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

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

Research Articles:

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

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

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

Table 1
Limitations for each manuscript type

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

References:

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

Journal Article:

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

Journal Article published in non-English Languages:

2. Altuntaş N, Çelebi DT, Koçak M, Andıran N. Yenidoğan bebeklerde direkt coombs testi taraması ve pozitifliğinin morbidite üzerine, etkisi; tek merkezd eneyimi. *Pam Tip Derg* 2015;8:39-44. (in Turkish)

Book Chapter:

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

Entire Book:

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

Software:

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

Online Journals:

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

Database:

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

World Wide Web:

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

URL (Uniform Resource Locator)

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

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Invited Review

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Postinfectious Bronchiolitis Obliterans

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Abstract

Childhood bronchiolitis obliterans (BO) is an uncommon complication that is characterized clinically by persistent and continuous obstructive respiratory symptoms, and has been described secondary to various etiologic factors, including drugs, exposure to toxic fumes, allergic reactions, collagen vascular disease or infections. BO occurs most commonly in children after an episode of acute bronchiolitis and is considered a long-term sequela of viral infection.

Postinfectious Bronchiolitis Obliterans (PIBO) is characterized by persistent airway obstruction with functional and radiological evidence of small airway involvement that is in general unresponsive to bronchodilator treatment.

Although the condition is relatively rare, and its exact incidence is unknown, it is important to keep it in mind. PIBO is complication of lower respiratory tract epithelial injury, and is often misdiagnosed, delaying recognition and potential treatment. A PIBO diagnosis is usually based on a few factors, including a good medical history, positive clinical findings, and lung function test and imaging results, although biopsy and histopathology remain as the optimum diagnostic approach. There have to date been few studies proposing treatments for the condition, and no accepted protocol exists in literature. There is usually a fixed airway obstruction in PIBO. Various treatment approaches have been extrapolated from studies of post bone marrow transplantations and lung transplant BO. The clinical course is variable, and good supportive therapy is essential, with anti-inflammatory therapy often being employed.

Keywords: Bronchiolitis obliterans, postinfectious bronchiolitis obliterans, mosaic pattern

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Introduction

Bronchiolitis obliterans (BO) is a rare obstructive lung disease that was first described by Lange in 1901.[1] It is an irreversible chronic lung disease that is characterized by subepithelial inflammation and a fibrotic narrowing of the small airways due to various etiologic and triggering factors.[2,3] To date, three main BO categories have been encountered: (i) postinfectious BO (PIBO), (ii) post-hematopoietic stem cell transplantation (HSCT) BO and (iii) post-lung transplantation (LT) BO. Cases in all three categories present with irreversible airway obstructions in the small airways, and respiratory symptoms secondary to this, with the most common cause being infection. PIBO is often seen in early childhood and is an obstructive lung disease that is generally irresponsive to bronchodilator treatment that is characterized by a fibrotic narrowing of the bronchioles secondary to severe lower respiratory tract infection.[4-7] Other rare causes in the BO etiology are connective tissue disease, exposure to toxic fumes and gastroesophageal reflux.[8,9]

Highlights

- Bronchiolitis obliterans is a rare obstructive chronic lung disease.
- The common features of Bronchiolitis Obliterans are tachypnea, wheezing and hypoxemia continuing for at least for 6 weeks following a causative event.
- CT in particular plays a central role in the diagnosis of PIBO, identifying such anomalies as patchy ground glass opacities, air retention, bronchial wall thickening, bronchiectasis, mosaic perfusion and unilateral hyperlucent lung.

Pathogenesis

The pathogenesis of bronchiolitis obliterans is still unclear as the causative organisms are numerous. T cells are known to play a key role in the development of various inflammatory diseases.[10]

In BAL studies of matrix metalloproteinases (MMP), reactive oxygen species and defensins, neutrophils have been shown to play a role in the pathogenesis of BO primarily after lung transplantations. Damaged epithelial cells following post lung transplantation have been suggested to cause an accumulation of inflammatory cells, including neutrophils, through the release of IL-8 and other proinflammatory cytokines. These neutrophils are considered to cause an increase in MMP, defensins and reactive oxygen species, thus leading to structural disorders of the matrix, collagen accumulation, fibroblast proliferation, and finally, peribronchial fibrosis.[11]

Recently, a Th17 cell mediated autoimmunity was detected against the type-V collagen that plays role in tissue remodeling in patients with lung transplant.[12] In a BO animal model, IL-17 expression was found to increase and peripheral Tregs to decrease in the allograft after LT.[13] Considering the induction of IL-8 secretion by IL-17, Th17 cells may be responsible for the neutrophilia observed in the BAL of patients with BO. PIBO, on the other hand, is characterized by a constrictive BO pattern and inflammation to a varying degree, along with airway obstruction.

In summary, epithelial damage occurs as a result of lower respiratory tract infections by viruses or microorganisms such as mycoplasma. Epithelial cells secrete IL-8 and other proinflammatory mediators that gather neutrophils and other inflammatory cells into the small airways. Subsequently, MMP, fibrotic cytokines and mediators are secreted by these cells, and matrix damage, collagen accumulation, fibroblast proliferation, and finally, peribronchial fibrosis occur. CD8 + T cells play a dominant role in epithelial damage and chronic inflammation following a viral infection. Th17 cells play role in tissue remodeling, while IL-17 induces the IL-8 release associated with airway neutrophilia. The development of obliteration in BO is detailed in **Figure 1**.

Definition

The common features of Bronchiolitis Obliterans are tachypnea, wheezing and hypoxemia continuing for at least for 6 weeks following a causative event.[14] Diagnoses are confirmed from persistent symptoms irresponsive to bronchodilator application, computed tomography findings and the exclusion of other diseases.[15]

Epidemiology

Postinfectious Bronchiolitis Obliterans (PIBO) is a rare disease, the incidence of which is currently unknown since a national and international database has yet to be established. The incidence may be even higher than expected, since most mild cases remain undiagnosed. While estimating the prevalence of PIBO is difficult, in a study of 3,141 autopsy and lung biopsy reports, BO was identified in 0.6%, and most were described as PIBO.[16] PIBO is encountered more frequently among certain populations, including Native Americans and Native Koreans, which suggests that genetic factors may play role in its etiology.[4,17] HLADQB1 * 0302 – an antigen with a high prevalence among Native Americans was found to be increased in children with BO in a previous study.

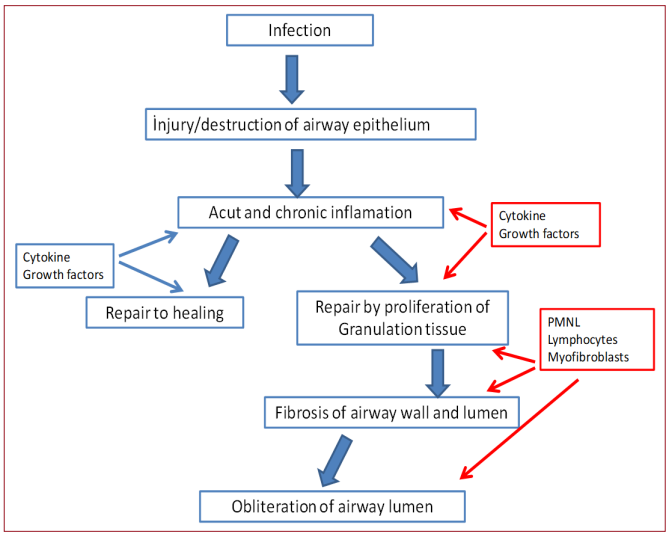

Figure 1. Histopathology in Bronchiolitis Obliterans

PIBO is most associated with adenovirus infections (3, 7, 11 and 21 serotypes), and has been reported secondary to influenza, parainfluenza, measles, chickenpox and Mycoplasma pneumoniae. Li et al., in their study conducted in China, reported adenovirus to be the most common cause in the 42 PIBO diagnoses of children over a five-year period.[18] Colom et al. diagnosed adenovirus in 71% of their patients with PIBO,[4] although various respiratory viruses or bacteria, including respiratory syncytial virus, influenza, Mycoplasma pneumoniae, type B Streptococcus, Legionella pneumophilia and Bordetella pertussis have been shown to lead to the development of PIBO.[19,20]

Respiratory signs and symptoms of acute viral bronchiolitis resolve after a few days, and so BO should be considered in children with acute lower respiratory tract infections with continued wheezing, tachypnea and the need for oxygen support for at least 2 months. Advanced diagnoses are necessary in such cases.[1,9] Adenovirus infection has been found to be an independent risk factor for the development of PIBO in children below 3 years of age with a requirement for mechanical ventilation.[4] PIBO is particularly common in children below 1 year of age, although age does not seem to be a risk factor for PIBO.[4,21,22]

Children with PIBO are heterogeneous in terms of the causative organisms and the age of onset. Pediatric pulmonologists have been able to determine the cause and initiation time from retrospective observations at the time of diagnosis. In a study with a 3.5-year follow-up, 22.6% of the cases were reported to be in remission, 67.7% were reported to have continuing respiratory symptoms and mortality was reported in 9.7%.[22]

Histopathology

The fibrotic changes in the small airways associated with BO can be divided into two types: proliferative bronchiolitis; obstructive or constrictive bronchiolitis, depending on their histologic features, the second of which is more common.[23] Constrictive bronchiolitis develops due to submucosal fibrosis, while proliferative bronchiolitis develops when intraluminal polyps caused by inflammatory granulation tissues obstruct the airways.[24] The mechanism of the development of obliteration in BO is detailed in **Figure 1**.

Lung biopsy is accepted as the optimum approach to the diagnosis of BO. Typically, biopsies reveal a progressive inflammatory response with tissue remodeling, fibrosis of the small airways and airway obstruction elements,[25] although such biopsies may be subject to sampling errors, since airway obstructions are distributed heterogeneously in the lung parenchyma and the level of chronic inflammation varies from patient to patient.

DIAGNOSIS

Clinical Picture

PIBO is diagnosed from the clinical criteria that define the symptoms, such as tachypnea, cough, wheezing, exercise intolerance and hypoxemia, continuing for at least 6 weeks following severe bronchiolitis or pneumonia with respiratory failure.

Differentiating between PIBO and ordinary bronchiolitis or viral pneumonia can be challenging, and may delay diagnosis and possible treatment, and such delays may result in deepening the severity of respiratory tract infections and even death from respiratory failure over 1–2 years.[15-26]

At the time of diagnosis, the level of respiratory tract disease may have advanced and irreversible fibrotic changes and airway obstructions may have occurred, making treatment even more difficult and decreasing the rate of success. Physical examination does not lead in a previously health child in the diagnosis of PIBO. There are nonspecific signs which point out PIBO such as crepitant rales, wheezing and hyperinflation on physical examination. A definitive diagnosis necessitates histopathological verification and so clinical and imaging criteria, pathological agent descriptions and the exclusion of other forms of chronic lung disease should be carried out as a priority. The diagnostic criteria for PIBO are given in **Table 1**.[27]

A scoring system to increase reliability in positive cases was developed and validated in a study carried out to establish the diagnostic criteria of the disease, and to determine the accuracy of the criteria in the evaluation of pediatric patients with PIBO – a chronic lung disease. The defined criteria were as follows: Typical clinical record in a previously healthy child with a severe bronchiolitis episode lasting for more than 60 days; presence of chronic hypoxemia (sat. O_2 <92%): 4 points; history of adenovirus infection: 3 points; and mosaic pattern on CT: 4 points. Scores of ≥7 predict a diagnosis of PIBO with a high accuracy (specificity 100%, sensitivity 67%), although scores of <7 certainly do not exclude a diagnosis of BO. The specificity criteria of PIBO are presented in **Table 2**.[22]

Table 1
Diagnosis of Postinfectous Bronchiolitis obliterans(PIBO)

1. History of lower respiratory infection, particularly Adenovirus, mycoplasma, measles.
2. Persistent airway obstruction symptoms and signs (≥ 6 weeks) or recurrent airway obstruction symptoms and signs in a mild form.
3. Sing of obstructions: FEV1 /FVC<0,8 or FEV1 percent predicted <%80.
4. Irreversible airway obstruction demonstrated by lung function test; absent BDT but positive BDR in some patient.
5. CT (inspiration/expiration): mosaic perfusion, air trapping, and/or bronchiectasis
6. Exclusion of other chronic lung disease (asthma, BPD, chronic aspiration, PCD, cystic fibrosis, immun deficiency).
7. Postinfectious bronchiolitis obliterans is clinically diagnosed when all of the above criteria are met.

