EFS rates. In a 2000 study by Schrappe et al. (5), 6-year EFS was reported as 78%. Although similar drugs are used in various parts of the world, there are small to moderate differences in leukemia treatment protocols with different outcomes. Five-year EFS rates were reported as between 75 and 87% in children with ALL treated with various ALL protocols, including BFM-95, SJCRH-13A, DCOG-9, IC-BFM 2002 and MRC UKALL 2003 (31,32,33,34). Dujua and Hernandez (16) reported a 5-year estimated EFS of 86% in 2016, Takahashi et al. (35) reported a 5-year EFS of 78% in 2017 (16,33). Koc et al. (17) reported a 5-year EFS of 69% in 2012, Degirmenci (28) reported a 5-year EFS of 41.51% in 2016 from Turkey. In our study, 5-year estimated EFS was found to be 78%, which was compatible with the literature.

Male sex is reported as a poor prognostic factor in childhood leukemias (8). The 5-year OS for female and male pediatric ALL patients was reported as 86%, and 70%, respectively, by Hussein et al. (29). The 5-year OS for children with ALL was 76% in girls and 66% in boys in the study by Koc et al. (17). In our study, although the follow-up period was shorter, 5-year estimated OS was 93% in girls and 86% in boys. Möricke et al. (20) reported a 6-year EFS of 81% in girls and 78% in boys in 2,169 pediatric ALL patients treated with the BFM-95 protocol . In the multicenter study by Pui et al. (34), 5-year EFS was 76% in girls and 68% in boys. Takahashi et al. (35) reported a 5-year EFS of 79% for girls and 81% for boys. In a study conducted in Edirne, Turkey, 5-year EFS was reported as 81% in girls and 49% in boys (27). In our study, the 5-year of EFS was 84% in female ALL cases, and 80% in male ALL cases. The 5-year OS and EFS was higher in both boys and girls than that has been reported in the literature. This was likely due to a short follow-up time.

In the study by Takahashi et al. (35), 5-year of OS for SRG, MRG and HRG patients was 96%, 91%, and 81%, respectively. Five-year OS for SRG, MRG and HRG patients was reported as 81%, 79%, and 60%, respectively, in the south eastern region of Turkey (17). In our study, 5-year OS was found to be 94%, 93%, and 59%, for SRG, MRG and HRG patients, respectively, which was compatible with the literature.

In the study by Schrappe et al. (5), EFS rates for SRG B-cell ALL, MRG B-cell ALL, and HRG B-cell ALL, were as 85%, 82%, and 34%, respectively, in 2178 pediatric ALL patients treated by the BFM-90 protocol. In the Takahashi et al. (35) study, EFS rates were found as 87%, 78%, and 65% in SRG, MRG, and HRG patients, respectively. In 2012, Steel et al. reported a 100% EFS rate in SRG, a 57% EFS in MRG and a 55% EFS in HRG B-cell ALL patients, respectively, whereas Koc et al. (17) reported a 76% EFS in SRG, a 69% EFS in MRG and a 53% EFS in HRG B-cell ALL patients, respectively. In our study, 5-year EFS for SRG, MRG, and HRG B-cell ALL patients was found to be 94%, 87%, and 50%, respectively.

In the studies by Bajel et al. (36) and Jabeen et al. (19), CNS involvement rates in ALL were reported as 6.2% and 11%, respectively. There were no patients with CNS involvement in 78 ALL cases reported by Dujua and Hernandez (16). In our country, CNS involvement rate was reported as 1.4% in the studies of Hazar et al. (18). In this study, there were no

patients with CNS involvement at the time of diagnosis among pediatric ALL patients.

In recent pediatric ALL trials, 5-year EFS and OS for B-cell ALL is reported as more than 85% and more than 90%, respectively, however outcomes for T-cell ALL are still 5%-10% lower than B-cell ALL in most studies (37). Hussein et al. (29) reported a 5-year OS of 80% in B-ALL and a 5-yea OS of 60.2% in T-ALL. In the study by Schmiegelow et al. (32), 5 years EFS and OS for B-cell ALL and T-cell ALL were 90% and 66%, respectively. Horibe et al. (38) reported a 5-year OS of 90% in B-ALL patients. Takahashi et al. (35) reported a 92% OS in B-ALL and a 72% OS in T-ALL. In our study, 5-year OS for B-cell ALL was 83%, which was similar to the literature, whereas it was 88% in T-cell ALL, a high survival rate compared to literature, probably due to the small number of T-cell ALL cases and the short follow-up period.

Event free survival for B-cell ALL and T-cell ALL was reported between 72 and 80% and 47%-62%, respectively, in various studies (29,35,38). In our country, Orhaner (27) reported a 70% EFS in B-cell ALL and a 50% EFS in T -cell ALL. In this study, 5-year estimated EFS for B-cell ALL was 83%, and was 57% in T-cell ALL. In the T-cell ALL, a high rate of EFS could not be achieved due to relapse and secondary leukemias.

Study Limitations

There are some limitations to the current study. First, it was a retrospective study a relatively small number of patients. A significant part of the patient data was obtained from patient files. Second, the follow-up time is short. Despite these limitations, we believe that this study's results are important in terms of being the first study of our pediatric hematology and oncology clinic to reveal treatment and toxicity outcomes in patients with ALL.

Conclusion

This study showed that the acute toxicity rate associated with childhood ALL treatment in our center was low with the current median follow-up period. The survival of children with ALL who were classified in standard and intermediate groups were good. However, the current study' results should be confirmed in a larger patient population and in a longer follow-up period.

Ethics

Ethics Committee Approval: Ethics Committee approval was obtained from the University of Health Sciences Turkey, Kanuni Sultan Suleyman Training and Research Hospital (no: 2018/03, decision no: KAEK/20 l8,3,24).

Informed Consent: Informed consent was obtained.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: A.A., Design: A.A., Data Collection or Processing: O.Ö., A.A., S.T., E.P.U., M.G., C.B., Analysis or Interpretation: O.Ö., A.A., Literature Search: O.Ö., A.A., Writing: O.Ö., A.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL ARTICLE

59

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Evaluation of the Adequacy of Blood Mixing by Echocardiographic Parameters in Neonates with the Transposition of Great Arteries

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What is known on this subject?

Transposition of the great arteries is hemodynamically one of the most significant congenital heart diseases. Echocardiography is the most important non-invasive diagnostic tool to evaluate the transposition of great arteries.

What this study adds?

Balloon atrial septostomy requirements of patients with transposition of large arteries can be predicted by evaluating new echocardiographic parameters.

ABSTRACT

Objective: Transposition of the great arteries (TGA) is one of the major causes of cyanotic heart disease in neonates and should be treated surgically in the early stages of life. In these patients, adequate blood mixing between systemic and pulmonary blood flow is required until surgery, and interatrial communication plays a major role during this period. This study aimed to evaluate the echocardiographic factors used to predict adequate interatrial communication with echocardiographic data.

Material and Methods: This study included newborn patients (who were) followed up in the pediatric cardiac intensive care unit with the diagnosis of simple TGA between August 1, 2020, and February 1, 2021. Patients were classified into those who underwent balloon atrial septostomy (BAS) (group I) and those who did not undergo BAS (group II). The atrial septal defect (ASD) size, interatrial septum (IAS) length, peak/mean interatrial pressure gradient, transverse diameter of the left atrium (LA), transverse diameter of the right atrium (RA), and the following ratios; ASD/IAS, LA/RA, mitral/tricuspid valve annulus, peak gradient of ASD/ASD diameter and ASD diameter/(LA: RA ratio) were calculated echocardiographically. The results were evaluated statistically.

Results: Eighteen patients were included (6 patients in group I and 12 patients in group II) during the study period. The median age was 3 days (interquartile range 2 days-7 days). 50% of the cases were male, and 50% were female. ASD peak gradient, ASD mean gradient, ASD peak gradient/ASD diameter, and LA: RA ratios were significantly higher, and ASD size, ASD diameter/(LA: RA ratio) were significantly lower in the group I compared in group II ($p<0.05$). ASD diameter/(LA: RA ratio) was found to independently predict the need for BAS with a cut-off value of 2.7 by multivariate analysis.

Conclusion: The echocardiographic measurement of ASD diameter/(LA: RA ratio) in TGA patients may be helpful in the prediction of BAS requirement.

Keywords: Newborn, transposition of great arteries, echocardiography, balloon atrial septostomy

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Introduction

Transposition of the great arteries (TGA) is one of the most common cyanotic congenital heart diseases in newborns. Today, the treatment of choice is an arterial switch operation in the newborn period (1).

There is a parallel circulation in fetal life, and the transition to a serial circulation occurs after birth. In cases with a diagnosis of TGA, this transition may have adverse effects on the baby. If mixing at the atrial, ventricular, or ductal levels is inadequate, hypoxia and metabolic acidosis that will occur until the operation is performed will lead to the death of these babies (2,3).

Prostaglandin E1 (PGE1) is widely used in many centers to increase this mandatory mixing. However, this treatment may not be enough for a sufficient increase in cerebral oxygen saturation values, especially in patients with restrictive interatrial communication.