FEV1: Functional expiratory volüme, FVC: Forced Vital Capacity, BDT: Bronchodilator Therapy, BDR: Bronchodilator Response, CT: Computed Tomography, BPD: Bronchopulmonary Dysplasia, PCD: Primary Ciliary Dyskinesia

Table 2
BO score, clinical X-Ray score for diagnosis PIBO

Predictor variable	Value	
	Present	Absent
Typical clinical record	4	0
Adenovirus history	3	0
Mosaic pattern in HRCT	4	0
Score range 0-11		
A score >7 predict diagnosis PIBO		

One of the most severe forms of PIBO caused by adenoviruses is Swyer-James Syndrome (SJS), which is defined as the unilateral hyperlucency of a single lobe or the entire lung secondary to pulmonary hypoperfusion, with a decrease in the vascular plexus or volume of the affected lung or lobe. SJS is functionally characterized by a decrease in volume during inspiration and air trapping due to bronchiolar obstructions during expiration. Given the rarity of the disease, understanding the general clinical picture of SJS is important in excluding other diseases associated with bronchiolitis for a differential diagnosis. The physiopathology of SJS includes inflammation of the bronchial walls and fibrosis of the interalveolar septa, resulting in decreased ventilation and perfusion, and vasoconstriction. Obliteration of the pulmonary capillary network decreases the flow of blood into the pulmonary artery segments and triggers arterial hypoplasia.[28,29]

Radiology

Among the available imaging techniques, CT in particular plays a central role in the diagnosis of PIBO, identifying such anomalies as patchy ground glass opacities, air retention, bronchial wall thickening, bronchiectasis, mosaic perfusion and unilateral hyperlucent lung.[30] The most common findings – mosaic attenuation and ground glass appearance – are essential for diagnosis. Some sample CT images of BO are presented in **Figure 2** and **Figure 3**. The two main mechanisms behind the development of mosaic attenuation are alveolar hyperinflation and hypoxic vasoconstriction.[31] Hypoxic vasoconstriction causes a redistribution of blood flow to the "healthy" lung. When the bronchial disease is extensive, a greater volume of blood is redistributed to the smaller volume healthy lung, finally becoming more condensed, and a ground glass appearance develops. Leung et al. reported the sensitivity, specificity and accuracy of CT in cases of air trapping syndrome to be 91%, 80% and 86%, respectively.[32] Obtaining a CT image during the expiratory phase would lead to this important feature, which occurs during the inspiratory phase, being overlooked, and so it is important in diagnoses of air trapping in less severe cases.[33] Obtaining scans from both respiratory phases may be challenging in pediatric patients with limited cooperation; and so more attention should be paid to the evaluation of ground glass opacities. Another role of CT in PIBO is as a marker of disease severity. Correlations have been observed between CT measurements of disease severity and lung function measurements in BO in the presence of varying etiologies.[34] Ventilation-perfusion (V/Q) defects in scintigraphic imaging in only PIBO patients have been reported in some studies.[35]

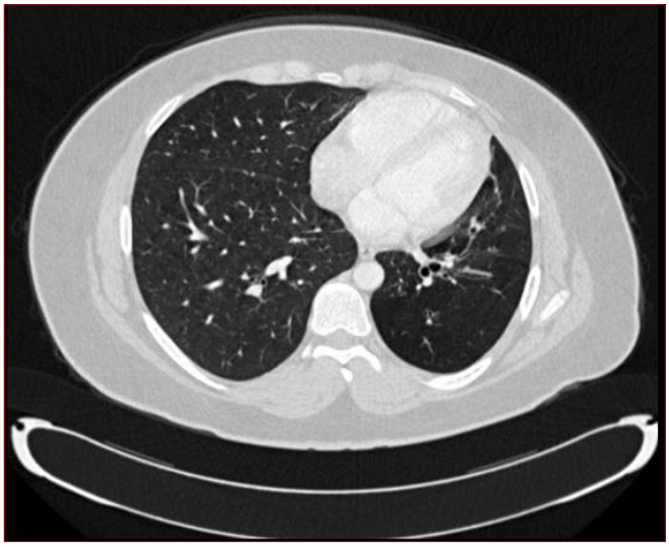

Figure 2. Swyer-James (Macleod Syndrome): radiographic hyperlucent appearance of a left pulmonary lobe.

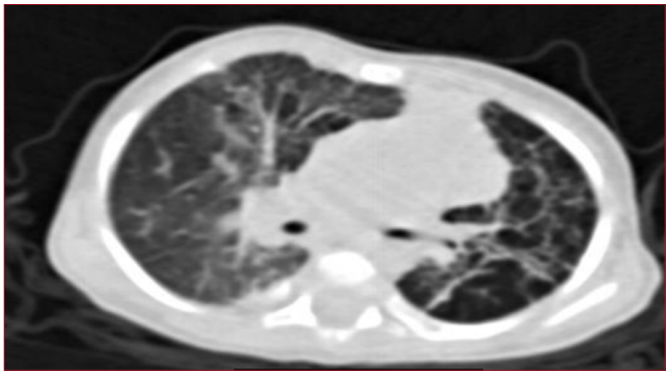

Figure 3. Swyer-James (Macleod Syndrome), CT demonstrate long-standing hyperlucency of the right lower lobe

Bo-Qia Xie et al. identified two further patterns, including incompatible perfusion pattern and incompatible ventilation pattern.[36] Airway inflammation is thought to lead to hypoxic vasoconstriction in the acute phase, and this inflammatory process is thus accepted as affecting the neighboring vessels, and to cause vascular remodeling in the following chronic phase.[37] Perfusion disorder may thus be less severe than ventilation disorder in the early phases of PIBO, and so an incompatible perfusion pattern may be seen on a V/Q scan. An incompatible perfusion pattern, on the other hand, may be a sign of early phase PIBO, and the incompatible ventilation pattern follows this.[36]

Pulmonary Function Tests (PFT)

Lung function tests are manifested as typical models in patients with PIBO. Pulmonary function tests are generally used to document an obstructive disorder, although the results of such tests may be normal in the early phases. Spirometry shows an irreversible of stable obstructive flow volume curve with a decreased forced expiratory volume (FEV1), and a decreased Tiffeneau index (FEV1/FVC) and end-expiration (FEF25). The body plethysmography shows hyperinflation and a residual volume (RV) with increased air trapping and an increased functional residual capacity (FRV).[17] Typically, response to bronchodilation is either low or lacking.[38] Patients with PIBO tend to experience milder disease forms than those with BOS following bone marrow transplantations.

Patients with PIBO have a common marked respiratory function disorder pattern that is characterized by marked airway obstruction, increased RV and specific airway resistance.

Mattiello et al. reported that airway obstructions varied between intermediate to very severe in children and adults with PIBO, noting also marked airway obstructions with air trapping.[39]

Teper et al. from Argentina reported that the respiratory functional disorder associated with PIBO developed in the early phases of the disease.[40] Kim et al. identified severe and fixed airway obstructions in the pulmonary function tests of 14 children out of 31 with PIBO in the United States and South Korea.[17] Cazzato et al. found a yearly 1% decrease in the FEV1, FEV1 / FVC and FEF25-75 values of 14 children in the long-term follow-up of pulmonary function tests.[38]

Castro-Rodriguez et al. identified a peripheral airway obstruction in 18 preschool children with PIBO in Chili using an impulse oscillometer technique.[41] In Brazil, Mattiello et al., after evaluating the functional capacity of 20 children during cardiopulmonary exercise, compared their results with the PFT results. The authors found decreased oxygen consumption to be positively correlated with FVC, FEV1 and FRC in children,[42] and reported that the CT findings early in life in a group of 21 children with PIBO predicted severely impaired lung function after 10 years.[43] This impairment which is probably attributable to the huge chronic damage in the intermediate and small airways, characterized by increased RV and specific airway resistance (sRaw), and decreased expiratory air flow. A combination of spirometry and plethysmography measurements may be more beneficial for the evaluation of functional damage, and for the follow-up of such patients when compared to use of only one technique alone.[44]

Mattielo et al. reported decreased FVC in PIBO, and a total lung capacity (TLC), RV and RV/TLC of over 80%, representing a significant increase. These data, obtained from plethysmography, confirmed the obstructive nature of PIBO. The authors also reported a positive correlation between RV/TLC and FEV1 and demonstrated that the decrease in FEF25-75% was in parallel with the severity of the airway obstruction. Although FEV1/ FVC and FEV1 are the most used spirometry parameters for the determination of airway obstructions, this parameter was an early predictor of disease severity since it shows a greater decrease when compared to FEF25-75, FEV1% or FEV1. RV, TLC and RV/TLC tend to increase in such patients as a result of the decrease in the elastic recoil of the lung.[42]

The FEV1 and FEV1/FVC and FEF25-75 of patients with PIBO should be carefully monitored.[44] Both the American Thorax Society (ATS) and the European Respiratory Society (ERS) recommend the determination of lung volumes in patients with obstructive lung diseases such as PIBO to allow a better understanding of the underlying respiratory disorder.[45,46]

Anatomical and functional changes in PIBO may lead to a progressive loss of power/ durability in the respiratory muscles, which in turn effects exercise tolerance negatively and may decrease daily life activities. A cardiopulmonary exercise test (CPET) and a 6-minute walking test may be more sensitive in the detection of early involvement in respiratory diseases the FEV1 measured by spirometry. Mattiello R et al. identified a decrease in exercise capacity in children and adolescents with PIBO.[44]

Recently, sensitive lung function indices have aided in the early diagnosis of small airway disorders in PIBO. Multiple breath washout (MBW) is an appropriate and sufficiently sensitive method for the detection of early small airway disorders in the presence of chronic lung disease in children and adults. Other studies have shown the lung clearance index (LCI) to be impaired in most patients with cystic fibrosis, despite the spirometry indices being normal. LCI measured by MBW can be helpful in the diagnosis in PIBO. LCI results were found to be correlated with CT findings in Kim et al.'s study of 20 babies diagnosed with PIBO who underwent pulmonary function tests, MBW and chest CT. LCI can thus be considered an appropriate and complementary tool for the evaluation of children with PIBO.[47,48] It offers a further advantage over Forced Oscillation Technique (FOT) spirometry in the pediatric population in requiring no respiratory maneuvers due to the small amplitude pressure oscillations added to the normal respiration. There have to date been no studies investigating the use of FOT in PIBO, although such may be of interest, and would facilitate pulmonary function studies.[49] In contrast to spirometry, which requires deep inspiration, the FOT requires minimal cooperation and does not alter the airway smooth muscle tonus.

Jang YY et al. reported a significant increase in serum YKL-40 levels in children presenting with exacerbations of PIBO, and these increased YKL-40 levels were found to be positively correlated with disease severity prior to PIBO. The measurement of serum YKL-40 levels was thus suggested to be helpful in differentiating between exacerbation in PIBO and acute bronchiolitis in small children, and it was concluded that YKL-40 could play a role in the pathogenesis of PIBO.[50]

Giubergia V et al., in their study evaluating the distribution of MBL2 polymorphism in children with PIBO, identified significantly more children carrying iMBL genetic variants in the PIBO group when compared to healthy controls, and more patients in the PIBO iMBL group required intensive care and mechanical ventilation.[51]

BAL

Cellular infiltrations of the lungs in children with PIBO involve CD3 + T cells, in which the CD8 + T cell subtype is dominant. Koh et al. identified increased CD8 + T cells and a decreased ratio of CD4 / CD8 in BAL and biopsy samples taken from children with BO and with a history of measles pneumonia during an outbreak in 2000–2001. The dominant role of CD8 + T cells in the development of BO following a viral infection was described in this study.

The bronchoalveolar lavage (BAL) of children with PIBO is neutrophil dominant and a significant increase in IL-8 is seen, with the degree of neutrophil increase in BAL being correlated with the BO stage.[10]

Biopsy

Biopsy is accepted as the optimum approach to diagnosis, although the National Institute of Health (NIH) came up with new criteria for the diagnosis and scoring of the severity of chronic Graft-versus-host disease (GVHD) of the lungs, since biopsy is invasive and is associated with a risk of bleeding and other complications. The criteria for a clinical diagnosis of BOS after HSCT were defined as FEV1/FVC <0.7, FEV1 <75% pred., >10% decrease in less than 2 years, and an absence of infection or air trapping in a CT or pulmonary function test. Similar follow-ups should be carried out for PIBO.[52]

Treatment

Standard treatment options are yet to be determined for PIBO, as it is a rare, chronic, irreversible and obstructive lung disease with no accepted protocol, and different centers follow different strategies. Most of the current knowledge of PIBO has been extrapolated from studies of patients who developed BOS following bone marrow or lung transplantations.[53]

Therapeutic decisions were empirically performed in the beginning, since PIBO is a rare disease in which there is little opportunity for randomized clinical experiments focusing on the treatment of the disease. The clinical course is variable, and supportive treatment is the main priority, although anti-inflammatory treatments are also frequently applied. The current BO treatments are details in **Table 3.**[54,55]

Table 3
Treatment of PIBO

Anti-inflammatory therapy	Supportive treatment
• Systemic steroid	• Oxygen support
• Azithromycin	• Nutritional support
• Combination therapy: FAM (fluticasone/azithromycin/ montelukast)	• Vaccination (influenza/ pneumococcus)
• Immunoglobulin therapy	• Avoiding cigarette smoke
• Steroid sparing antiinflammatory agents	• Airway clearance if there is bronchiectasis
• Anti-TNF	• Inhaler bronchodilator if response
	• Exercise therapy/pulmonary rehabilitation

In general, PIBO treatments should be planned to include a combination of optimal supportive therapy and anti-inflammatory treatment to prevent lymphocyte proliferation and activation, since inflammation plays an important role in the pathogenesis of PIBO.[56] An appropriate drug protocol may include: 1) Oral/inhaled corticosteroids and other anti-inflammatory treatments; 2) hydroxychloroquine, for the treatment of severe or long-lasting obstructions; and high dose methylprednisolone pulses; 3) Short-acting and long-acting bronchodilators or anticholinergic agents; and 4) oral or intravenous antibiotics.[57]