Balloon atrial septostomy (BAS) is one of the preferred methods for reducing hypoxemia and mortality. However, some studies have reported that the procedure increases the risk of stroke (3).

In patients with TGA, inadequate mixing should be evaluated with various clinical and laboratory methods until the arterial switch operation. A profound cyanosis is a sign of poor mixing. Therefore, blood oxygen saturation is a helpful parameter for showing the septostomy requirement in these patients (3,4,5,6).

Echocardiography is a widely available, simple, affordable, non-invasive diagnostic tool for managing congenital heart diseases. It provides data about blood mixing in different levels of the heart and vessels, especially in patients with TGA. Interatrial communication plays a key role in this regard (6,7).

This study evaluates the factors that predict adequate interatrial communication by using echocardiographic data.

Material and Methods

This study was conducted retrospectively on newborns diagnosed with simple TGA and hospitalized in our hospital's pediatric cardiac intensive care unit between August 1, 2020, and January 31, 2021. Premature, patients older than one month old, and patients with complex TGA (presence of hemodynamically significant ventricular septal defect, pulmonary stenosis, aortic arch hypoplasia, or aortic coarctation) were excluded from the study. The study was conducted in accordance with the Declaration of Helsinki and was approved by the University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital Local Ethics Committee (2022.04.143).

The patients were grouped into two categories: Those who underwent BAS (group I) and those who did not (group II). Each group was evaluated regarding demographic characteristics, oxygen saturation, blood lactate levels and echocardiographic measurements.

Echocardiographic evaluations were performed using the Philips Affiniti 50 cardiac ultrasound system (Philips Affiniti 50 Cardiac Ultrasound, Bothell, WA, USA) with a 9-MHz probe. In patients who required BAS, the last echocardiographic acquisition just before the BAS was reviewed.

A standard pediatric transthoracic echocardiographic imaging study with a segmental approach was conducted, including parasternal, apical, subcostal and suprasternal windows. Atrial situs, systemic and pulmonary venous returns, atrioventricular concordance, ventricles, ventriculoarterial concordance, the spatial position of great arteries, septal defects and extracardiac vascular anomalies were reviewed, respectively. Following echocardiographic parameters were measured for study: Atrial septal defect (ASD), interatrial septal (IAS) length, peak/mean interatrial pressure gradient, transverse diameter of the left atrium (LA) and right atrium (RA), diameter of mitral and tricuspid annulus, ductus arteriosus (DA). All measurements were performed in subcostal bicaval view for ASD and IAS, apical four chamber view for LA, RA, mitral and tricuspid annulus, and suprasternal view for DA. Additionally, ASD/IAS, LA/RA, mitral/tricuspid annulus ratios, the ASD peak gradient/ASD diameter and ASD diameter/(LA: RA ratio) were calculated (Figure 1a, b).

Statistical Analysis

The distribution of variables was analyzed in a computer environment. Descriptive values were obtained using the SPSS (Statistical Package for the Social Sciences for Windows) software package and expressed as median [interquartile range (IQR)] and percentage-percentile values. Pearson's chi-squared and Mann-Whitney U tests were used to compare the variables between groups. Multivariate analysis was carried out using logistic regressions. The BAS requirement is used as the dependent variable. The covariates were the mean interatrial pressure gradient, ASD diameter/(LA: RA ratio) and ASD peak gradient/ASD diameter. Receiver-operating characteristic curves were constructed, and areas under the curve were calculated. Sensitivities and specificities were determined to identify patients requiring BAS. A p value of <0.05 was considered statistically significant.

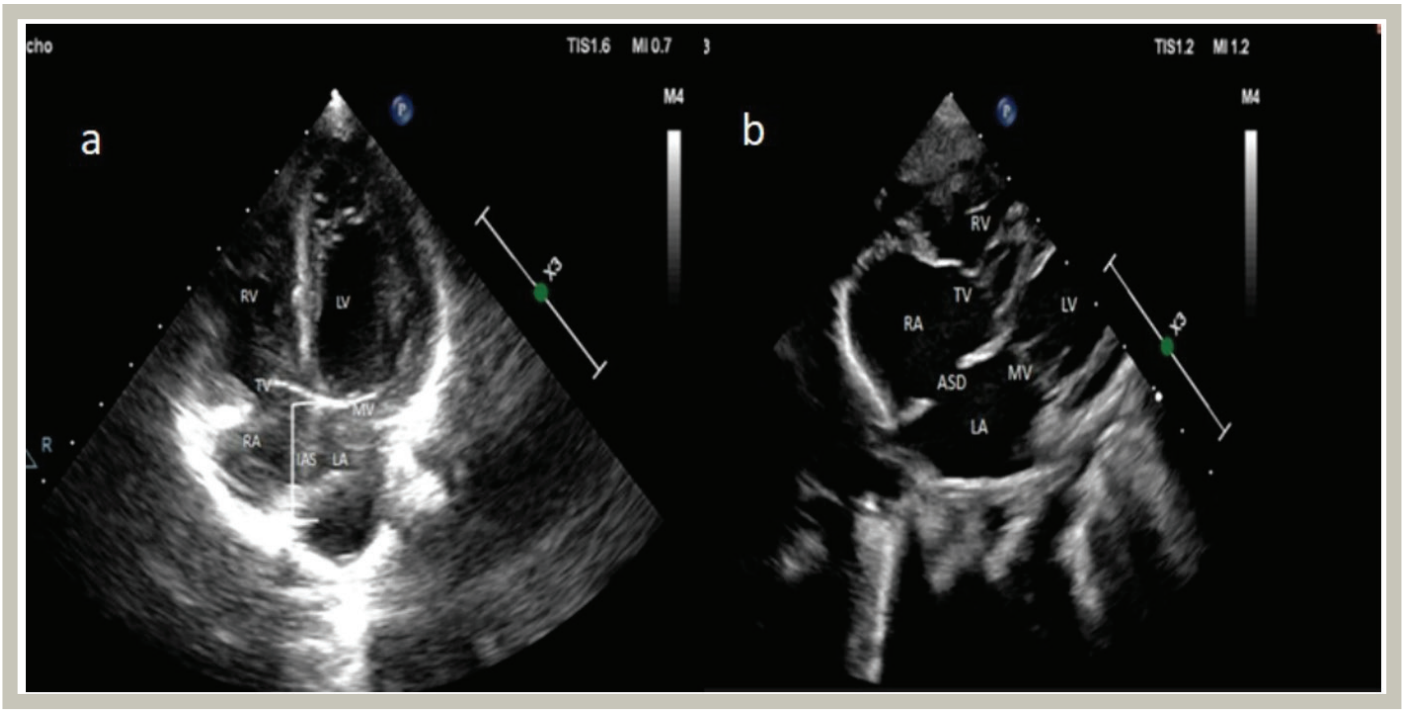

Figure 1a, b). Ten days old male patient with transposition of the great arteries. a) Modified four chamber view on echocardiographic examination, b) modified subcostal chamber view on echocardiographic examination

ASD: Atrial septal defect, IAS: Interatrial septum, LA: Left atrium, LV: Left ventricle, MV: Mitral valve, RA: Right atrium, RV: Right ventricle, TV: Tricuspid valve

Table 1. Demographic features of the patients

	Group I (BAS +) n=6	Group II (BAS -) n=12	p
Gestational week (week)	39 (38-40)	39 (38-40)	NS
Gender (male)	3 (50)	6 (50)	NS
Weight (kg)	3.2 (2.9-3.3)	3.1 (3-3.2)	NS
Prenatal diagnosis (yes)	1 (16)	3 (25)	NS
Saturation (%)	65 (60-72)	81 (78-85)	0.001
Lactate (mmol/liter)	5 (4.5-7)	1.6 (1.2-3)	0.001
Echocardiography time (hours)	8 (6-10)	30 (24-36)	0.030

n (%) or median (IQR). BAS: Balloon atrial septostomy, IQR: Interquartile range, NS: Not significant

Results

There were eighteen patients, six of whom were in group I (underwent BAS) and twelve in group II (without BAS). Fifty percent of the cases were male, and the median weight was 3 kg (IQR 2.8-3.4 kg).

Patients' characteristics are summarized in Table 1. In group I, the oxygen saturation at the time of echocardiography was significantly lower, and the peak blood lactate level was considerably higher than that in group II ($p<0.05$).

Echocardiographic measurements according to group are summarized in Table 2. ASD peak gradient, ASD mean gradient, ASD peak gradient/ASD diameter, and LA: RA ratio were significantly higher, and ASD size, ASD diameter/(LA: RA) ratio was significantly lower in the group I compared to group II ($p<0.05$).

A multivariate logistic regression test was performed on the parameters, which were found to be significant after univariate analysis. The ASD diameter/(LA: RA ratio) result could predict the need for BAS (Odds ratio: 6.1, confidence interval: 2-14.5, $p=0.02$).

In the receiver operating characteristic curve analysis, the ASD diameter/(LA: RA ratio) predicted the need for BAS with a cut-off value of 2.7 (Figure 2).