Inhalers and systemic steroids:

Systemic steroids should be administered in the early phases of the disease, prior to the development of fibrosis, although the small airways might already be obstructed by fibrosis when the PIBO diagnosis was made. Since the duration of inflammation following the development of PIBO is unknown, it is hard to know when the systemic steroid treatment should begin and end.[8] The preferred approach is a pulse steroid treatment with intravenous methylprednisolone for 3 consecutive days in a dose of 10–30 mg/kg. Consensus is that the treatment should be repeated every 3–6 months, as is the case with pediatric interstitial lung disease. Yalcin et al. gave prednisolone in a dose of 1 mg/kg/day in their patients as the initial dose. Treatment lasted between 6 and 27 months, and the steroid dose was decreased gradually 3 months after the initiation of treatment.[58]

Macrolides

The adverse effects of long-term systemic glucocorticoid and inhaled corticosteroid administration has led investigators to seek an alternative treatment for BO.[59,60] The anti-inflammatory and immunomodulator effects of macrolides have recently been noted, leading to their use in the treatment of BO following transplantation. Azithromycin is a macrolide-group antibiotic that has proven to be effective in the treatment of diffuse pan bronchiolitis and cystic fibrosis in prospective, double-blind and placebo-controlled studies.[61] Macrolide antibiotics are known to show immune modifying effects in addition to their antimicrobial roles, while Azithromycin was shown to improve FEV1 and to decrease mortality in patients with BO syndrome following lung transplantation in an extensive study in 2014 and a large scale randomized clinical study in 2015.[62–64] The recommendation for the use of macrolides in the treatment of BO after lung transplantation is recommended for Grade IA and Grade 2C stages of allograft rejection.[65]

Leukotriene Receptor Antagonists

The effectivity of leukotriene receptor antagonists is linked to their ability to inhibit airway inflammation.[66] Montelukast provided a high treatment efficacy in BO patients after transplantation.[67] A recent study reported that a combination treatment including budesonide, montelukast and azithromycin improved pulmonary function and respiratory symptoms in children with PIBO aged <5 years. Concurring with this finding, Williams et al. reported that fluticasone, azithromycin and montelukast, alongside pulse steroid treatment, could halt the decrease in pulmonary functions in newly developed BO, and could lead to a decrease in systemic steroid exposure in most patients.[68,69] In another study, concurring with the studies mentioned above, use of budesonide, azithromycin and montelukast in combination for at least 3 months was said to improve respiratory function and respiratory symptoms in children with PIBO.[70]

Recently, treatment strategies have become more personalized. Systemic steroids or inhaled corticosteroids are recommended in all patients, although the route of steroid application should be chosen empirically, based on the severity of the case. In theory, no bronchodilator

response is expected in children with permanent airway obstructions such as in PIBO, however a positive bronchodilator response can be seen ranging from 10% to 42.9%. Inhaled bronchodilators (short-acting ß-2) are recommended for all patients with pulmonary exacerbations and who are clinically responsive.[71-73]

Oxygen support may also be used in addition to drug treatment, especially in the first few years of the disease, and clinical improvement can permit the cessation of supplementary oxygen completely in most cases. The requirement of supplementary oxygen at night is a source of concern, although significant desaturation is experienced only severe cases during sleep.[74]

Nathan et al. reported increased pulmonary pressure in 42.3% of patients (PH) with BO following LT.[75] Pate et al. reported that three out of four patients (75%) with BO were diagnosed with PH 91 days after HSCT.[76] Chen et al. reported that two out of the eight children with PIBO in their study had PH (25%), leading them to add sildenafil to the treatment protocol. Considering the association between BO and PH, patients with PIBO should be screened regularly for PH. Furthermore, since hypoxemia is present in both BO and PH, hypoxemia in patients with BO is typically due to worsening PH, and PH also worsens hypoxemia.

GER has been reported to contribute significantly to the deterioration of respiratory function in patients with BO, making it mandatory to treat the condition when diagnosed.

Other immunosuppressive agents, including methotrexate, azathioprine, cyclophosphamide, thalidomide, imatinib and etanercept, have been tested on patients with BOS following lung transplantation or HSCT. Although most studies are retrospective, case reports or case-controlled studies, the results are not promising, and no reports are found associated with the use of these drugs in children with PIBO.[77–81] Recent case studies have reported that the administration of intravenous immunoglobulin alongside pulse steroid treatment or methylprednisolone in a dose of 1mg/kg as an effective treatment.[82,83] Lung transplantation remains as the final option in children with BO following LT or HSCT that progresses to end-stage lung disease. In one hospital-based study, two of the 31 cases with diffuse lung disease other than cystic fibrosis and pulmonary vascular disease who underwent lung transplantations were patients with PIBO.[84] Accordingly, LT should be considered in patients with PIBO in whom the disease has progressed to end-stage lung disease.

Clinical progress

Most patients require oxygen support for an average of 5 months following admission to hospital. Oxygen saturation improves slowly over several years, and only a few patients need additional oxygen support past the age of 10 years. Child patients require readmissions to hospital, although the frequency of admissions decreases over the years,[21] with such readmissions being required mainly due to respiratory tract infections that require treatment with antibiotics, bronchodilators and physiotherapy.[85]

Perfusion defects that are present at the outset of the disease continue in most patients but may resolve occasionally. The clinical improvements seen in such patients may be due to pulmonary enlargement, rather than being a sign of regression of a small airway pathology.[86]

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Fertility Preservation Methods in Childhood and Adolescence Cancers: A Review

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Abstract

In childhood and adolescence cancers; survival rates increase with the use of treatment options such as hematopoietic stem cell transplantation, chemotherapy and radiotherapy. One of the long-term effects of primary disease and cancer treatment is the irreversible damage to gonadal tissues, resulting in impaired fertility. Especially chemotherapeutic drugs; causes germ cell defect, affects the secretion of pituitary hormone, and also damages the anatomical structures of internal genital structures such as the uterus.

Gonadal preservation methods are limited in prepubertal male patients. It is a good option to place the testicles in a different area before radiotherapy. Before chemotherapy or whole body irradiation, freezing of testicular tissue and ensuring pregnancy from frozen tissue is still in the experimental stage. After the ejaculation begins, obtaining and storing sperm is successfully done. A limited number of pregnancies were obtained oocytes frozen ovaries in the prepubertal girls. It is possible to freeze oocytes after puberty begins. In addition, recently, as a noninvasive method, gonadotropin-releasing hormone (GnRH) analogues have been used successfully, as it suppresses the hypothalamic-pituitary-gonadal axis and protects germ cells from cytotoxic effects.

This article aims to provide information on fertility preservation methods in patients receiving childhood cancer treatment

Keywords: Childhood cancers, fertility, gonadal protection

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Introduction

The survival rates of child and adolescent cancer patients have recently been increasing with the use of different treatment options such as chemotherapy, radiotherapy, and hematopoietic stem cell transplantation (HSCT). In the last decade, pediatric cancer survival rates have exceeded 80%.[1] These developments have led to a higher desire in patients to have children in the long term.

Before starting cancer treatment, long-term and late effects of the treatment should be considered, as well as its acute side effects. An important issue regarding long-term effects that should be discussed with families is the risk of gonadal dysfunction and infertility. Long-term survival rates have resulted in increased patient concern for fertility, prompting advances in fertility preservation methods. Today, infertility risk and fertility preservation methods are considered together with families before starting cancer treatment to select an appropriate approach to protect gonadal function.

Highlights

- One of the most important side effect of cancer treatment is the long-term deterioration of gonadal functions. This situation can cause infertility and poor quality of life. With the onset of puberty, collection and storage of mature gametes becomes easy. There are various successful and standardized techniques. In the prepubertal period, the same success has not yet been achieved today.

Chemotherapeutic agents, radiotherapy, total body irradiation, and surgical procedures can disrupt gonadal function, causing germ cell defects, affect pituitary hormone secretion, and damage the anatomy of internal genitalia such as the uterus. Although solid tumor and hematologic malignancy treatments have been modified to reduce side effects, there is an ongoing interest in fertility-preserving treatments and assisted reproductive technology.

Alkylating agents are the drugs with the highest level of genotoxicity. These agents, frequently used in childhood cancers, can cause permanent germ cell damage depending on the cancer stage of the patient and the cumulative doses administered. Radiation therapy to the head, spine, pelvis, testicles, or whole body has detrimental effects on pubertal development and eventual fertility. This impact varies depending on the child's age when treated, their susceptibility, and the treatment dose and duration. Besides, the course of the primary disease also impinges on gonadal function (**Table 1** and **Table 2**).

In boys, due to their high mitotic index spermatogonia are highly susceptible to chemotherapy-induced damage, unlike Leydig and Sertoli cells. Posttreatment azoospermia can reach up to 82%, according to the type of chemotherapy.[3] A study on 214 adult male survivors of childhood cancer, who had received chemotherapy including alkylating agents only, reported normospermia in 48%, oligospermia in 28% and azoospermia in 25%.[4] Spermatogonia are more sensitive to radiotherapy than adult spermatozoa; 4 Gy may be sufficient for total destruction. Leydig cells are more resistant but can be damaged at doses of 20 Gy at prepuberty and 30 Gy at puberty.[5]

In women, radiotherapy and chemotherapy can cause premature decrease of the ovarian follicular reserve, resulting in primary ovarian insufficiency (POI) and infertility. POI is considered menopause before the age of 40. The absence of menstruation for more than three months should instigate relevant assessment. High follicle-stimulating hormone (FSH) values should also be premonitory in this regard. Another indicator of ovarian reserve in childhood cancer survivors is serum Anti-Müllerian Hormone (AMH) concentration. AMH levels are lower in patients with ovarian insufficiency due to cancer treatment than healthy controls, constituting a vital parameter to guide POI diagnosis.[6]

Acute ovarian failure occurs in 6% to 12% of childhood cancer survivors.[7] Infertility problems due to decreased ovarian reserve may even occur in women with regular

Table 2
Gonadal dysfunction risks in terms of chemotherapeutic agents[2]

Low	Moderate	High
Vincristine	Cisplatin	Cyclophosphamide
Vinblastine	Carboplatin	Ifosfamide
Bleomycin	Doxorubicin	Procarbazine
Mercaptopurine		Chlorambucil
Methotrexate		Chlormethine
Dactinomycin		Melphalan
		Busulfan

Table 1
Hypofertility risk after cancer treatment in children and adolescents regarding tumor pathology[2]

Low	Moderate	High
Nephroblastoma	Hepatoblastoma	Testicular or pelvic radiotherapy
Acute lymphoblastic leukemia Cerebral tumor (surgery alone or with cranial irradiation < 24 Gy)	Acute myeloblastic leukemia	Soft tissue sarcoma
Retinoblastoma	Soft tissue sarcoma Neuroblastoma	Hodgkin's lymphoma (Alkylating agents)
Soft tissue sarcoma	Osteosarcoma	Ewing's Sarcoma (metastatic)
Malignant germ cell tumors	Cerebral tumor (cranial irradiation > 24 Gy)	Chemotherapy before HSCT
	Ewing's sarcoma	Total body irradiation
	Non-Hodgkin's lymphoma	

menstrual cycles after cancer treatment.[8] The follicle pool is undiminished in the prepubertal period due to the absence of ovulation, so patients receiving chemotherapy are less affected in this period than in the pubertal period.[9]

Ovarian irradiation at doses lower than 2 Gy is sufficient to destroy the follicles. Since girls are born with an established pool of germ cells, susceptibility to radiation-induced damage increases with age.[5] Besides, pelvic radiation may adversely affect the uterine muscle and vessels, entailing a reduced uterine volume. Accordingly, an increased risk of pregnancy complications such as preterm birth, miscarriage, or intrauterine growth restriction may ensue.[10]

HSCT is the highest-risk treatment concerning gonadal dysfunction. The most common complication after HSCT for hematological malignancies, POI, develops in more than 90% of women.[11]

On the other hand, high-dose cranial radiotherapy (35-40 Gy) may affect the hypothalamic-pituitary region, causing hypogonadotropic hypogonadism. Decades of cumulative experience have substantiated no increase in congenital malformations in the biological offspring of survivors conceived naturally.[12]

The burden and cost of fertility preservation options differ for girls and boys. The alternatives should be evaluated concerning whether the patient should receive treatment in the preadolescent or postadolescent period. Some treatments are well-established empirically-supported, while others are still tentative. It is crucial to distinguish between clinically approved treatments and experimental ones when advising patients and families on fertility preservation options.

Fertility Preservation Options for Prepubertal Patients

Prepubertal Boys

Contemporary methods for gonad and gamete preservation in prepubertal male patients are mainly theoretical, except for testicular shielding or relocation from the field of radiation. Most techniques involve interventions to protect the testicles during cancer treatment. Primordial germ cells are sensitive to toxicity at all stages of puberty. During gonadal-sparing irradiation, the gonads can be temporarily relocated on the thigh or anterior abdominal wall.[13] This procedure is named as reverse orchiopexy.

Total or partial testicular tissue cryopreservation has mainly remained theoretical and is not routinely practiced. Similarly, testicular transplantation has not been successfully performed in humans yet; nevertheless, the birth of a primate from sperm produced after testicular autotransplantation has been a remarkable milestone.[14] Besides, animal studies have proven the efficacy of in vitro maturation of frozen testicular tissue as a fertility preservation method.[15] Currently, testicular tissue cryopreservation is successfully applied in patients ranging between 5 months to 34 years of age, but none of these have resulted in spermatozoa formation from the frozen tissue.[16] Only one study has reported spermatogonial stem cell transplantation by injection into the rete testes of seven patients treated for non-Hodgkin's lymphoma.[17]

Transplantation of testicular tissue is more complicated than similar applications involving the ovaries due to developmental differences between male and female gonads. In any case, testicular tissue cryopreservation may prove valuable since future treatment options may potentially render in vitro maturation or germ cell transplantation a reality.

In addition, the use of angiogenic factors, such as vascular endothelial growth factor, is reported to positively affect revascularization after testicular transplantation.[18]

Prepubertal Girls

Most fertility preservation methods for girls in the prepubertal period are experimental with unclear long-term results. Using the ovaries to produce mature eggs is not possible in prepuberty, which is also the case for oocyte and embryo cryopreservation.[19] Besides, oocyte in vitro maturation is still in the experimental phase.[20]

Some authors have recommended ovarian tissue cryopreservation (OTC) to preserve fertility in girls treated for cancer. In contrast to oocyte cryopreservation, functional ovarian tissue is cryogenically stored in OTC (removing part of the ovary or its cortex), which is currently the only promising fertility preservation method in prepubertal cancer patients.[21,22]

Preserving gonadal functions by applying this method is theoretically possible in prepubertal children since the ovaries contains more primary follicles in prepuberty. Once the treatment is complete, the stored ovarian tissue is unfreezed and transplanted back to the donor. Limited viability of autotransplant gonadal tissue, therefore, recovery of endocrine function appears more likely than recovery of reproductive function.[23] So far, only one live birth after autograft of cryopreserved ovarian tissue in a 9-year-old prepubertal girl has been reported, the youngest case in the literature.[24]

In adult females, more than 70 cases of live birth with cryopreserved ovarian tissue have been published. However, the functioning of the natural ovarian tissue probably enabled these pregnancies instead of the autotransplant tissue.[25,26]

Flow cytometry studies demonstrated the presence of contaminated leukemia cells in normal ovarian tissue samples from patients with leukemia and lymphoma taken before the initiation of therapy. This finding has raised concerns that tumor cells could return to the body after autotransplantation.[27]

Before radiotherapy, oophoropexy can be performed to protect the ovaries by removing them from the radiation field. However, minimal radiation exposure of the gonad may still be possible. In any case, while ovarian transposition is comparatively effective in preserving the endocrine functions of the ovary (almost 60%), fertility preservation is much harder, and only 15.3% of patients can achieve pregnancy.[28]

Fertility Preservation Options for Postpubertal Patients

Fertility preservation is easier in the postpubertal period when obtaining a mature oocyte or sperm is possible.

Adolescent Males

It is easier to obtain and store semen samples in boys in puberty, especially after ejaculation has begun. Sperm should be collected before cancer treatment to avoid compromising DNA integrity or sample quality. Infertility centers and andrology laboratories facilitate the long-term storage of samples. Some types of cancer, such as testicular cancer, leukemia, and Hodgkin's disease, may reduce sperm quality.[29]

Testicular aspiration or extraction, electroejaculation or obtaining sperm after micturition are alternative sperm retrieval methods.[30] In vitro maturation of spermatocytes into spermatids has been possible in cases of primary testicular failure without ejaculation, but fertility was rarely achieved.[31,32]

Pregnancy rates are higher with fresh sperm samples than frozen sperm. In cases with low sperm count, fertilization and pregnancy can be achieved by with intracytoplasmic sperm injection.[33]

It has been shown in animal studies that the use of G-CSF (Granulocyte Colony Stimulating Factor) after alkylating agent exposure has a protective and restorative effect on spermatogenesis by stimulating the proliferation of immature spermatogonia. It acts by binding to the surface receptor (CSF3R) of undifferentiated spermatogonia.[34]

Studies in mice have demonstrated that antioxidant agents such as melatonin alleviate busulfan-induced toxicity through the elimination of reactive oxygen radicals and apoptosis inhibition of spermatogonial progenitor cells.[35]

Adolescent Females

Pregnancy rates of up to 50% have been reported with cryopreserved oocytes in adult women, with an even higher expectation in younger women and adolescents.[36]

Oocyte cryopreservation before treatment has become routine in patients who are planned for gonadotoxic treatment.[37] This method involves controlled ovarian hyperstimulation (COH) with subcutaneous gonadotropin hormone injections over approximately ten days. Then, the patient is sedated and the oocytes are collected by fine needle aspiration under the guidance of transvaginal ultrasound. Since this method is invasive, its application in the adolescent age group is limited. In some cases, cancer treatment may need to be started immediately, and a week or more delay may be unacceptable. Besides, adolescents and their parents may be reluctant to ovarian stimulation and egg retrieval due to psychological and emotional reasons. Also, high estrogen levels can be reached during COH, leading to spontaneous ovulation before the eggs are collected. Furthermore, there is a risk of triggering hormone-sensitive cancers. However, these risks are reportedly eliminated using aromatase inhibitors and selective estrogen receptor modulators without causing pregnancy loss.[38]

Babies born from cryopreserved oocytes are increasing day by day, so it has become necessary to investigate their potential health problems and chromosomal abnormalities. Studies have reported a higher rate of birth defects, chromosomal abnormalities or developmental anomalies in these babies than other procedures such as spontaneous pregnancies and IVF.[39]

Evidence has already shown the successful transplantation of cryopreserved ovarian tissue in adults, with more than 90 babies born with this technique so far. About 50% of these are considered spontaneous fertilization.[40,41]

Pelvic irradiation may cause permanent damage to the uterus, tuba, and vagina, preventing conception or continuation of pregnancy. Parents may have a child through egg donation and surrogacy in such cases, but these are not legal in every country.

If gonadal protection is not possible, gonadotropin suppression may be an option, although its efficacy has not been fully proven. In general, there is limited information on the mechanism of action of gonadotropin-releasing hormone (GnRH) analogs (GnRHa) for gonadal protection, but some evidence suggests their efficacy. Accordingly, rapidly dividing cells are particularly more vulnerable to cytotoxic drugs, and the administration of GnRHa during cancer treatment may slow their proliferation rate that otherwise leads to gonadal function arrest and protection of cells from apoptosis. In this way, suppression of the hypothalamic-pituitary-gonadal axis leads to decreased egg and sperm production, rendering it more resistant to chemotherapy.[42] This method cannot be applied in prepubertal girls since the axis is not active yet.

The American Society of Clinical Oncology (ASCO) 2018 guidelines suggest that GnRHa will be an alternative option for the preservation of gonadal function when other methods are not feasible.[43]

Various studies and meta-analyses have shown that the administration of GnRHa in combination with chemotherapy reduces POI and increases the pregnancy rate.[44-48] Some studies indicate that the combination also improves menstruation, but available data is insufficient to evaluate outcomes for ovarian function and fertility.[49] Besides, Moore et al. have reported that combined therapy with GnRHa resulted in more favorable disease-free survival and overall survival rates, as well as the preservation of ovarian function.[50] In another study, lymphoma patients undergoing total body irradiation were started on GnRHa 10 to 14 days before treatment. The normal ovarian cycle was restored in 66.7% of the patients who received GnRHa, whereas in 11.1% of those without GnRHa. The use of GnRHa is especially considered beneficial in women undergoing HSCT for lymphoma.[51]

The use of GnRHa (triptorelin, goserelin, leuprolide) combined with chemotherapy as a noninvasive, inexpensive, and accessible option to prevent POI in pubertal and adult patients has recently been integrated into clinical guidelines as well.[52,53] The updated European Society for Medical Oncology (ESMO) recommendations include using GnRHa in adolescents and young women, among other options.[54,55]

Conclusion

All the treatment options mentioned above have been a source of hope for the fertility of cancer patients. Fertility-preserving treatment options should be evaluated by a specialist team of oncologists, radiation oncologists, endocrinologists, urologists, and gynecologists, considering the diagnosis and stage of the primary disease, the chemotherapy to be administered, the gender and pubertal stage of the patient. The patients and their families should be fully informed throughout the process. In the future, standardized fertility preservation protocols must be established for experimental and approved treatment options. A broad range of experimental and clinical studies on this subject is necessary for further advancements.

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Evaluation of Clinical and Follow-up Results of Patients with Congenital Nephrotic Syndrome

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Abstract

Congenital nephrotic syndrome (CNS) is characterized by severe proteinuria, hypoalbuminemia, and edema within the first three months of life. Congenital nephrotic syndrome can occur due to perinatal infections or mutation of genes encoding structural or regulatory proteins of the glomerular filtration barrier. Treatment includes albumin infusions, nephrectomy, dialysis, and transplantation. In this study, we aimed to evaluate the demographic, clinical, and follow-up results of patients with CNS followed up in our center between 2010 and 2020. Demographic, clinical, laboratory values of 8 patients diagnosed with CNS between 2010 and 2020, kidney biopsy results, genetic examinations, and follow-up results were retrospectively evaluated. A total of 8 patients (4 girls) were included in this study. The median age at diagnosis was 36 days (3 days-8 months) and the follow-up period was 34 months (7-114 months). There was a history of prematurity and consanguinity in 5 patients. Edema was detected at the admission of all patients. Albumin infusion and captopril therapy were started from the diagnosis. No pathology was seen in the tests for perinatal infection, and ultrasonographic examinations were normal. In the genetic analysis, NPHS1 (Nephrin) homozygous mutation was detected in six patients, and coenzyme Q2 mutation was detected in one patient. Peritoneal dialysis treatment was performed in four patients during the follow-up, and unilateral nephrectomy was completed in one patient. During the follow-up, four of eight patients (three due to sepsis while on dialysis, one on the postoperative after the first day of transplantation) died. Three patients are followed up with kidney transplantation and one with supportive treatment. According to our results, most CNS cases are genetic, and nephrin mutation is the most common cause. Management of complications in CNS is crucial for patient survival.

Keywords: Congenital nephrotic syndrome, nephrin mutation, dialysis, transplantation, pediatric

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Introduction

Congenital nephrotic syndrome (CNS) is a rare kidney disease characterized by severe proteinuria, hypoalbuminemia, and edema that manifests after birth.[1] It is a genetic disorder caused by the disruption of the glomerular filtration barrier, mainly due to mutations in the genes called Nephrin and Podocin. Also, CNS may result from perinatal infections or may be part of various syndromes as Galloway–Mowat syndrome.[2] Genetic analysis is the definitive diagnosis of congenital nephrotic syndrome, and it is recommended to be done in all of these patients.

Highlights

- The nephrotic syndrome occurring in the first three months of life is defined as congenital NS. Nephrin mutation is the most common cause.
- The management should plan on a case by case basis, depending on the severity of nephrosis, complications, the response of antiproteinuric therapy.

Immunosuppressive therapy is ineffective in CNS of genetic origin, but kidney transplantation provides the curative treatment. In many cases, daily infusion of albumin is required to prevent life-threatening edema in the first months. In addition, a high-calorie diet, thyroxine, and mineral support are applied. Prevention of thromboembolic complications and opportunistic infections that may develop due to immune deficiency is required. Unilateral nephrectomy is an effective alternative to bilateral nephrectomy for patients with NS.[3,4]

This study aimed to evaluate the demographic, clinical, and follow-up results of patients with CNS who were followed up in our center between 2010 and 2020.

Material and Method

Ondokuz Mayıs University, Faculty of Medicine Ethics Committee was obtained for this study (Date: 12.11.2021, Number: 2021/493). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Eight patients with a diagnosis of CNS were included in this study and analyzed retrospectively. CNS was defined as the onset of NS within three months of birth.

Patients were classified according to the following definitions of nephrotic syndrome: the presence of profound proteinuria (random urine protein creatinine ratio >2 or greater than 40/mg/m2/hour), hypoalbuminemia (serum albumin <2.5 g/dl), and edema.

The data for individual patients, including demographic details and clinical information about the age of onset, syndromic features, a workup for infective etiology, genetic mutation study, and clinical outcomes, were recorded for each patient.

Statistical Analysis

Analyses were done using Statistical Package for the Social Sciences 22.0 (SPSS IBM Corp, Armonk, New York, USA). The characteristics of patients were determined using descriptive statistics. The data were expressed as number, percentage and range.

Results

Eight patients with CNS were included in this study between 2010 and 2020. Baseline demographic and clinical characteristics of children with congenital nephrotic syndrome are reported in **Table 1**.

The median duration of follow-up was 34 months (7months -9.5 years). The sex ratio (female/male) was one, and consanguinity concerned 62.5 % of families. The median age of initial diagnosis was 36 days (3 days- 8 months). Two of our patients were siblings. The patient was admitted when he was eight months old (his sibling died due to CNS complication), although the family noticed the swelling in the first three months, but admitted in the 8th month. He had less edema compared to other patients on the first visit. There was a history of prematurity in 5 patients. Edema was detected at the admission of all patients.