Table 2. Evaluation of the echocardiographic parameters

	Group I (BAS +) n=6	Group II (BAS -) n =12	p
ASD diameter (mm)	3.0 (2.5-3.5)	5 (4.5-6)	**0.001**
Interatrial septum length (mm)	18 (16-20)	17 (14-19)	NS
ASD diameter/IAS length	0.2 (0.1-0.3)	0.40 (0.3-0.45)	NS
ASD peak gradient (mmHg)	12 (10-14)	4 (2-6)	**0.020**
ASD peak gradient/ASD diameter	3.5 (3-4)	1.3 (1-1.5)	**0.010**
ASD mean gradient (mmHg)	5 (4-6)	2 (1-3)	**0.006**
Presence of IAS aneurysm	2 (34)	5 (40)	NS
LA transverse diameter (mm)	16 (15-17)	15 (14-16)	NS
RA transverse diameter (mm)	14 (13-15)	15 (14-17)	NS
LA/RA ratio	1.1 (0.9-1.2)	1.0 (0.8-1.1)	**0.012**
ASD diameter/LA: RA ratio	2.7 (2.5-3)	6 (5-7)	**0.001**
MV annulus (mm)	10 (9-11)	10 (9-11)	NS
TV annulus (mm)	11 (10-12)	12 (11-14)	NS
MV/TV annulus	0.8 (0.6-1)	0.9 (0.8-1.1)	NS

n (%) or median (IQR). ASD: Atrial septal defect, IAS: Interatrial septum, LA: Left atrium, MV: Mitral valve, NS: Not significant, RA: Right atrium, TV: Tricuspid valve

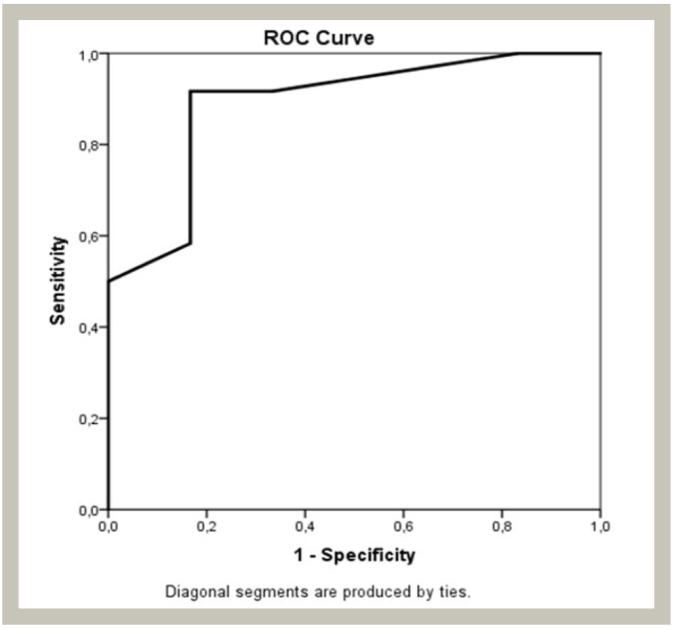

Figure 2. ROC analysis of ASD diameter/(LA: RA), showing an AUC of 0.85 (95% CI 80-92%; p=0.003), with a sensitivity of 92% and a specificity of 88%

ROC: Receiver operating characteristic curve, ASD: Atrial septal defect, LA: Left atrium, RA: Right atrium, AUC: Area under the ROC curve, CI: Confidence interval

Discussion

In this study, we attempted to determine the echocardiographic parameters that predict BAS requirements in newborn patients diagnosed with TGA. In those requiring BAS, peak and mean gradient through ASD, ASD peak gradient/ASD diameter ratio, and LA to RA ratios were significantly higher. In contrast, ASD size and ASD diameter/(LA: RA) ratios were significantly lower. An ASD diameter/(LA: RA) ratio of 2.7 was the optimal cut-off point for predicting the need for septostomy. Our study is one of the limited studies conducted in the literature with these features.

TGA is hemodynamically one of the most significant congenital heart diseases. Both patients with antenatal diagnosis and postnatally diagnosed newborns should be followed up in the intensive care unit to monitor postnatal changes due to the transition from parallel to serial circulation. It is necessary to protect the babies against the adverse effects of hypoxemia until the surgery. PGE1 and/or BAS may be required for this purpose. The most critical passage in considering the blood mixing is through interatrial communication (5,6,7,8). In our study, 22% (n=4) of all patients had antenatal diagnoses, and 33% (n=6) required BAS.

Echocardiography plays an essential role in the management of critical congenital heart diseases. It is a radiation-free, reproducible, repeatable, and reliable diagnostic tool. Algorithms derived from echocardiographic measurements can be used in the management of congenital heart disease. For example, in cases of pulmonary atresia with an intact ventricular septum or borderline left ventricular patients, treatment decisions are usually based on echocardiographic Z score measurements (9,10).

Echocardiographic evaluation of the interatrial septum is crucial in newborns with critical congenital heart disease, such as hypoplastic left heart syndrome, total anomalous pulmonary venous return and TGA. Especially in patients with TGA, adequate interatrial communication provides a much better blood mixing than interventricular or ductal mixing. Restrictive atrial septal communication may quickly impair patients' hemodynamic status and lead to mortality. There is no consensus in the literature regarding which echocardiographic parameter best predicts restrictive interatrial communication. Some authors proposed that the mean gradient through ASD above 8 mmHg is restrictive, between 3 and 8 mmHg acceptable and below 3 mmHg is non-restrictive (11). Also, the largest ASD diameter smaller than 4 mm and peak velocity through ASD above 2 m/sec was considered restriction criteria in some studies (12). Others have suggested that clinical findings are more important than echocardiographic measurements in restriction decisions.

Muntean et al. (13) proposed a new echocardiographic parameter for estimating the need for BAS in the TGA. In their thirty-seven case series (21 patients with BAS), the LA/RA ratio, ASD diameter/(LA: RA ratio) and ASD peak gradient/ASD diameter was significantly elevated in those needing septostomy, whereas PDA size was not significant. The most important predictor of septostomy was ASD diameter/(LA: RA ratio) (cut-off 2.58).

In our study, the patients' clinical condition was the most important parameter for predicting septostomy. Our results are consistent with that of Muntean et al. (13). We found that the PDA diameter was not a significant factor and that ASD diameter/(LA: RA ratio) (cut-off 2.7) was the most important parameter.

Study Limitations

This study was conducted in a single center with a limited number of patients and was retrospective. Another limitation is that the echocardiographic measurements were performed retrospectively through the PACS system.

Conclusion

As a result, the BAS requirement of patients with TGA can be predicted by evaluating echocardiographic parameters such as ASD diameter/(LA: RA). However, multicenter studies involving more patients are required to confirm our findings.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and was approved by the University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital Local Ethics Committee (2022.04.143).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.C.T., Concept: E.Ö., Design: E.Ö., Data Collection or Processing: E.Ö., Analysis or Interpretation: E.Ö., İ.C.T., Literature Search: İ.C.T., Writing: E.Ö., İ.C.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL ARTICLE

65

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Asepsis Techniques Prior to Amniocentesis; Which Technique is Better?

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What is known on this subject?

Amniocentesis is the most common invasive technique used for prenatal diagnosis. Cutaneous asepsis before the procedure id a critical step for a safe procedure. There is no consensus or a standard for the asespsis technique before amniocentesis. We still do not know exactly which is better or may reduce the complications of the procedure.

What this study adds?

In this study, we have compared the results of the cases that the asepsis before amniocentesis was made by different techniques and we did not find a significant difference between the techniques. We conclude that the asespsis technique choice may depend on the basal risk of the pregnant women.

ABSTRACT

Objective: The aim of this study was to analyze the indications of second-the trimester amniocentesis in a tertiary center and evaluate the difference between aseptic techniques before amniocentesis.

Material and Methods: The study sample was drawn from the patients who had amniocentesis between 16th and 22th weeks of pregnancy at Trakya University high-risk pregnancy unit between 2015 and 2018. The patients were divided into two groups according to the antiseptic solutions, which used before the operation. Group I comprised of patients in whom 10% povidine- iodine solution was used for aseptic skin preparation. Group II consisted of patients in whom 10% povidine- iodine solution with 70% isopropyl alcohol solution was used.

Results: One hundred fifty eight patients were in group I and took 10% povidine- iodine solution was used for aseptic skin preparation before the procedure and 119 (42.9%) patients were in group II and 10% povidine-iodine +2% chlorhexidine gluconate were used for skin preparation. There were no fetal loss in either group. Two patients (0.7%) in group II was admitted to the hospital in the first week after amniocentesis with increased vaginal discharge and slight abdominal pain.

Conclusion: Although the lack of evidence for the superiority of any asepsis technique, a combination of aseptic solutions may be an option for the patients with a high risk of fetal loss.

Keywords: Amniocentesis, povidone iodine, chlorhexidine, fetal loss, amniotic leakage, vaginal discharge

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Introduction

Amniocentesis was first introduced in the 1950s for sex determination, and was applied to clinical practice in 1966 to obtain fetal cells for karyotyping (1). During the last 30 years, clinical indications of amniocentesis were increased by new screening tests. Advanced maternal age and a positive screening test for aneuoploidies are the most common indications of amniocentesis.

The safety of the procedure has been assessed by several trials (2,3,4,5,6,7). Reports of fetal loss due to amniocentesis differ greatly among authors, varying from 0.13 to 2.2%. New studies concluded that the procedure related fetal loss rate is are lower than that currently quoted for women (8).