Perinatal infections or extra-renal findings were not detected in any of the patients. Ultrasonographic examinations were normal. In the genetic analysis, NPHS1 (Nephrin) homozygous mutation was detected in six patients, and coenzyme Q2 mutation was detected in one patient. This child had no extra-renal symptoms. He progressed to the end-stage renal disease shortly after the diagnosis of CNS and died due to sepsis during the peritoneal dialysis. No mutation was found in one patient, but his sibling had a nephrin mutation who was admitted at eight months.

Table 1
Baseline demographic and clinical characteristics of children with congenital nephrotic syndrome

Clinical characteristic	Results
Number of patients	8
Gender (m/f), number (n)	4/4
Prematurity, n (%)	5 (62.5)
Consanguinity, n (%)	5 (62.5)
Age at initial diagnosis, days, median (IQR)	36 (3 days-8 months)
Follow-up time, months, median (IQR)	34 months (7months -9.5 year)
Edema at admission, n (%)	8 (100)
Genetic testing, n	
	6 patient : NPHS1 (Nephrin) homozygous mutation
	1 patient : coenzyme Q2 mutation
	1 patient : no mutation
Extrarenal symptoms	None
Treatment, n (%)	
Antiproteinuric therapy, n (%)	8(100)
Unilateral Nephrectomy, n (%)	1 (12.5)
Peritoneal Dialysis, n (%)	4 (50)
Transplantation, n (%)	3 (37.5)
Complications, n (%)	4 (50)
Sepsis	3 patient (on dialysis , ex) 1 patient ,ex (first day of postoperative transplantation)

All patients were hospitalized at the diagnosis of CNS. Daily albumin infusions, angiotensin-converting enzyme inhibitor (ACEi), a high caloric diet, and mineral support were started. Four patients eventually progressed to end-stage, and peritoneal dialysis treatment was started during the follow-up. Unilateral nephrectomy was completed in one patient due to severe edema. During the follow-up, four of eight patients (three due to sepsis while on dialysis, one on the postoperative after the first day of transplantation) died. Three patients are followed up with kidney transplantation and one with supportive treatment.

Discussion

Congenital nephrotic syndrome (CNS) consists of heavy proteinuria, edema, hypoalbuminemia defined within the three months of birth. Management is very challenging as patients are prone to complications such as infection, thrombosis, and failure to thrive. CNS has a low incidence and a poor prognosis; end-stage renal disease (ESRD) often develops, requiring dialysis and renal transplantation therapy.[4-6] This is the largest series in our tertiary center that analyzed CNS.

Congenital Nephrotic syndrome is mainly caused by mutations in genes encoding structural or regulatory proteins of the glomerular filtration barrier. NPHS1, NPHS2, NPHS3 (PLCε1), WT1, and LAMB2 mutations are responsible for more than 80% of cases. Mutations in the NPHS1, NPHS2 genes are responsible for 95% of the cases. Genetic causes do not respond to glucocorticoid and other immunosuppression treatments.[4,7]

The NPHS1 mutation is also a major cause of CNS, more represented in the Finnish people, which was associated with Finnish-type CNS.[7-9] Premature birth, increased placental weight (>25% of the newborn weight), fetal edema, are the common findings of Finnish type CNS but there is no specific histopathology. The diagnosis is based on clinic and genetic analysis. In this present study, the disease type was Finnish in 7 patients, non-Finnish without syndrome in 1 patient. The number of male and female patients was similar (4 female and four male respectively). As Finnish-type CNS is inherited in an autosomal recessive manner, the incidence in both sexes tends to be similar.[10,11] Patients with Finnish-type were diagnosed earliest because clinical manifestations of the disease, such as the enlarged placenta and the massive edema, become evident shortly after birth in most patients with Finnish-type CNS. In our study, the earliest diagnosis of age is three days, and the median age of admission was 36 days. Seven patients presented with severe edema. The patient, who had the latest admission, was diagnosed when he was eight months old. The patient had minimal edema at presentation. The first child of the family was diagnosed with CNS and died due to sepsis. In the first three months, there was mild edema that the mother noticed. Or contrast to his other ex-sibling, he did not have severe edema since birth. Homozygous mutation p.Asn1077Ser is detected in the NPHS1 gene. This may be a “mild” mutation that causes a different phenotype other than the common primary mutation or the minor mutation.[11-13] Fin major and minor mutations were severe and presented with early symptoms. To date, more than 200 mutations have been identified all over the world.[10,11]

Patients with NPHS1 mutations do not have extra-renal malformations, but growth retardation was the most common extra-renal symptom.[14] The present study found only short stature as extra-renal symptoms, no other urogenital, mental retardation, eye-ear, or skeletal problems.

Mostly, patients with Finnish-type and non-Finnish-type with CNS do not respond to corticosteroids and immunosuppressive treatments because it is not an immunological disease. In these patients, CNS is progressive, often leading to end-stage renal disease or even death. Supportive treatment such as high caloric sodium-free diet, albumin infusion, mineral supports, unilateral/bilateral nephrectomy, and dialysis is the treatment modalities until kidney transplantation.[4,7,14,15] Early unilateral nephrectomy to reduce proteinuria and decrease the intense albumin infusions or bilateral nephrectomy with the initiation of dialysis followed by kidney transplantation have been reported to be effective in CNS . Recent reports stated that unilateral nephrectomy is more suitable than bilateral nephrectomy in CNS.[3,4,10]

Daily albumin infusion and ACEi, a high-calorie diet, mineral support were given to all patients in this study. Four patients eventually progressed to the end stage, and peritoneal dialysis treatment was started during the follow-up. Unilateral nephrectomy was completed in one patient due to severe edema and severe infections due to catheter-associated sepsis. After the unilateral nephrectomy, the need for albumin infusion decreased to once in 15 days.

Reports suggest unilateral nephrectomy with ACE inhibitor and indomethacin to reduce proteinuria with severe edema and related complications. Patients with mild proteinuria may require unilateral nephrectomy to facilitate proteinuria and albumin replacement, and patients with severe proteinuria may require bilateral nephrectomy.[4,5,15] A recent study by Murakoshi et al.[16] found that unilateral nephrectomy reduced proteinuria and shortened hospitalization with CNS. Recent reports showed that bilateral nephrectomy could cause life-threatening complications such as hypotension, infections and this rate was similar in the conservative approach. The decision for nephrectomy should be considered in the presence of severe complications of the CNS, including growth retardation, thrombosis, and difficulties in maintaining euvolemia despite optimization of conservative therapy.[17,18] During the follow-up, four of eight patients (three due to sepsis while on dialysis, one on the postoperative after the first day of transplantation) died. Three patients are followed up with kidney transplantation and one with supportive treatment with ACEi. Two patients underwent kidney transplantation at the age of 1 and the other patient at two years. Transplantation is the curative treatment for the majority of CNS patients. Early treatment of daily albumin infusions, nutrition, and timely bilateral nephrectomy followed by transplantation at the age of 1–2 years showed dramatic improvement in neurodevelopmental skills.[19]

Conclusion

According to our results, the underlying cause of most CNS cases are genetic, and the nephrin mutation being the most common. Management of complications in CNS is crucial for patient survival. Management of CNS should be individualized case by case in the presence of severe complications, including growth retardation, severe nephrosis, infections, thrombosis, and difficulties in maintaining euvolemia despite conservative therapy.

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

Conflict of Interest: There are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

Ethics Committee Approval: Ondokuz Mayıs University, Faculty of Medicine Ethics Committee was obtained for this study (Date: 12.11.2021, Number: 2021/493).

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Informed Consent: Informed consent was obtained from the parents of the patients.

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Original Article

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Paediatric Behçet's Disease: Data From A Single Center Experience in Turkey

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Abstract

Behçet's disease (BD) is a multisystemic inflammatory disease with unknown etiology. It is characterized by recurrent oral and genital ulcerations, uveitis, and skin lesions, various musculoskeletal, gastrointestinal, central nervous system, and vascular manifestations. The aim of this study was to analyse the demographic characteristics and clinical features, treatment in Turkish paediatric BD from a single center experience. The records of 36 patients with BD who were diagnosed according to the International Study Group criteria between January 2017 and January 2019 in the department of paediatric rheumatology, were retrospectively reviewed. Data on demographic, clinical features and therapy were collected. A total of 36 (19 male) patients were included in this study. Mean age at disease onset was 9.36±4.45 years and mean age at diagnosis 13.99±2.83 years. The frequencies of signs/symptoms were: recurrent oral aphtosis 100%, genital ulcers 80.6%, musculoskeletal 30.6%, ocular 16.7%, neurological 11.1% and vascular involvement 11.1%, gastrointestinal 2.8%. Colchicine and corticosteroids were the main treatments. In this single-center retrospective study, we analyzed the data of paediatric BD and their treatment from a single center in Turkey. The presented small series and the literature review suggest that paediatric BD is a heterogeneous disease with varied clinical manifestations.

Keywords: Juvenile, Behçet syndrome, oral ulcer

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Introduction

Behçet's disease (BD) is a systemic auto-inflammatory disease affecting all sized vessels and is therefore classified as a variable vasculitis. It has unknown origin that was first demonstrated by a Turkish dermatologist, Dr Hulusi Behçet in 1937.[1] It is commonly seen in the region of the 'Silk Road', which also includes our country. It is well known that it may affects many organ and/or systems such as central nervous system, musculoskeletal system, and gastrointestinal system, and it is characterized by ocular and cutaneous findings, as well as recurring oral and genital ulcers.[2] BD generally presents in the second to fourth decades of life and although the incidence of paediatric onset is rare.[3,4] But it is rising in children gradually due to awareness. Unfortunately, there is no pathognomonic test to make the correct diagnosis, which is based on clinical criteria. The mostly wide criteria used are those developed by an international study in 1990 called the International Behçet's Study Group (ISG) with 85% sensitivity and 96% specificity.[5,6] Recently, the Paediatric BD group (PEDBD) has developed a new set of criteria for the diagnosis of BD in children.[2] This PEDBD criteria has higher sensitivity (91.7%), but lower specificity (42.9%) when compared to ISG.[7] There are limited data regarding treatment and outcomes of paediatric patients with BD especially in Turkey. The primary aim of this study was to collect information on demographic and clinical features from paediatric patients with BD in a single center and compare them with the reports from the literatüre.

Highlights

- Behçet's disease is characterized by recurrent oral and genital ulcerations, uveitis, and skin lesions, various musculoskeletal, gastrointestinal, central nervous system, and vascular manifestations.
- The main treatment in mucocutaneous involvement is colchicine, and in organ and system involvement, treatment varies according to the site of involvement.

Material and Method

The files of patients who had been seen in our outpatient department (during routine follow-up visits) between January 2017 and January 2019 were retrospectively evaluated. Demographic, clinical and laboratory data of patients were collected from the patients' files and hospital database. An information form was completed about demographic features (sex, age at onset, age at diagnosis), ethnicity, family history, follow-up time, clinical manifestations (mucocutaneous, musculoskeletal, ocular, gastrointestinal, vascular, neurological manifestations), the presence of human leucocyte antigen (HLA)- B51 positivity and treatment.

Behçet's disease was diagnosed according to the ISG criteria.[5,6] The parents gave their written informed consents prior to the present study, which was approved by our hospital ethics committee. The study was carried out with the permission of Dr. Sami Ulus Maternity and Child Health and Diseases Training and Research Hospital Clinical Research Ethics Committee (Date: 04.03.2021, Decision No: E-21/03-121). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients were excluded from the study if no approval from their families to participate in the study. Disease onset after the age of 16 was considered a reason for exclusion. Patients who had no clear diagnosis of BD were excluded.

Statistical Package for Social Sciences (SPSS) (version 22.0; Chicago, IL, USA) was utilized for statistical analysis. According to the determination of distribution tests, continuous variables were summarized as mean and standard deviation (SD) and as median and minimum-maximum where appropriate. Clinical and demographic characteristics were summarized by mean and standard deviation for continuous variables and count and percent for categorical variables.

Results

The study group comprised 36 paediatric Behçet's disease with a mean age of 16.61±3.10 years. Mean age at onset was 9.36±4.45 years and mean age at diagnosis 13.99±2.83 years. There was a mean of approximately 4 years between the initial manifestation and diagnosis. All patients were Turkish except one patient (from Syria). The ratio of male to female in the study was 1.11 (female: 17, male:19). The time between the development of uveitis and the diagnosis of Behçet disease was 6 years for this patient. Among all pateints, the most frequent of sign/symptom was recurrent oral aphtosis with 100%. The patients' demographic characteristics and clinical findings are summarised in **Table 1**. Ocular involvement occurred in 6 patients: 2 (33.3%) as anterior uveitis, 2 (33.3%) posterior uveitis, 2 (33.3%) bilateral panuveitis.

Among 4 patients (11.1%) who were found to have vascular involvement in the follow-up, one had arterial involvement, three had venous involvement. Venous involvement occurred in 6 site in 3 patients, including cerebral venous thrombosis (one patient had sagittal venous thrombosis and transverse sinus thrombosis, one patient had right iliac vein thrombosis and left femoral vein thrombosis, one patient had sagittal venous thrombosis and right femoral vein thrombosis). The patient with arterial involvement had thrombosis in the percheron artery. Among four patients who were found to have central nervous system (CNS) involvement, one had parenchymal involvement, and three had non-parenchymal involvement. In the patient with parenchymal involvement had other clinical findings for seven years. He was admitted with a history of walking disability. He had parenchymal and spinal cord involvement at MR images compatible with BD. Two patients with non-parenchymal involvement were admitted with headache as the initial neurological symptom. They revealed benign intracranial hypertension. Two of them had cerebral venous sinus thrombosis. The other patient with non-parenchymal involvement was presented with fever, occult onset of blurry vision, which progressed to vision loss, and consciousness. He had percheron artery thrombosis.