The technique of amniocentesis and the experience of the operator are also important tools for the success of the procedure. In the transplacental route, the fetal loss rate of the procedure has been reported as 1.4% in a review of nine reports (9).

As a part of the amniocentesis technique, before the procedure, the operator cleans the abdomen with an antiseptic solution. Many kinds of antiseptic solutions have been used for this purpose and there is no clear evidence which antiseptic solution has better results.

In this study we have analyzed the indications of the second the trimester amniocentesis in the tertiary center and evaluate the difference between aseptic techniques and to find the best asepsis technique before the amniocentesis, if any.

Material and Methods

The study samples were drawn from the patients who had amniocentesis between 2015 and 2018 at Trakya University, Faculty of Medicine, Maternal-Fetal Unit. Pregnant was between 16 and 22 weeks of gestation. Ethical approval was undertaken from Trakya University, Ethic Committee (decision no: 04/26, date: 21.05.2018). Patiens consent was undertaken for the study. All procedures were performed by experienced operators with 22 gauge needle, under ultrasound guidance using commercially available real time machines (Voluson 730 Expert/Voluson E6, General Electric, Tiefenbach, Austria) with a 4-to-8-mHz probe (RAB 6D). The mean volume of the obtained amniotic fluid was 20 mL. Different solutions were used for skin preparation according to operator's choice. All the steps were recorded in the patient's file. Every patient was warned about the signs of fetal loss and ıt was advised to come to the hospital in cases of any bleeding, abnormal vaginal discharge, pain, or cramping. All patients were called by phone for controlling after two weeks.

Demographic data of the patients, indications for amniocentesis, and the route of the operation (non-placental-transplacental) were recorded. Patients with multiple pregnancy, known uterine anomalies, fibroids and cervical incompetence, history of three or more abortions in the first trimester and the second trimester miscarriages were excluded from the study. Women with serious maternal illness, morbid obesity and bleeding that occurred in last two weeks were also excluded from the study.

The patients were divided into two groups according to the antiseptic solutions that used before the operation.

Group I consisted of patients in whom 10% povidine-iodine solution was used for aseptic skin preparation.

Group II consisted of patients with 10% povidine- iodine solution and 2% chlorhexidine with 70% isopropyl alcohol solution were used.

The necessity of hospital visit before the control exam at the second week of the procedure was recorded. Pain, vaginal discharge and other complaints were questioned at the control exam and the fetus was controlled for fetal heart activity by sonography.

Fetal loss, amniotic leakage and the other complaints of the patiens were analysed in both groups.

Statistical Analysis

Statistical analyses were performed using the Number Cruncher Statistical System (NCSS 2007) (Kaysville, Utah, USA). Data were analyzed using descriptive statistical procedures (mean, median, frequency, standard deviation, minimum, and maximum). Student's t-test was done to compare normally distributed variables, while Mann-Whitney U test was used to compare variables, which were not normally distributed. Fisher's Exact test and Yates' continuity correction test were preferred to compare the data. $p<0.05$ was considered statistically

Results

During the study period 277 patients were fulfilled the inclusion criteria. mean maternal age was 32.3 (17-46) of the patients.

The indications for amniocentesis were triple test in 77 (27.7%) patients, triple test and the second trimester sonographic marker in 25 (9%) patients, triple test and advanced maternal age in 20 (7.2%) patients, sonographic findings and major anomalies in 86 (31%) patients, a double

test in 37 (13.3%) patients, non-invasive prenatal test in 5 (1.8%) patients, maternal request in 5 (1.8%) patients and advanced maternal age and sonographic marker in (113.9%) patients.

The remaining (3.9%) patients underwent amniocentesis because of genetic indications as familial genetic disorders and previously born of a child with a genetic anomaly.

The route, which used during the procedure was transplacental route in 75 (27.7%) patients and placental route in 202 (72.9%) patients.

Of 158 patients in group I, 10% povidine- iodine solution was used for aseptic skin preparation before the procedure and 119 (42.9%) patients were in group II and 10% povidine-iodine +2% chlorhexidine gluconate with 70% isopropyl alcohol solution were used for skin preparation.

There were no fetal loss in both groups. Two patients (0.7%) in group II were admitted to the hospital in the first week after amniocentesis with increased vaginal discharge and slight abdominal pain. In the vaginal examination, there were no signs of amniotic leakage, but amnisure tests were positive for amnion fluid. There was no amniotic leakage in the following observation at 24 h and was thought to have stopped spontaneously.

There were no statistically significant differences between the complaints and hospital visits of the groups during the follow-up. There were also no statistically significant differences between the clinical findings of the patients on the control exam day (Table 1).

Table 1. Findings of the patients after the procedure

	Group I (n=158)	Group II (n=119)	p-value
Amniotic leakage	2	0	NS
Pain	2	2	NS
Hospital visit before control	2	1	NS
Pathologic findings at the control visit	0	0	NS

NS: Not significant

Discussion

In this retrospective controlled study, we evaluated the solutions used for abdominal skin preparation before amniocentesis. In our study population, 10% povidine-iodine solution and 10% povidine- iodine solution and 2% chlorhexidine were used for skin preparation according to operator's choice.

There was no clear evidence for the superiority of one solution to oher and combination of solutions before amniocentesis. We also still do not know exactly that complications of amniocentesis may be affected by the asepsis technique.

The literature on the efficacy of these agents is conflicting. Some studies found alcohol-based chlorhexidine (0.5 2%) to be superior to povidone iodine 10% for cutaneous antisepsis (10,11).

Several studies report equal effectivity for these agents (12,13,14).

No difference has been found between 2% chlorhexidine and 10% povidine-iodine for skin disinfection with regard to costs, efficacy and side effects in a prospective randomized study (14).

The most important challenge of the amniocentesis is the risk of loss of a healthy fetus during a diagnostic test. So the factors, which increase the background risk of fetal loss after amniocentesis are critical. It has been reported thar advanced maternal age, bleeding in the current pregnancy and history of the three or more first trimester abortions and/or the second trimester miscarriages seem to be significant predisposing factors for fetal loss (15).

We have excluded the patients with a history of the three or more first trimester abortions and/or the second trimester miscarriages from our study. Bleeding during the current pregnancy was also an exclusion criterion.

Some studies on this topic have been reported but it is still unknown whether the choice of antiseptic solution impacts the fetal loss risk of amniocentesis.

The reduction of fetal loss has been reported with the change of aseptic procedure from 2% clorhexidine to more potent chlorapep (2% chlorhexidine and 70% isopropyl alcohol) from a retrospective cohort (16).

The bacterial flora of the abdominal skin was assessed by abdominal swabs and has been shown that 2%. Chlorhexidine with 70% isopropyl alcohol is superior to povidine- iodine for cleansing the maternal abdomen before amniocentesis (17).

In that study, no statistically significant difference was detected between baseline colony counts between the left and right side of each patient's abdomen before cleansing. Post cleansing colony counts were revealed that chlorhexidine is a more effective abdominal cleanser.

We do not know whether these findings affect the fetal and maternal side effects of amniocentesis.

In our study, we compared the clinical findings and adverse events in both groups for 15 days after amniocentesis that could be related to the procedure itself.

We found no significant differences in the clinical findings between the groups. Although it was found to be unsignificant, two cases of amniotic leakage occurred in group I. The complaints of these two patients were "increased vaginal discharge". We could not unable to see the leakage in the vaginal exam, but the amnisure tests of the patients were positive for amniotic leakage. The vaginal discharge stopped and the pregnancy continued in both cases. The patients were observed for 24 h and called for a control examination one week later The sonographic findings of amniotic volume, fetal cardiac activity and the other sonographic measurements of the fetuses were completely normal at the control examination. Maternal fever, infectious markers in the blood test and clinical findings of the pregnant were also evaluated and found as completely in normal ranges.

Despite the high ratio of good prognosis, transient amniotic leakage is an important event after amniocentesis because of the possible association with fetal loss and chorioamnionitis.

In the review of the literature, it was found that amniotic leakage is an uncommon complication of amniocentesis. Conservative management with bed rest seems to yield good results. If the leakage does not persist, spontaneous resolution usually occurs (18).

Transient amniotic leakage has been reported as 2% after fetoscopic laser coagulation for twin transfusion syndrome (19).

Prolonged residual effect and the bactericidal effect of chlorhexidine against *Staphylococcus* make it a preferable agent for cutaneous antisepsis; but there is no clear evidence for its superiority of for antisepsis before amniocentesis.

Study Limitations

In this study, we have retrospectively evaluated the cases of amniocentesis that met our inclusion criteria. In our study time interval 277 patients met the inclusion criteria of the study. One hundred fifty nine patients were in group I and 119 patients were in group II. The antiseptic solutions were the choice of the operator. We have found the details of the operations and the clinical findings on the control exam day from the patient's files. Thus, the study was meticulously selected but the sample size was small to evaluate the effects of antiseptic solutions because of the rarity of the complications.

Conclusion

To determine the superiority of the solutions to each other and combination of the solutions before the amniocentesis and to ro evaluate the relation of the amniotic leakage cases with antiseptic solutions, larger prospective studies are needed.

Nevertheless, it is logical to use a combination of both the antiseptic solutions especially in the patients who have a high background risk of fetal loss and infection.

Ethics

Ethics Committee Approval: Ethical approval was undertaken from Trakya University Ethics Committee (decision no: 04/26, date: 21.05.2018).

Informed Consent: Patiens consent was undertaken for the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: I.U.Ç., C.S., F.V., C.İ., H.S., S.E., Concept: I.U.Ç., C.S., F.V., H.S., S.E., Design: I.U.Ç., C.S., F.V., C.İ., S.E., Data Collection or Processing: I.U.Ç., C.S., S.E., H.S., Analysis or Interpretation: I.U.Ç., F.V., C.S., C.İ., Literature Search: I.U.Ç., F.V., C.S., S.E., H.S., Writing: I.U.Ç., F.V., H.S., S.E.

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Ultrasound-guided Breast Biopsy: Evaluation of the Correlation Between Radiologic and Histopathologic Findings

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What is known on this subject?

Image-guided breast biopsy is commonly used for diagnosis of breast lesions. Breast ultrasound (US), which is also used for screening purposes, is an important tool for guiding biopsies.

What this study adds?

Our findings demonstrate a high radiologic-histopathologic correlation rate in US-guided breast biopsy samples. We observed the highest discordance in Breast Imaging Reporting and Data System (BI-RADS) 4 lesions. Therefore, histopathological verification is necessary in patients with BI-RADS 4 lesions to exclude malignancy.

ABSTRACT

Objective: Image-guided breast biopsy is commonly used for diagnosis of breast lesions. Breast ultrasound (US), which is also used for screening purposes, is an important tool to guide biopsies. In this study, we evaluated the radiologic-histopathologic correlation in patients who underwent US-guided breast biopsy.

Material and Methods: A total of 126 biopsies from 116 consecutive cases were included. Patients' US and histopathological findings were retrospectively reviewed.

Results: All patients were female. Median age was 44±12 (range; 16-66 years old). Two patients (2%) had bilateral, 8 (7%) had multifocal lesions. Breast Imaging Reporting and Data System (BI-RADS) was used for 115 lesions (91%). Three cases (2%) were BI-RADS 2, 27% (n=34) BI-RADS 3, 35% (n=44) BI-RADS 4, 25% (n=32) BI-RADS 5 and 2% (n=2) BI-RADS 6. Eight biopsies composed of normal breast tissue, which had been scored as BI-RADS 3 or 4, were considered inadequate. More than one-third (37%; n=47) were malignant as 28% (n=35) were consistent with fibroepithelial lesions and 11% (n=14) with inflammatory lesions. Major radiologic-histopathologic discordance was observed in only 2 cases, while there was minor discordance in 14. Ten of the 14 cases (11%) with minor discordance were BI-RADS 4 lesions and minor discordance was more common for benign lesions (p=0.013).

Conclusion: Our findings demonstrate a high radiologic-histopathologic correlation rate in US-guided breast biopsy samples. We observed the highest discordance in BI-RADS 4 lesions, suggesting that histopathological verification is necessary in patients with BI-RADS 4 lesions to exclude malignancy.

Keywords: Biopsy, breast, histopathology, radiology, ultrasonography

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Introduction

Image-guided breast biopsy is commonly used for the diagnosis of breast lesions, especially for evaluation of lesions suspicious for malignancy. Breast ultrasound (US), which is also used for screening purposes, is an important tool for guiding biopsies. Although findings on imaging usually provide good insight into the breast masses, definitive diagnosis is made via histopathological examination, and inconsistencies between radiological and histopathological examination may occasionally occur (1,2,3,4).

In this study, we evaluated the radiologic-histopathologic correlation in patients who underwent US-guided breast biopsy.

Material and Methods

University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital Ethics Committee (no: KAEK/2021.11.262) approved the study protocol. Informed consent was unsought because of the retrospective nature of the study. A total of 126 biopsies of 116 consecutive cases whose biopsy samples had been evaluated in the Department of Pathology between June 1, 2020 and December 1, 2020, were included. Patients' US and histopathologic findings were retrospectively reviewed using the hospital information system.

Statistical Analysis

Statistical analysis was performed using the software SPSS Statistics, version 24.0 (Armonk, NY, IBM Corp.). In addition to descriptive analyses, χ^2 test was used to compare frequencies. $P<0.05$ was considered as statistically significant.

Results

All patients were female. Median age was 44±12 (range; 16-66 years old). Two patients (2%) had bilateral, 8 (7%) had multifocal lesions. Of the 126 biopsies that were evaluated, 63 (50%) were located in the right breast and 59 (47%) in the left.

Breast Imaging Reporting and Data System (BI-RADS) was used for the radiological evaluation of 115 lesions (91%). Eight biopsies scored as BI-RADS 3 or 4 on imaging were considered inadequate because they involved only normal breast tissue, i.e., failure rate was 6.3%. Three cases (2%) were BI-RADS 2, 27% (n=34) BI-RADS 3, 35% (n=44) BI-RADS 4, 25% (n=32) BI-RADS 5 and 2% (n=2) was BI-RADS 6. More than one-third (37%; n=47) were malignant as 28% (n=35) were consistent with fibroepithelial lesions and 11% (n=14) with inflammatory lesions (Table 1, Figure 1).

Major radiologic-histopathologic discordance was observed in only 2 cases, while there was minor discordance in 14. In two cases (2%) with major discordance, US findings had been interpreted in favor of fibroepithelial lesions, but the biopsy revealed invasive carcinoma (Figure 2). However, these cases had also been classified as BI-RADS 4, indicating a suspicion of malignancy. Ten of the 14 cases (11%) with minor discordance were BI-RADS 4 lesions and minor discordance was more common for benign lesions (p=0.013) (Table 2, Figure 3).

Discussion

Image-guided biopsy has become a major method in evaluation of the breast masses in the last two decades, and our findings demonstrate a high radiologic-histopathologic correlation rate in US-guided breast biopsy samples. As expected, several studies have shown that the use of classification systems such as BI-RADS increases the radiologic-histopathologic agreement in adult patients, although its utility in pediatric cases has still not been proven (5,6,7,8). Image-guided breast biopsy is particularly important in the early diagnosis of breast cancer. Currently, many institutions use BI-RADS classification system in the radiological evaluation of breast masses. However, although small, there is always a possibility of misdiagnose the patient based on radiological findings only, and this is the main reason for the multidisciplinary approach that combines the clinical, radiological and histopathological findings still being the gold standard for definitive diagnosis (1,2,3,4).

We observed major radiologic-histopathologic discordance in only 2 patients (2%), which is similar to previously reported. False negativity rates have been reported to be between 0.1% and 3.7% (1,9,10,11,12,13). The biopsy revealed invasive carcinoma in these two patients whose US findings had been interpreted in favor of fibroepithelial lesions. On the other hand, these cases had also been classified as BI-RADS 4 (suspicious for malignancy), supporting the high predictive value of BI-RADS classification.

There was minor discordance in 14 patients and 10 of these 14 cases had BI-RADS 4 lesions. Moreover, minor discordance was more common for benign lesions, especially for sclerosing adenosis. These findings indicate the tricky aspects of BI-RADS4 lesions, i.e., although the risk of malignancy is high for BI-RADS 4 lesions (14,15), lesions such as adenosis, intraductal papilloma, ductal hyperplasia may also demonstrate radiological characteristics that qualify for the BI-RADS 4 category. In such cases, magnetic resonance imaging may be helpful in the differential diagnosis (16).

Table 1. Detailed comparison of the radiologic and histopathological diagnoses given per the number of the biopsies

BI-RADS category (115 lesions; 91%)		Histopathologic diagnosis
BI-RADS 2 (benign)	2% (n=3)	Granulomatous mastitis (n=2) Periductulitis (n=1)
BI-RADS 3 (probably benign)	27% (n=34)	Fibroepithelial lesion (n=18) Mastitis (n=9) Fibrocystic changes (n=2) Inadequate (n=5)
BI-RADS 4 (suspicious)	35% (n=44)	Fibroepithelial lesion (n=12) Invasive breast carcinoma (n=9) Adenosis (n=7) Fibrocystic changes (n=4) Papillary neoplasia (n=3) Preneoplastic lesions (n=2) Plasmablastic lymphoma (n=1) Granulomatous mastitis (n=1) Fat necrosis (n=1) Microcalcification (n=1) Inadequate (n=3)
BI-RADS 5 (highly suggestive of malignancy)	25% (n=32)	Invasive breast carcinoma (n=31) Metastatic carcinoma of the lungs (n=1)
BI-RADS 6 (known biopsy-proven malignancy)	2% (n=2)	Invasive breast carcinoma (n=2)