Table 1
Clinical features of paediatric BD in the literature

	Çirkinoğlu 2019 (Turkey)	Hu 2019 (Taiwan)	Shahram 2018 (Iran)	Gallizzi 2017 (Italy)	Yıldırım 2020 (Turkey)	Tekin Ekici 2021 (Turkey)	Batu 2020 (Turkey)	Present Study
Total number	34	55	204	110	57	72	165	36
Male/female ratio	1,1	0,6	1,02	1,3	0,72	0,8	0,91	1,1
Mean age at onset	11.1	11	10.5	8.3	10	11	11	9.3
Recurrent oral aphtosis (%)	97	100	91.7	94.5	100	100	100	100
Genital ulcers (%)	62	69.1	42.2	33.6	56	68.1	64.8	80.6
Pseudofoliculitis/Pustular lesions (%)	82	36.4	43.1	39.6	35	19.4	26.8	38.9
Erythema nodosum (%)	N/A	N/A	10.3	N/A	14	9.7	19.4	25
Vascular manifestations (%)	32	1.8	6.4	10	17	18.1	11.5	11.1
Pathergy test positivity (%)	50	N/A	57	14.5	19	28.8	27.3	33.3
Ocular manifestations (%)	35	27.3	66.2	43.6	47	20.8	13.3	16.7
CNS* involvement (%)	18	3.6	4.9	30.9	9	15.3	15.8	11.1
Gastrointestinal involvement (%)	5.8	N/A	N/A	42.7	9	20.8	12.1	2.8
Joint involvement (%)	38	27.3	30.9	N/A	31	36.1	44.8	27.7
Positive family history for BD (%)	N/A	N/A	N/A	12	31	41.7	29.1	41.7

* CNS: central nervous system * N/A, not available

Gastrointestinal system (GIS) involvement developed in one patient (ulcerated lesions in the terminal ileum). No case pulmonary artery aneurism and heart involvement developed in our cohort. Pathergy test was positive in 12 (33.3%) of cases in which it was performed (25/36). Table summarises the clinical phenotype of our paediatric cohort compared to other paediatric series.

Median frequency oral aphtosis was 24 (4-120) /year in before colchicine and 3.5 (0-12) /year in after colchicine. Median frequency genital ulcer was 1 (0-5) /year in before colchicine and 0 (0-2) /year in after colchicine. All patients had significant benefit from colchicine for oral aphtosis and genital ulcers. Only azathioprine was received in 2 patients because of colchicine-resistant aphthosis lesions. There were familial cases in 41,7% of our patients. Two of them were first-degree relatives, others were second-degree relatives. HLA-B51 testing was performed in 12 patients and was present in 7 (58.3%). Most of our patients (77.7%) had increased acute phase reactants (erythrocyte sedimentation rate and C-reactive protein). Mean ESR values at the time of diagnosis was 28 mm/hour (15-98) and mean CRP values at the time of diagnosis was 27 mg/L (6-75). Genetic testing for Familial Mediterranean Fever (FMF) was performed in 9/36 patients because of recurrent fever and abdominal pain. Results were negative in 6 cases and the other 3 patients had heterozygous mutations. M694V heterozygous mutations were detected in two of them, and M680I heterozygous mutation was detected the other patient. These mutations didn't change the treatments. All patients received topical steroid therapy (for ocular and/or oral aphthous lesions) and colchicine. Immunosuppressants recevied in 16 patients (44.4%) with the following drugs: 9 azathioprine, 4 cyclophosphamide, 2 methotrexate, 1 sulphasalazine. Anti-tumor necrosis factor-alpha (anti TNF-α) was used in 2 patients (adalimumab). The patient who was found to have GIS involvement (ulcerated lesions in the terminal ileum) were treated with sulphasalazine and adalimumab. The other patient using adalimumab had chronic arthritis in the right knee. Anticoagulant treatment was given additionally to patients who had vascular involvement. Four patients who had have central nervous system (CNS) involvement were treated with cyclophosphamide in addition to high-dose intravenous steroid treatment. Non Steroidal Anti-Inflammatory Drugs (NSAIDs) were used in 20 cases for arthritis and arthralgia. The follow-up of all patients who were evaluated in the study is still continuing.

Discussion

In this single-center retrospective study, we analyzed the data of paediatric BD and their treatment from a single center in Turkey and compared our findings to those of other paediatric studies (**Table 1**). BD is less frequent in childhood. In the literature, there are few data on paediatric BD in Turkey, mostly limited to adult data. The mean age of disease onset was 9.3 years in our study, similary to most of the studies. A reported as 8.3 years in a multi-center study conducted from Italy by Galizzi et al. in which 110 paediatric patients with BD were evaluated.[8] Atmaca et al and Çirkinoğlu et al showed in their cohort average age at onset was 11.6 and 11.1, respectively.[9,10] But in some studies it has been shown to present extremely very earlier.[11,12] The reason for this is not known exactly. In our study, we noted a diagnostic delay of 4 years, similar to in previous studies.[8,12] In the literature, adult and paediatric studies have reported that the mean delay is two or four years.[12,13] Nanthapisal et al noted a significant diagnostic delay up to 13.5 years in their cohort. They commented that the disease is not well known in the world.[11]

The male/female ratio was 1,1 in our cohort and was consistent with the literature. Shahram et al was reported as 1,02 in their stduy.[14] Male predominance seems to be slightly more common in children like adults studies.

Most of studies showed that recurrent oral aphtosis was the most frequent clinical manifestation (**Table 1**). Our cohort demonstrated that recurrent oral aphtosis is the most common symptom. Similar to that of adults, the most common initial manifestation of BD in children is oral ulcers: 97.3% in our study, and 100% and 75% in others.[12-14]

The second most common clinical finding in our patients was genital ulcer (80.6%) similarly Hu et al. and Nanthapisal et al. studies.[11,12] Galizzi et al showed that in 110 pediatric patients with BD, the second most common clinical finding was reported to be ophthalmologic involvement.[8] Another study from Turkey the second most common cause for presentation was cutaneous lesions (82%).[10] Interestingly, only 16.7 % of the children had ocular involvement in our series, this contrasts with the high frequency of 30-35 % reported in other Turkish studies[9,10] and 43.6 % in Italian children.[8]

Pathergy test positivity has been reported to be very different, especially in children.[8-10] We found a positivity of 33.3%.

We observed 41,7% of our patients had a positive family history for BD. This rate seems to be higher than the literature. Galizzi et al. showed that this rate to be 12%.[8] Also Koné-Paut et al. found familial cases in 15% of children.[15] This may be due to the frequent occurrence of BD in Turkey.

Although HLA-B51 may be positive in healthy people, it is known that highlier positive in patients with BD than in healthy people.[16] HLA-B51 testing was performed in 12 patients and was present in 7 (58.3%).

Ocular involvement has a wide range (8-66%) in the literatüre.[11-14] Ocular involvement occurred in 6 patients (16.7%) in our study. Two of them had bilateral panuveitis. In the literature, it is reported that panuveitis is the most common ocular involvement in BD. Similarly Atmaca et al showed that panuveitis in 13 eyes (23.6%).[9] Similar to our observation, a retrospective study of 86 paediatric BD cases by Kone-Paut et al reported that panuveitis in 28% patients.[15] In a study from Italy, ocular involvement is the second manifestation in their cohort (43.6%).[8] Shahram et al reported ocular lesions were more frequent (66.2%) compared to other reports.[14] This difference could be due to patients with different ethnic backgrounds in different countries.

Gastrointestinal system involvement rates reported in studies from Italy and United Kingdom has been reported 42-58% that seems to be higher rate especially according to studies reported from Turkey.[8-11] Prevalence of GIS involvement changes signifcantly across diferent ethnicities, being much more common in the Far East.[17-23] The frequency was as high as 50% in a Japanese cohort and 1% in a study in Turkey.[17-23] In the children as was the case in adult studies of GIS involvement is less common in Turkey.[10,19]

Consistent with the literatüre vascular involvement developed in 11.1% of the our patients. In our series, the patients who had vascular involvement, but did not have pulmonary involvement, were treated with heparin infusion or subcutaneous enoxaparin and warfarin. There were no complications or side effects.

In BD, there is no definite recommendations for the treatment of pediatric patients. Treatment is usually based on adult studies and according to the severity of organ involvement. The systemic treatments more commonly used were colchicine and corticosteroids, followed by immunosuppressants. All our patients received colchicine as monotherapy, presented by recurrent oral aphtosis, genital ulcer and skin lesions. All patients had significant benefit from colchicine for oral aphtosis and genital ulcers. Only azathioprine was received in 2 patients because of colchicine-resistant oral aphthosis lesions. Two patients received biologic therapy. Pulmonary artery aneurism wasn't found in our cohort. No patient died.

There are some limitations to our study. Retrospective study and limited number of patients may be considered as our limitations.

Conclusion

Our data showed a slightly male predominance in juvenile Behçet disease. The clinical spectrum of our cohort in this study was similar to that of other reports; however, genital ulcers were noticed to occur more frequently; while vascular, gastrointestinal and neurologic involvement was seen rarely in our series. Demographic and clinical features of paediatric BD may vary according to geographical region, gender and ethnicity. We hope that this study will contribute to the epidemiologic data of paediatric BD which may exhibit different clinical and demographic features in different parts of the world.

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

Conflict of Interest: There are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

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Evaluation of Adolescents with Restless Legs Syndrome: Relation to School Success

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Abstract

Restless Legs Syndrome (RLS), which may be a missed diagnosis in children, is seen at an important frequency. The aim of this study was to investigate the clinical characteristics of patients with RLS and to show the effect of RLS on school success. Forty-three patients with RLS and 43 healthy volunteers were included to the study. Blood samples were taken to measure ferritin. The averages of school exam scores were recorded. The patient group was classified as mild, moderate, severe, and very severe according to the RLS rating scale. The daytime sleepiness was measured by the Epworth Sleepiness Scale (ESS). The"Turgay DSM-IV-Based Child and Adolescent Disruptive Behavioral Disorders Screening and Rating Scale (T-DSM-IV-S)" was completed by parents, and patients' inattention, and hyperactivity-impulsivity scores were compared with the control group. According to the RLS rating scale scores 25.6% (n:11) were evaluated as mild, 60.5% (n:26) were moderate and 14% (n:6) were severe. The mean ferritin level was significantly lower in the patient group. The mean score of inattention and hyperactivity-impulsivity in the patient group to be significantly higher than the control. The mathematics and science course mean grades were significantly lower in the patient group than the controls (66.7±17.7 vs 74.2±11.7). ESS scores were found to be significantly higher in the patient group. In this study, RLS has been found associated with ADHD and iron deficiency, similar to previous studies. There are not many studies on the effects of RLS in children on daily life and this study has objectively shown that RLS reduces patients' school achievement.

Keywords: Adolescents, restless legs syndrome, sleep related movement disorders, Fabry's disease

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Introduction

Restless Legs Syndrome (RLS) is a sensory-motor disorder that causes a need of movement in the limbs. It is classified as sleep related movement disorder.[1,2] Typically, symptomsget worse during rest especially in the evening, and are relieved with movement.[2,3] RLS can be seen as primary, or secondary to chronic renal failure, iron deficiency anemia, and pregnancy. Primary RLS is seen at younger ages and often has a familial history.[3]

Genetic factors, dopaminergic dysfunction of the central nervous system (CNS), and iron deficiency in brain tissues are shown among the causes of RLS.[2,4] Iron deficiency is the most common cause of RLS.[3] Iron acts as a cofactor for tyrosine hydroxylase, a rate-limiting enzyme in dopamine synthesis. Iron dysregulation may cause dopamine abnormalities in RLS.[1,4] It is known that iron treatment improves symptoms when serum ferritin is below 50 ng/mL.[5]

Highlights

- Restless Legs Syndrome (RLS) is a sensory-motor disorder that causes a need of movement in the limbs and classified as sleep related movement disorder.
- It affects patients' sleep quality, daily activities, emotional states, and energy negatively. Patients have difficulty initiatingand maintaining sleep. This causes impaired concentration, depression, anxiety, sleepiness, and poor work performance leading to sleep disorders.