BI-RADS: Breast Imaging Reporting and Data System

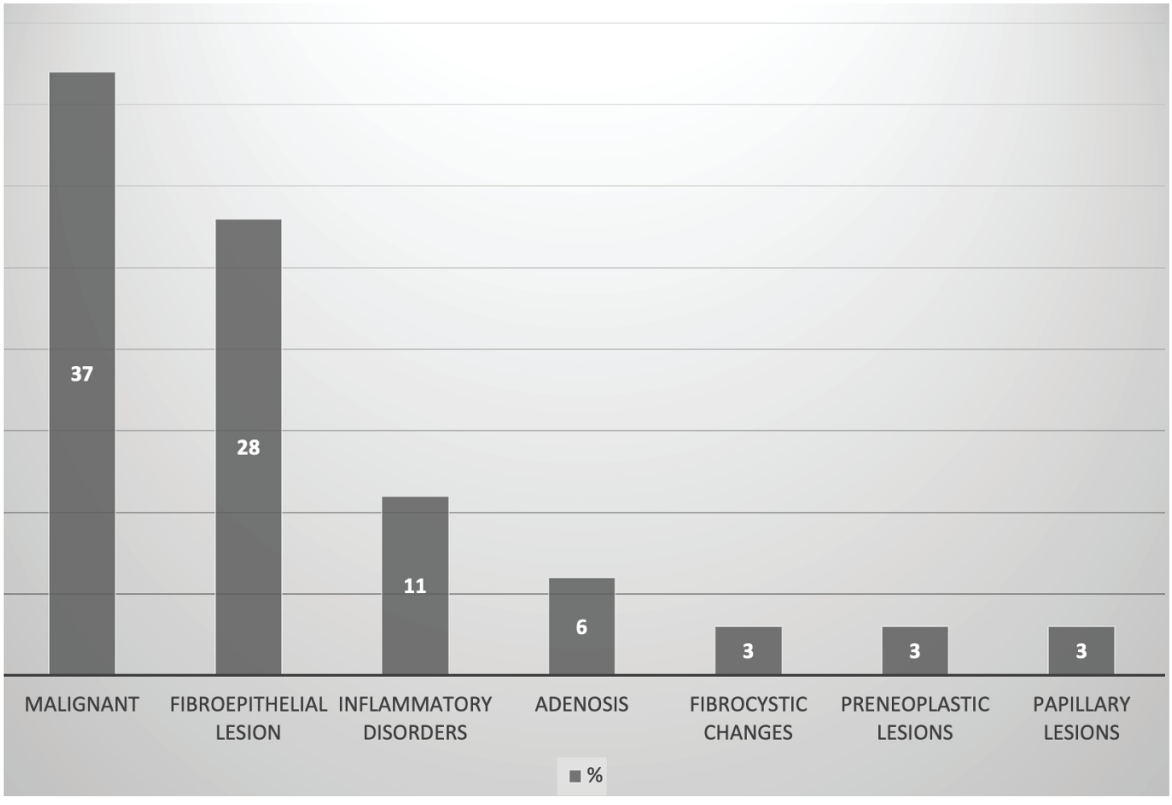

Figure 1. Distribution of the cases in the study group

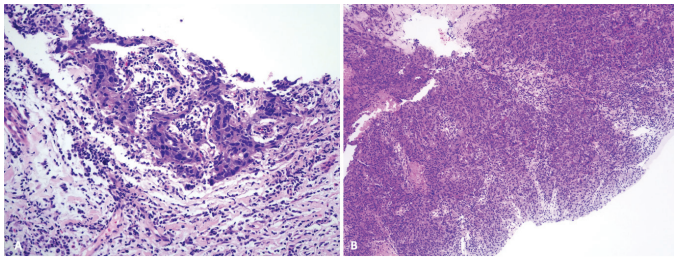

Figure 2. Two cases with major discordance. Biopsy revealed invasive carcinoma in these two patients. A) Invasive neoplastic glands with prominent nuclear atypia and B) a more cellular invasive breast carcinoma composed of sheets of tumor cells

Table 2. Histopathological findings in 14 patients with minor radiologic-histopathological discordance

BI-RADS category	Histopathological findings
3	Fibrocystic changes
3	Breast parenchyma fragments showing intraductal, periductal and stromal foamy histiocytic infiltration
3	Fibrocystic changes
4a	Ductal hyperplasia
4a	Fibrocystic changes
4	Granulomatous mastitis and abscess
4a	Adenosis and fibrocystic changes
4	Microcalcification in breast acini
4	Fibroepithelial lesion
4	Fibroepithelial lesion (consistent with benign Phillodes tumor)
4a	Adenosis and fibrocystic changes
4a	Fibroadenomatoid changes
4c	Adenosis
5	Intraductal papilloma with a focus of ductal carcinoma in situ

BI-RADS: Breast Imaging Reporting and Data System

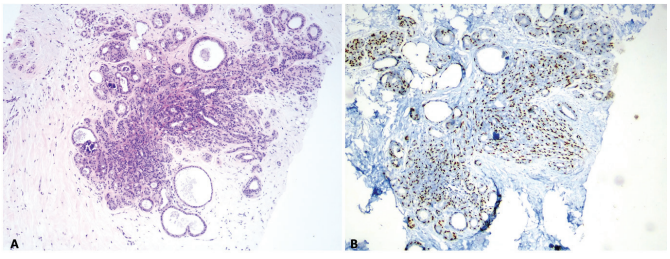

Figure 3. Sclerosing adenosis, which may be frequently mistaken for malignancy. A) Small tubules without significant cellular atypia embedded in a sclerotic stroma. Note the microcalcification in some of the tubules. B) P63 was positive in the myoepithelial cells of these tubules (immunohistochemistry)

Conclusion

In conclusion, considering that patient management will be carried out according to radiologic-histopathologic concordance, a multidisciplinary approach that combines the radiological and histopathological findings is of utmost importance in the management of patients with breast mass. Histopathological verification is necessary especially in patients with BI-RADS 4 lesions, to exclude malignancy or to avoid unnecessary surgery in patients with adenosis. Further investigation may be required in patients with radiologic-histopathologic discordance to adopt the optimal treatment strategy.

Ethics

Ethics Committee Approval: University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital Ethics Committee (no: KAEK/2021.11.262) approved the study protocol.

Informed Consent: Informed consent was unsought because of the retrospective nature of the study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.A.N., E.S., S.A., Concept: H.E., T.S.A., H.I.O., B.P., Design: H.E., T.S.A., H.I.O., B.P., Data Collection or Processing: H.E., T.S.A., H.I.O., B.P., Analysis or Interpretation: H.E., T.S.A., H.I.O., B.P., Literature Search: H.E., T.S.A., H.I.O., B.P., Writing: H.E., T.S.A., H.I.O., B.P.

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CASE REPORT

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Lovebird-induced Aspergillus Infection in a Child with Chronic Granulomatous Disease

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What is known on this subject?

Chronic granulomatous disease (CGD) is characterized by life-threatening bacterial and fungal infections.

What this case report adds?

Here, it is aimed to emphasize that pets may be a possible source of aspergillus infection in people with CGD and that surgically obtained tissue cultures may be required for diagnosis.

ABSTRACT

Chronic granulomatous disease (CGD) is a primary immune deficiency in which the phagocytic system is affected. The disease is inherited X-linked or autosomal recessive and is characterized by life-threatening bacterial and fungal infections. Invasive fungal infections are one of the most important causes of mortality in this disease. Here, we discuss an 8-year-old male patient with CGD considering literature. The patient developed invasive aspergillus infection due to the pet bird. Here, it is aimed to emphasize that pets may be a possible source of Aspergillus infection in people with CGD and that surgically obtained tissue cultures may be required for diagnosis.

Keywords: Aspergillosis, chronic granulomatous disease, diagnosis, treatment

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Introduction

Chronic granulomatous disease (CGD) is a primary immune deficiency affecting the phagocytic system via defects in the subunits of NADPH oxidase system. It is inherited through X-linked and autosomal recessive patterns (1,2). It is characterized by life threatening bacterial and fungal infections which affect the skin, respiratory tract, liver, brain, lymph nodes, and bones. The most common pathogens causing infections are *Staphylococcus* spp., *Klebsiella* spp., *Burkholderia* spp., *Serratia marcescens, Mycobacterium* spp., and *Aspergillus* spp. (2,3,4,5,6,7).

CGD has the highest prevalence of invasive fungal infections among the immune deficiencies. Invasive fungal infections are a major cause of mortality and morbidity in 20-40% of patients. Fungal infections often affect the chest wall and lungs. Most common pathogens are *Aspergillus fumigatus* and *Aspergillus nidulans*. Less frequently, infections with other *Aspergillus* spp. and other fungal strains such as *Mucormycetes*, *Trichosporon* spp., *Histoplasma* spp. have also been reported (8,9,10,11).

Aspergillus spp. are mainly found in soil, air, vegetation, and dead organic materials. The risk factors increasing the susceptibility to Aspergillus infections are warm and humid environment, poor ventilation and hygiene conditions, stored food for a long time, chronic diseases affecting the immune system, and long-term use of immunosuppressant drugs. Aspergillus spp. cause disease not only in humans, even in all domestic birds, waterfowl, wild and ornamental birds (12,13).