Muscle disorders, muscle cramps, positional disturbances, vascular diseases, peripheral nerve diseases, joint disorders, attention deficit hyperactivity disorder (ADHD), periodic leg movement disorder (PLMD), Fabry's disease and growth pains are included in the differential diagnosis.[1,6,7] Coexistence with iron deficiency, ADHD, or chronic renal failure are more frequent.[8] Iron deficiency and CNS dopaminergic dysfunction plays a role in the pathophysiology of ADHD such as RLS.[8] Fabry's disease is a X-linked recessive disorder characterized by a deficiency in the activity of α -Galactosidase A. Symptoms are defined as burning, tingling and disturbing pain in hands and feet. It usually starts in the first decade and decreases with age. Fabry disease is very rare, but symptoms can be confused with RLS and patients may be misdiagnosed.[7] Restless Legs Syndrome is rated as mild, moderate, severe, and very severe, according to the RLS rating scale developed by the International Restless Legs Syndrome Working Group (IRLSSG). This scale, which is used to determine the severity of the disease and the need for treatment, assesses how much the symptoms affect quality of life and the frequency of symptoms.[9]

Restless Legs Syndrome may get worse if not treated. It affects patients' sleep quality, daily activities, emotional states, and energy negatively. Patients have difficulty initiatingand maintaining sleep.This causes impaired concentration, depression, anxiety, sleepiness, and poor work performance leading to sleep disorders. All of these have been shown to reduce the quality of life of patients.[10,11]

RLS is seen with a high frequency, but it is often misdiagnosed.The number of studies examining the effects of RLS on school success is very few.The aim of this study was to investigate the clinical characteristics of 43 patients with diagnosed RLS and to show the effect of RLS on school success.

Material and Method

This study was performed at Erciyes University's Faculty of Medicine after Erciyes University Clinical Research Ethics Committee approval. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

There was an earlier study conducted in Kayseri provincial central to determine the prevalence of RLS in 13-16-years old adolescents. Fourty three voluntary patients who had been diagnosed with RLS by survey and telephone interview, from the previous study were included in the present study.[13] Fourty three healthy volunteers of similar age and sex were identified as the control group.

Detailed physical examinations of the patients and control groups were performed. Blood samples were taken from both groups to measure complete blood count, liver and kidney function tests, ferritin and vitamin B12, and cholesterol levels. Blood sample was also taken from the patient group to measure the level of α -galactosidase for use in the Fabry disease marker. The average history, literature, mathematics and science exam scores from the end of the last year were recorded.

The RLS Rating Scale, consisting of ten questions, was applied and patients were classified as mild, moderate, and severe according to this scale. There were no patients classified as very severe. These groups were compared according to ferritin levels and lesson exam scores.

The daytime sleepiness of the patient and control groups were measured by the Epworth Sleepiness Scale (ESS). The Turgay DSM-IV-Based Child and Adolescent Disruptive Behavioural Disorders Screening and Rating Scale (T-DSM-IV-S) is scale, developed by Turgay, which is mainly used for screening disruptive behavior disorders including ADHD, oppositional defiant disorder, and general behavioral disorders; and its reliability and validity studies for the Turkish version were done by Ercan et al.[14,15] The scale consists of 41 questions, 9 for hyperactivity, 9 for attention deficit, 8 for oppositional defiance, and 15 for general behavioural disorders. The severity of each item is measured by a four-point Likert-type scale. In our study, the T-DSM-IV-S was fulfilled by parents of both the patient and control groups. Parents were informed how to complete and use the scoring system of the T-DSM-IV-S.

The data was evaluated using the SPSS 15.0 package program. In statistical analysis, the Pearson Chi-square test, Fisher's exact test, unpaired t test, one way ANOVA test (post hock Scheffe test), and logistic regression analysis were used. Values of $p<0.05$ were considered significant.

Results

Gender and age distributions of patients and control groups were equal; 60.5% of the groups (n=26) were girls and 39.5% (n=17) were boys. The mean age was 14.5± 1.0 years (min: 13 max: 16). In the patient group,2 people had iron deficiency, 2 people had ADHD, and 1 person had chronic hepatitis B. Totally, five patients were receiving treatment. None of the participants in the control group had additional pathology. In both groups, the physical examinations of the participants were normal and there were no orthopaedical problems or any infection findings.

According to the RLS rating scale scores 25.6% (n: 11) were mild, 60.5% (n: 26) were moderate and 14% (n: 6) were grouped as severe.

Mean ferritin level found 29.2±16.0 ng/mL in the patient group and 44.8±28.0 ng/mL in the control group. The difference was statistically significant (p=0.002). Ferritin values were significantly higher in the milder group but no difference was found between the moderate and severe groups (**Table 1**).

There was no significant difference between the patient and control groups from the standpoints of vitamin B12, triglyceride and cholesterol levels (**Table 2**). Alpha Galactosidase enzyme level was measured for Fabry disease diagnosis in patient group and enzyme deficiency was not detected.

Table 1
Ferritin Values According to RLS Severity

RLS Severity	n	Ferritin (ng/mL) (Mean±SD)
Mild	11	41.0 ± 11.0[a]
Moderate	26	25.8 ± 16.8[b]
Severe	6	21.9 ± 7.5[b]
Total	43	29.2 ± 16.0

F= 5.01, p=0.011, [a,b]: The difference between groups with different letters is significant.

Table 2
Comparison of B12 vitamin, Triglyceride and Cholesterol Values in Patient and Control Groups

Values	Patient (n=43) (Mean±SD)	Control (n=43) (Mean±SD)	p
B12 (pg/mL)	291.1±119	288±88.2	0.786
Triglyceride (mg/dL)	114.3±57.8	97.9±44.2	0.146
Cholesterol (mg/dL)	138.2±25.2	137.4±24.4	0.881

The mean grades of mathematics and science courses were found significantly lower in the patient group than the controls. (66.7±17.7 vs 74.2±11.7) (p=0.022). However, the mean grades of history and literature in the study groups were not significantly different (75.2±13.5 vs 77.2±9.0) (p>0.05). In patients classified as severe, the mean grade point was lower than in the other groups; but there was no statistically significant difference between the groups (**Table 3**)

The "DSM-4 based Scanning and Assessment Scale for Behavioral Disorders in Children and Adolescents" was filled out by parents. The mean score of inattention and of hyperactivity-impulsivity in the patient group (9.30±6.63/8.91±6.14) was significantly higher than the control group (5.84±3.81/4.91±3.09). Additionally, the mean scores of mild, moderate, and severe groups were compared and no significant difference was found between the groups (**Table 4**).

Daytime sleepiness was accepted when the ESS score was 10 or more. Mean ESS scores and daytime sleepiness in the patient and control groups were compared. Both ESS scores and percentage of daytime sleepiness were found significantly higher in the patient group (**Table 5**).

Discussion

The number of studies on the effect of RLS on daily life in children is increasing. Studies have been carried out to examine the daily life effects of RLS, which is known to distrupt sleep quality and to cause the patients to work poorly; but there have been few studies on school achievement. In a study performed by Yılmaz et al, children were asked to describe their school success as good-medium-poor and school performance was found to be poorer in RLS cases.[16] Similarly, in this study, the lesson's exam scores of the patients and control groups

Table 5
ESS Scores and Daytime Sleepiness in Patient and Control

Groups	n	ESS score	Daytime Sleepiness	
		Mean ± SD	Number	%
Patient	43	10.8±3.4	29	67.4
Control	43	6.5±3.6	9	20.9

t=5,641, p<0.001, X^2=18.860, p<0.001

Table 3
History and Literature) and Mathematics and Science Lessons Scores According to the severity of RLS

Lesson	Severity of RLS				p
	Mild (n=11) (Mean±SD)	Moderate (n=26) (Mean±SD)	Severe (n=6) (Mean±SD)	Total (n=43) (Mean±SD)	
History and Literature	71.5±14.5	77.0±13.0	74.7±15.3	75.2±13.6	0.536
Mathematics and Science	64.9±18.4	70.0±16.2	55.6±20.5	66.7±17.6	0.187

Table 4
Inattention and Hyperactivity-Impulsivity Scores According to the severity of RLS

Scores	Severity of RLS			F	p
	Mild (n=11)	Moderate (n=26)	Severe (n=6)		
Inattention Score (Mean±SD)	8.91±6.38	8.69±6.42	12.67±7.37	0.927	0.404
Hyperactivity-Impulsivity Score (Mean±SD)	7.00±7.04	9.19±5.41	11.17±7.49	0.963	0.390

were compared. The Mean grade of mathematics and science courses were found significantly lower in the patient group. In patients classified as severe, the mean grade point was lower than in the other groups; but there was no statistically significant difference between the groups. This situation has been associated with RLS causing problems in focusing on the lesson. This may be preceded by the fact that RLS causes leg pain, sleep and movement problems. Further studies are needed to quantitatively measure focus and attention skills in RLS patients.

Iron deficiency is known to be involved in the causes of Restless Legs Syndrome and improvements in the symptoms of patients with iron treatments were achieved, even if serum iron levels and haemoglobin levels were normal. In some adult studies, ferritin margins that are considered normal, such as 50 ng/mL for 75 ng/mL, have been shown as limit values for starting treatment in RLS.[17-19] In our study, Ferritin values of the groups were compared and were found lower in the patient group than in the control group. According to the degree of disease, Ferritin values were found highest in the mild disease group than in the other two groups. There was no difference between the moderate and severe groups, but this could be due to the small number of cases in the group. Considering that sensory disturbances that may develop due to lack of vitamin B12 might be mixed with the disturbing sensations in RLS, vitamin B12 levels were compared in the patient and control groups; and there was no significant difference between the groups.

In a study conducted by Dominguez et al. in Fabry patients; it has been shown that RLS symptoms may be related to neuropathic pain, and symptoms are reduced by enzyme treatment.[7] In this study, the enzyme activity of alpha galactosidase was checked for Fabry's disease in the patient group, and enzyme deficiency was not detected.

ADHD is a disorder associated with RLS, and in both, the pathophysiology is characterized by iron deficiency. According to previous studies, approximately 25% of RLS patients have ADHD, whereas 12% to 35% of ADHD cases have RLS.[19] Picchietti et al. found that 23.9% of children between 8-11 years of age and 26.8% of children between 12-17 years of age, have RLS accompanied with ADHD.[20] In our study, carelessness and impulsivity-hyperactivity scores in the patient group were significantly higher than the control group.

Restless Legs Syndrome worsens the quality of life of patients when their diagnosis is delayed or untreated. RLS has been shown to cause depression, anxiety, daytime sleepiness, and poor work performance, with sleep disturbance the leading problem.[20-22] Picchietti et al. found sleeping disorders in 69.4% of patients with RLS.[20] In our study, the mean EES score was found to be 10.8±3.4 in the RLS group, and 6.5±3.6 in the control group. 67.4% of the RLS patients had daytime sleepiness similar to the above mentioned study (ESS score> 10).

Conclusion

In this study, RLS has been found to be associated with ADHD and iron deficiency, like previous studies. There are few studies on the daily life effects of RLS, which is difficult to diagnose, in children and this study has shown objectively that RLS reduces patients' school achievement.

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Evaluation of COVID-19 Patients Admitted to Pediatric Emergency Department

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Abstract

The Coronavirus disease (COVID-19) rapidly spread all around the world and was declared a worldwide pandemic by World Health Organization in March 2020. We aimed to investigate the clinical, demographic and laboratory characteristics of COVID-19 in children admitted to the pediatric emergency triage. Epidemiological, clinical, laboratory, and radiological data of children were collected retrospectively and analyzed to compare by symptoms. A total of 213 pediatric cases with COVID-19 were included. Most of the patients were asymptomatic (63.8%). The main clinical features were mild symptoms including fever (7.5%), cough (6.5%), myalgia (6.3%) or no (63.8%). Of the patients who had CT scan, 25% had specific findings of COVID-19. Ground-like opacities were common radiological findings (25%). Symptomatic patients had higher lymphopenia rate (p=0.03), higher CRP and procalcitonin (PCT) values (p=0.04, p=0.04), lower age (p<0.001) and lower neutrophil count (p=0.01). The rate of neutropenia and leukopenia were higher in asymptomatic patients (p=0.15, p=0.05, respectively). The most common cause of transmission in children is family contact. Home isolation was recommended for 89.6% of the patients, 10.3% were hospitalized, 2.3% needed an intensive care unit (ICU). Only one death was reported. We found found that children with COVID-19 are generally mild severe or asymptomatic clinic. Young children were relatively more symptomatic than older children, and those with underlying diseases often needed intensive care unit. The most important laboratory findings difference between symptomatic and asymptomatic patients are lymphopenia, increased CRP and PCT values (p=0.04 for all three parameter).

Keywords: COVID-19, children, pediatric emergency

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Introduction

In the middle of December 2019, an outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) occurred in Wuhan, Hubei Province, China, and from there it spread worldwide.[1] The number of cases outside China rapidly increased, urging the World Health Organization (WHO) to declare COVID-19 as a pandemic on March 11, 2020.[2] The first case from Turkey was reported on March 13, 2020. As of 24 June 2020, a total of almost 9 million COVID-19 patients including 477 634 deaths (5.2%) in 216 countries have been confirmed by the WHO.[3] COVID-19 can rapidly spread from human-to-human and is more contagious than other notable members of the coronavirus family, such as Middle Eastern respiratory syndrome (MERS) and SARS.[4,5] This virus is air borne, and thus transmitted via respiratory droplets and direct contact. Common symptoms reported so far include fever, myalgia and dry cough.[6]

Highlights

- The coronavirus disease (COVID-19), which caused a pandemic by the World Health Organization in March 2020, affects both children and adults. COVID-19 usually progresses with mild or asymptomatic clinical condition in children compared to adults.
- Home isolation is recommended for the most of patients, but children with underlying diseases (such as prematurity, lung and heart diseases, immunodeficiency, allergic diseases) may need hospitalization.
- There are no significant laboratory findings of COVID-19 disease in children, but symptomatic patients may have a higher lymphopenia rate, higher CRP and procalcitonin values, lower age, and lower neutrophil counts.