Case Reports

An eight-year-old male followed up with a diagnosis of autosomal recessive inherited CGD for seven years admitted to the hospital with a complaint of swelling in the back for a week. He had been suffering from night sweats, loss of appetite, weight loss and disseminated muscle pain for four months. The patient came to out-patient clinic follow-ups irregularly and was last seen 10 months ago. He was receiving co-trimoxazole and itraconazole prophylaxis. A physical examination revealed a pale, cachectic appearance. On the left scapula, there was an 8 x 10 cm sized non-fluctuating solid mass fixed to the underlying tissue. The first laboratory examinations revealed leukocyte as 12570/mm^3, absolute neutrophil as 8740/mm^3, eosinophils as 50/mm^3, hemoglobin as 10.1 gr/dL, etc. as 34.9%, platelet as 336000/mm^3, C-reactive protein as 105 mg/dL, and sedimentation rate as 49 mm/h. The chest radiography showed loss of ventilation in the left middle upper zone of the lung and marked periosteal reaction in the 3rd, 4th, 5th, 6th, 7th, and 8th ribs. Thoracic computed tomography (CT)revealed a subperiosteal abscess affecting 3rd-6th ribs and a solid lesion extending from the lung parenchyma below the skin (Figure 1). Initial culture samples (blood, gastric lavage) were obtained and broad-spectrum antibiotics (teicoplanin and meropenem) were started empirically. Afterwards, based on his anamnesis, probable Mycobacterial and fungal infections were prioritized since the patient's complaints slowly came out of a long time. Four anti-tuberculosis (TB) regimens (isoniazid, rifampicin, pyrazinamide, and ethambutol), caspofungin and voriconazole, were initiated. Following days, he had persistent fever above 39°C and new infiltration developed on the right lung. He rapidly developed into respiratory failure and transferred into an intensive care unit. Mechanical ventilation was initiated. Granulocyte transfusions were administered five times a week based upon critical clinic condition. After remaining on ventilator support for 15 days, the patient was disconnected from the ventilator

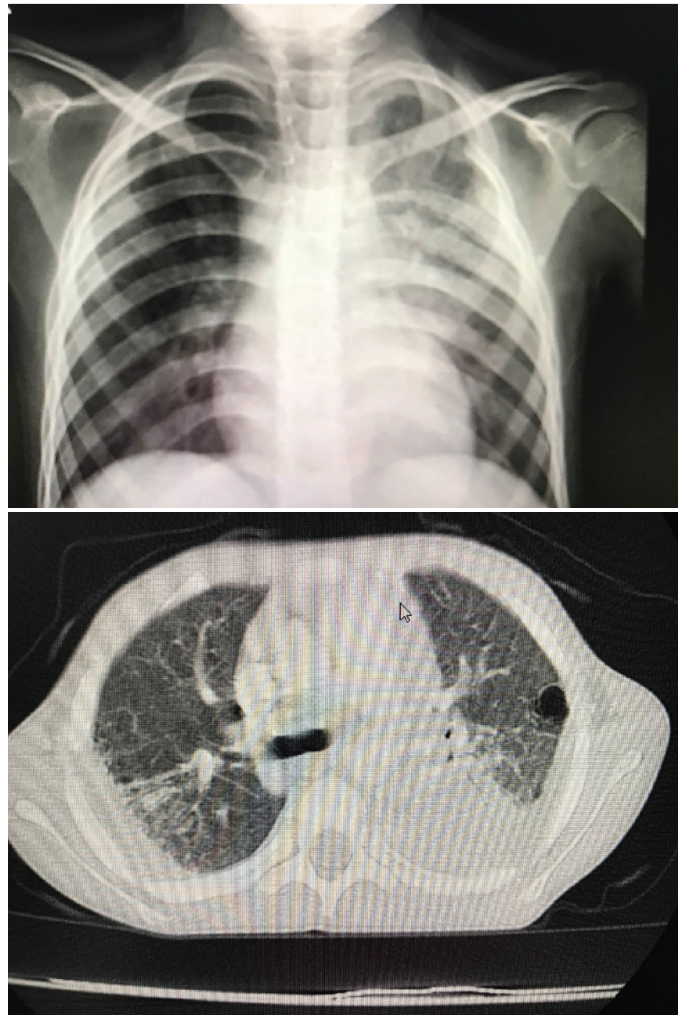


Figure 1. Chest radiography and thorax CT of the patient
CT: Computed tomography

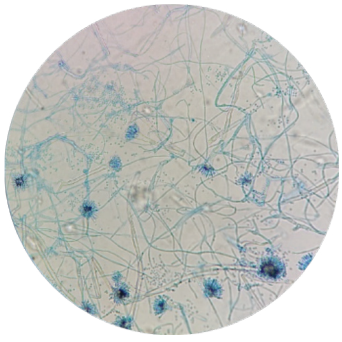
since his clinical findings recovered and the infiltration on the right lung regressed. During this period, the bacteria and fungi were not reproduced in the serial cultures; the acid-resistant bacilli were not detected in the gastric lavage samples; and serum galactomannan antigen was found negative. At the end of the first month of treatment, the chest CT scan showed that the infiltration in the left lung parenchyma was regressed, whereas the lesions in the ribs and subperiosteal abscess persisted. Because of thoracic surgery consultation, partial resection and drainage of the abscess were applied to the left third and fourth ribs, which were in the worst condition. Abscess material was sent for pathology and microbiological examinations (bacteria, fungi and mycobacteria). In addition to morphologically compatible findings with CGD, fungal hyphae and spores were observed with Grocott and periodic acid schiff staining in the histochemical examination, and the acid-resistant bacteria were not detected in Ehrlich-Ziehl-Neelsen staining. The fungal growth was shown in cultures. The typing studies indicated *Aspergillus terreus* that was sensitive to caspofungin and voriconazole. There was no growth in automatized (Bactec) and manuel (Löwenstein-Jensen medium) mycobacteria cultures. Initial antibacterial agents and anti-TB drugs were discontinued. The treatment was rearranged with antifungal drugs.

The patient's home condition was re-questioned for a predisposing factor for invasive fungal infection. His parents admitted that he had been keeping a love bird (*Nymphicus hollandicus*) for a year. The feathers of the bird were brought and inoculated on Sabouraud dextrose agar medium and incubated at 25 °C and 37 °C for 5-7 days. Lactophenol cotton blue was prepared from the colonies that grew when the incubation period was over, and the length of the conidia for, the shape and width of the vesicle, and the shape of the conidia were examined under the microscope (Figure 2). The same microorganism, *A. terreus*, was detected in the feathers of the bird (Figure 2). The demonstration of the same strain in the patient and the bird suggested that the infection might be transmitted from the animal. When this situation was shared with the family, the bird was taken to the veterinarian, treated and removed from the house.

We observed that the infiltration in the parenchyma completely regressed in control imaging under antifungal treatment. His general condition and oral intake improved and he began gaining weight. At the end of the third month of his treatment, he was discharged with voriconazole and itraconazole and co-trimoxazole, which he received as prophylaxis.

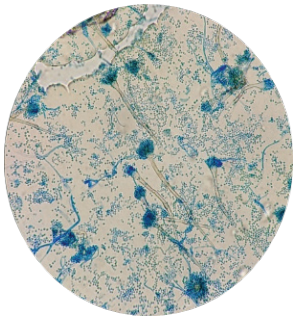
Discussion

Invasive pulmonary aspergillosis is one of the most important causes of death in patients with a suppressed immune system and CGD (14). Aspergillus causes airborne infections through its conidia, the respiratory tract being the most frequently affected area (14). Additionally, there may

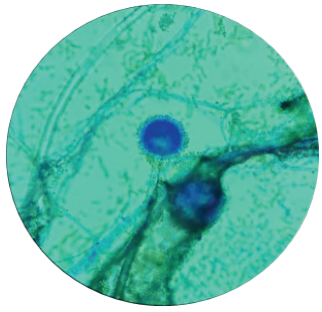


Aspergillus terreus

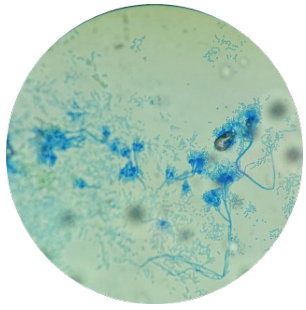
- The following culture growths were detected in the sampling made from the feather of the same patient, which he has fed at home.
- Domestic Bird Feather
- ***Aspergillus terreus***



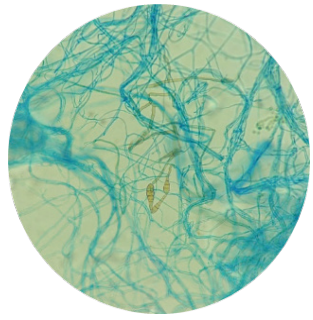
- Domestic Bird Feather
- ***Aspergillus terreus***



- Domestic Bird Feather
- ***Aspergillus niger***



- Domestic Bird Feather
- ***Penicillium* spp.**



- Domestic Bird Feather
- ***Alternaria* spp.**

Figure 2. Lactophenol cotton blue microscopy image of mold fungus growing in tissue biopsy culture

be widespread involvement in the central nervous system, liver, kidney, eye, and heart (3,14).

Although *A. fumigatus* is the most common type of opportunistic infection in humans, infections might occur with *A. flavus*, *A. niger*, *A. nidulans*, *and A. terreus* (1,3,14).

A. terreus is common in our environment like other species and causes invasive and disseminated infections as well as respiratory tract involvement (15). *A. terreus*-related infections occur worldwide, however they are more common in some geographical regions such as Innsbruck, Austria and Houston, USA (15). In an international prospective multi-center study, the prevalence of *A. terreus*-related infection among all fungal infections was reported as 5.2% (15). Our patient was diagnosed with immune deficiency and the involvement of the lungs and ribs due to *A. terreus* was detected.

For the diagnosis of invasive aspergillosis, both histopathological evidence and growth in a sample culture taken from a sterile tissue is required. In cases where biopsy is impossible, serum biomarkers such as galactomannan, beta-D-glucan, as well as direct staining and culture of the fungus from sputum and/or bronchoalveolar lavage fluid can be used (14). Galactomannan was found negative in our patient, and there was no growth in the tracheal aspirate and in the blood cultures. For this reason, material was taken from the lung tissue and cultured, and *Aspergillus* species was demonstrated in tissue cultures.

Effective treatment of invasive aspergillosis is possible with early antifungal initiation, immunomodulation, and, in some cases, surgical intervention (15). Given that Aspergillus infections are extremely fatal in immunocompromised patients, it is recommended to immediately initiate empirical antifungal treatment when suspected, and to revise the treatment based on an antifungal sensitivity test in confirmed cases. In proven Aspergillus infections, treatment should be continued according to the antifungal sensitivity test (14). We also started antifungal treatment in our patient empirically, without waiting for the culture results and continued in the same way when it was seen that he was responsive to the treatment he received according to the antifungal sensitivity test when there was a growth in the tissue culture. Despite contrasting reports, interferon-gamma (IFN-γ) has been found to be beneficial in these patients as an immunomodulator of both severe infections and prophylaxis (1). We could not apply IFN-γ for our patient because our order was not obtained due to a problem. Since we could not get enough clinical and radiological response despite regular antifungal treatment, partial resection of the two worst ribs and abscess drainage was performed.

Aspergillosis can be seen not only in humans but also in poultry. Particularly, all domestic birds, waterfowl, wild and ornamental birds can be affected by the disease. Young animals are more susceptible to disease, for which infections are acute and severe while the mortality rate is high. In older animals, the disease is characterized by atypical symptoms, and has a chronic and milder course. It has been reported that there occur frequent diarrhea, hair irregularity/loss, and weakening. The prognosis in animals is not known clearly due to inadequate and ineffective approaches in diagnosis and treatment (12,13). It can be transmitted from animals to humans. Although our patient was susceptible to aspergillosis because of his known immune deficiency, the inquiry of home conditions revealed his contact with a domesticated bird at home for a year that had long-term diarrhea and feather loss.

As a result, invasive aspergillosis is most commonly seen in individuals with a suppressed immune system and can be mortal. Considering the differential diagnosis, early and effective treatment is life-saving. While the treatment continues, home conditions and the existence of pets should be questioned. Families with immunocompromised individuals should be advised not to keep pets at home.

Ethics

Informed Consent: The patient's consent and signature were stored with hand writing.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Ç.A., S.Y., Design: Ç.A., Data Collection or Processing: Ç.A., A.G., S.K., Analysis or Interpretation: A.G., S.K., Literature Search: H.N., Writing: Ç.A., H.N., S.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Diffuse Bone Marrow Involvement of Langerhans Cell Histiocytosis Detected with F-18 FDG PET/CT

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What is known about this subject?

Importance of fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) imaging in langerhans cell histiocytosis (LCH).

What this clinical images adds?

FDG PET could detect unknown involvement site of LCH.

Keywords: Langerhans cell histiocytosis, FDG, PET, bone marrow

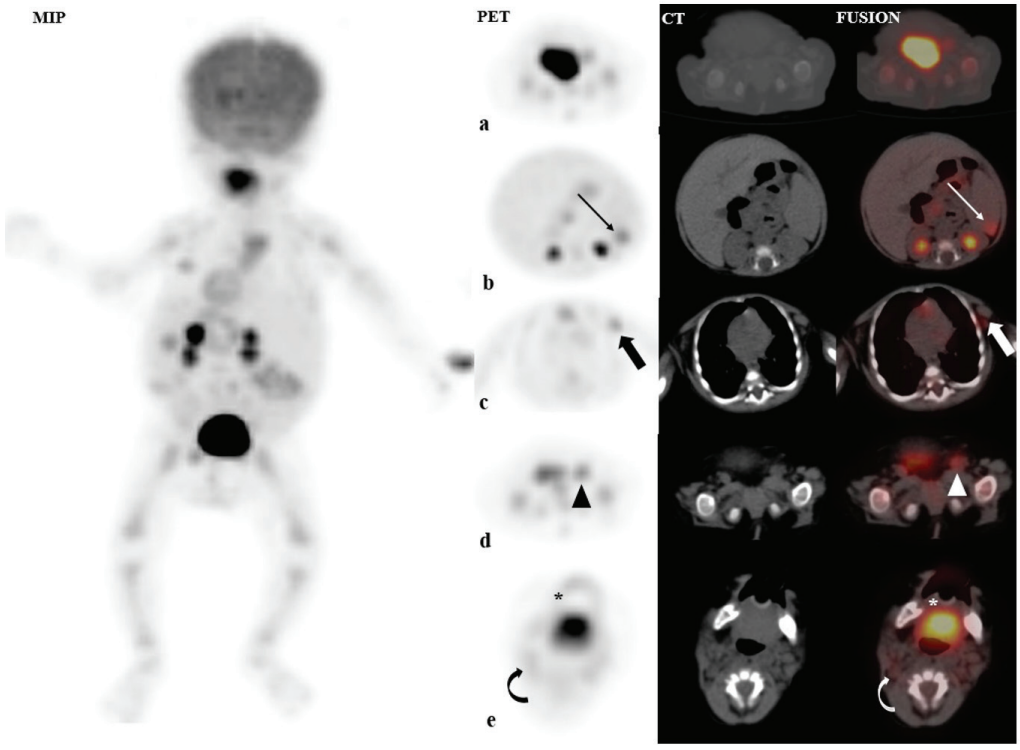

Figure 1. A four months-old girl infant presented with eczematous and squamates rash that began from the cranium and spread to the trunk in a day. Physical examination revealed disseminated erythematous, papules skin lesions. Blood test revealed only thrombocytopenia as pathologic (platelet:

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76 109 mg/dL; range: 247-580 109 mg/dL). Hemangiomatous suspected lesions were detected in the spleen, and liver with ultrasonography (USG). Therefore; F-18 fluoro-2-deoxyglucose positron emission tomography/computed tomography (F-18 FDG PET/CT) performed with Langerhans cell histiocytosis (LCH) prediagnosis. Maximum intensity projection image (left column) of PET demonstrates diffuse bone marrow FDG uptake, which is more prominent in the appendicular skeleton [maximum standardized uptake value (SUV_{max}): 1.4 g/mL]. Transaxial CT images (line a) do not reveal any abnormalities in the skeleton. Transaxial PET and fusion images show focal FDG uptake at the posterior aspect of the spleen (line b; thin arrow, SUV_{max}: 2.2) and mildly hypermetabolic enlarged lymph nodes in bilateral axillary (line c; thick arrow, SUV_{max}: 1.8), inguinal (line d; arrow head, SUV_{max}: 2.1), and cervical lymphatic stations (line e; curved arrow, SUV_{max}: 1.1). Because of crying during the uptake phase of radiopharmaceutical, intense FDG uptake was detected in the tongue base (line e; asterix, SUV_{max}: 6.5). Interestingly, no pathologic uptake was detected in skin lesions. USG confirmed pathologic axillary lymph nodes, but cervical lymph nodes were considered reactive. Skin punch biopsy revealed parakeratosis, and some horseshoe-shaped cells, some of which destroyed the dermoepidermal junction of the epidermis and formed nest up to the upper layers. Immunohistochemical staining was positive for S-100, CD1-a, langerin, CD48. Ki-67 was 5%. These findings were consistent with the diagnosis of LCH. LCH is a rare disease with an incidence of 4.6 cases per 1 million children under 15-years of age (1). Although bone involvement of LCH is common (2); bone marrow involvement of LCH is detected only in one-third of cases (3). Survival is poor in children with liver, spleen, or bone marrow involvement in LCH (4). Generally, conventional radiography was chosen as the first imaging modality. Magnetic resonance imaging (MRI), and diagnostic computed tomography are useful especially for identification of central nervous system and lung lesions (5). However, to evaluate the extent of the disease, and to monitor treatment response F-18 FDG PET/CT is a valuable imaging modality (6,7). Combined PET/MRI can improve sensitivity during primary staging (8). In this study, clinically unknown bone marrow involvement of LCH was detected with F-18 FDG PET/CT. Close observation of patients during the uptake phase of the radiopharmaceutical is critical to avoid false positive interpretation of PETs like tongue involvement in this study.

Ethics

Informed Consent: Informed consent for F-18 FDG PET scan was obtained from the case's parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.A., F.G., Concept: E.A., B.Y., Design: E.A., B.Y., Data Collection or Processing: E.A., F.G., B.Y., Analysis or Interpretation: E.A., B.Y., Literature Search: E.A., Writing: E.A., F.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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