Children with COVID-19 have been reported to be asymptomatic or with mild clinical symptoms compared to adults. The reason why it is less common in children and has a milder clinical prognosis is unknown.[7-9] Therefore, knowledge about COVID-19 in children is limited. Although there are many studies on COVID-19 in adults, studies on children are very few compared to adults. In this study, we aimed to evaluate the symptoms and characteristics of children with COVID-19 who were evaluated in the pediatric emergency department.

Material and Method

A total of 213 children were included in this retrospective study who presented at the Pediatric Emergency Department Triage from March 25 to July 31, 2020. According to the clinic presentation of the patients who admitted to the pediatric emergency triage, the patients were examined in the pediatric pandemic outpatient clinic or the pediatric emergency yellow room. Epidemiological, clinical, laboratory, and radiological data were collected, including the age, sex, clinical signs and symptoms, outcomes, laboratory data, chest X-ray (CXR) findings, chest computed tomography (CT).6,9 All the children were tested with COVID-19 reverse transcriptase-polymerase chain reaction (RT-PCR) tests and were found to be positive. These RT-PCR tests and blood samples were performed in pediatric pandemic outpatient clinics and pediatric emergency yellow areas rooms due to close contact with a confirmed case or with someone presenting with symptoms of COVID-19, such as fever, cough, myalgia, diarrhea, and/or vomiting. Blood tests were complete blood count (CBC), electrolytes, C-reactive protein (CRP), and procalcitonin (PCT). Nasal or nasopharyngeal swab specimens tested positive for 2019-nCoV nucleic acid using RT-PCR assay. Those who were over the age of 18, had no contact history and no complaints, and applied to have a test because of their curiosity were excluded from the study. Patients aged 0-18 years, who had contact with COVID-19 positive people and had symptoms of COVID-19 were included in the study. In addition, patients were divided into two according to their symptoms (symptomatic and asymptomatic group). The two groups were also compared according to epidemiological, clinical, laboratory and radiological findings.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov- Smirnov test was used to evaluate the normality of the parametric data. Numerical variables are presented as mean±SD or median (min-max). Mann-Whitney U test was used for of data that were not normally distributed, and Chi-square test was used for analysis of categorical variables. Values of $p < 0.05$ was considered statistically significant.

Results

In our study 106 (49.8%) of the patients were male and 107 (50.2%) were female. The mean age of the patients was 9.55±5.15 years. The body temperature mean was 37.1±0.68°C and the oxygen saturation mean was 96.2±2.78%. The median time between the onset of symptoms and diagnosis was 3 (0-6) days. Vaccines of 96.2% of the patients were complete, 3.8% of them were unknown. Most of the patients (99.1%) had a history of contact with COVID-19 patients, 0.9% did not know. The contact environment was within the family, social environment and the unknown, respectively. Contact with patients was generally within the family, and they were mothers, fathers, parents, grandparents, and friends, respectively. None of the patients had a history of alcohol or smoking. CXR had that of 95 patients and 12.6% of these patients had consolidated areas. CT scan had 48 patients and 25% of them had findings consistent with COVID-19 (ground glass opacities, local patch shadow). Home isolation was recommended for 89.6% of the patients, 10.3% were hospitalized, 2.3% needed an intensive care unit (ICU). Patients who needed an ICU had underlying diseases (2.3%) such as obesity, asthma and prematurity. The rate of those who were discharged after recovery was 99.5% , only 1 patient with a history of prematurity died of pneumonia. No treatment was initiated in 71.8% of

the patients, only antipyretic was prescribed to 8.5% of the patients, and antibiotic (Azithromycin: 15 mg/kg the first day, then 7.5 mg/kg once a day for other 4 days or Amoxicillin 90 mg /kg/day in 3 doses, in case of possible oral intake) and antipyretic (10–15 mg/kg every 4–6 h) drugs were prescribed to 15.5% of the patients (**Table 1**). There were 136 (63.8%) asymptomatic patients and 77 (36.2%) patients were symptomatic. The symptoms of the patients were fever, cough, myalgia, diarrhea, nausea-vomiting and rash respectively. Important laboratory findings in our study were 5.1% leukopenia, 8.9% neutropenia, 16.4% lymphopenia and 0.5% thrombocytopenia (**Table 2**). Symptomatic and asymptomatic patients were compared according to data. There was no significant difference between the groups in terms of gender, leukocyte count, eosinophil count, platelet count and MPV values. Symptomatic patients had lower age, higher fever, lower oxygen saturation, lower neutrophil count and lower lymphocyte count ($p<0.05$) (**Table 3**). Leukopenia, neutropenia and thrombocytopenia rates were higher in the asymptomatic group but not statistically significant ($p>0.05$). In addition, symptomatic patients had significantly higher PCT and CRP values ($p=0.04$) and higher lymphopenia rate ($p=0.04$) (**Table 3**). PCT values of 19.9% of the patients were above 0.1 ng/ml and most of them were symptomatic patients (82.8%).

Table 1
Demographic findings and clinical presentation of Covid-19 pediatric patients

Age (year) (mean±std)	9.55±5.15	
Gender (n) (%)		
Male	106	49.8
Female	107	50.2
Fever (°C)	37.1±0.68	
SpO_2 (%)	96.2±2.7	
Contact environment (n) (%)		
Family	193	90.6
Social	18	8.5
Unknown	2	0.9
Hospitalization (n) (%)		
No	191	89.7
Service	17	8.0
ICU	5	2.3
CXR (n) (%)		
No	118	55.4
Normal	83	38.9
Consolidation	12	5.7
CT (n) (%)		
No	165	77.5
Normal	36	16.9
COVID specific	12	5.6
Underlying disease	5 2.3	
Treatment (n) (%)		
No	153	71.8
NSAİ	18	8.5
Ab and NSAİ	33	15.5
Ab, NSAİ, plaquenil	9	4.2
Discharge		
Yes	212	99.5
Death	1	0.5

Abbreviations: Ab, antibiotic; CXR, Chest X-ray; CT, computed tomography; ICU, intensive care unit; NSAİ, non steroidal anti inflammatory; SpO_2, oxygen saturation.

Table 2
Clinical and laboratory findings of Covid-19 pediatric patients

WBC (µL) (mean±std)	6949±2802	
PLT (109 /L) (mean±std)	278±124	
MPV (fL) (mean±std)	9.6±0.9	
CRP (mg/L) (mean±std)	5.6±12.4	
PCT (ng/mL)		
<0.1	143 (67.1)	
>0.1	70 (32.9)	
Neutrophil (µL) (mean±std)	3218±1912	
Lymphocyte (µL) (mean±std)	3157±2706	
Leukopenia (n) (%)	11	5.1
Neutropenia (n) (%)	19	8.9
Lymphopenia (n) (%)	35	16.4
Thrombocytopenia (n) (%)	1	0.5
Symptom (n) (%)		
Fever	16	7.5
Cough	14	6.5
Fever and cough	6	2.8
Myalgia	13	6.3
Nausea-vomiting	9	4.2
Diarrhea	11	5.2
Rash	3	1.4
Conjunctivitis	2	0.9
Loss of taste and smell	3	1.4
Clinic types (%)		
Asymptomatic	63.8	
Mild	27.9	
Moderate	6.0	
Severe	2.3	

Abbreviations: WBC, white blood cell; PLT, platelet; MPV, mean platelet volüme; CRP, C-reaktif protein; PCT, procalcitonin.

Table 3
The comparison of demographic, clinic and laboratory data between symptomatic and asymptomatic patients

	Symptomatic Patients Median (min-max)	Asymptomatic Patients Median(min-max)	p
Age (year)	8 (1-17)	12 (2-17)	<0.001
Gender (male) (n)	67	39	0.84
Fever (°C)	37.4 (36-39.1)	37 (36-37.9)	<0.001
SpO_2 (%)	96 (88-99)	97 (90-99)	<0.001
WBC (µL)	6355 (2680-18000)	6140 (3950-20450)	0.77
Neutrophil (µL)	2720 (690-14270)	3230 (650-16390)	0.01
Lymphocyte (µL)	2475 (630-31550)	2670 (310-7860)	0.03
PLT (109 /L)	267 (32-546)	255 (159-510)	0.16
MPV (fL)	9.4 (8-13.6)	9.5 (8-12)	0.36
CRP (mg/L)	1.8 (0-116)	1.3 (0-73)	0.04

Abbreviations: WBC, white blood cell; PLT, platelet; MPV, mean platelet volüme; CRP, C-reaktif protein; SpO_2, oxygen saturation.

Discussion

Coronavirus disease 2019, which causes pandemics all over the world, affects both children and adults. It presents a milder or asymptomatic clinical prognosis in children compared to adults. Children of all ages can be infected, including newborn infants and young children.[10] In the largest Chinese paediatric case series to date, of 2143 subjects, the median age at paediatric diagnosis was 7 (2-13) years and 1213 cases (56.6%) were boys.[11] In another study with 820 pediatric COVID-19 cases, it was reported that the mean age of the patients was

7 years 3 months (range of 1 day to 17 years) and 466 (56.8%) cases were male.[12] The mean age of our patients 9.55±5.15 years and 49.8 % were male. There was no significant sex difference in our cases, but the symptomatic group was significantly younger. Still, there is no direct evidence supporting whether male or female are more susceptible to SARS-CoV-2 infection. Children with positive COVID-19 PCR tests mostly have a history of social and/or familial environmental contact. This condition can be accepted as a definite indicator of high human-to-human transmission and contagiousness. Intra-family transmission is very important.[7,13] 94.8% of our patients had contact with patients who were positive COVID-19 PCR test within the family, and these were mothers, fathers, parents, grandparents and friends, respectively. The median time from onset of illness to diagnosis was 2 day (range: 0–42 day).[11] In our study, the median time from onset of the disease to diagnosis was 3 (0-6) days.

According to clinical characteristics of existing pediatric cases, children with COVID-19 can be divided into five clinical types: asymptomatic infection, mild, moderate, severe, and critically severe.[14,15] Multiple reports have demonstrated that children and young adults have a milder form of the disease compared to adults. Asymtomatic, mild and moderate infections comprise over 90% of all children who have tested positive for COVID-19.[16-18] In the review of the studies regarding COVID-19 in children published before March 2020, most children with COVID-19 had mild symptoms, showing a good prognosis, and recovered within 1 to 2 weeks.[19] A minority of children with COVID-19 require hospitalization. By March, among 2572 cases of COVID-19 in children reported from the US, the estimated rate of hospitalization differed from 6% to 20%, and 0.58%–2.0% of them were admitted to an ICU.[18] Of 171 children treated at Wuhan Children's Hospital, three (1.8%) required intensive care and all of those had underlying diseases.[11] In our study, 63.8% of our patients were asymptomatic and rate of hospitalization 10.3%. Five patients required ICU, all of those had underlying diseases such as prematurity, asthma, obesity, and Down syndrome. There was only one death of a 2-month -old child with prematurity and pneumonia. Although the certain cause is unknown, children with COVID-19 appear to have a milder clinical course compared to adults, and reports of death are scarce. The prognosis seems to be very good, with recovery described in the vast majority of reported cases.[20] In our study, 99.5% of the patients had a good prognosis and they recovered. The possible reasons for lower number and milder infections in children and young adults include lower exposure to virions, being isolated at home and minimal exposure to pollution and cigarette smoke contributing to healthier respiratory tracts. Additionally, the distribution, maturation and functioning of viral receptors such as angiotensin converting enzyme 2 (ACE2) may be important in age-dependent susceptibility to severe COVID-19.[11,21]

The most common symptoms described at onset in children are fever and cough. Other clinical features include sore throat, fatigue, myalgia, nasal congestion, runny nose, sneezing, headache, dizziness, vomiting, and abdominal pain. Some children and newborns exhibit atypical symptoms, manifested as vomiting, diarrhea, and other gastrointestinal symptoms, or only asthma and shortness of breath.[22-24] In a study of 2143 children, the patients' symptoms were typical of acute respiratory infections and included cough, fever, myalgia, sore throat, sneezing and fatigue.[11] In a series of 291 pediatric cases from the (US), the most common symptoms were fever, cough, and shortness of breath, respectively.[18] Similar to the literature, the most common symptoms in our patients were fever, cough, myalgia and gastroenteritis, respectively.

The most common investigations used for imaging COVID-19 patients are CXR and CT. CXR is usually the first-line investigation due to ease of availability. CXR findings in children appear to be non-specific. Children with mild disease should not routinely need computed tomography (CT) chest imaging in view of the high radiation exposure.[24-26] The main radiological features in pediatric patients with COVID-19 have been reported to be ground-glass opacities, consolidations with surrounding halo signs, patchy shadows are considered typical of pediatric patients.[18,20,25] Yasuhara et al.[27] founded that 54% of the pediatric patients had ground-glass opacities, and most of them had mild symptoms or were without any symptoms. Lu et al.[20] reported that ground-glass opacity was seen in a third of 171 diagnosed children. Local or bilateral patchy shadowing was seen in 18.7% and 12.3%, respectively. Overall, 15.8% of children did not have symptoms of infections or radiological features of pneumonia.[20] 7.3% of our patients who underwent CXR had consolidated areas, and all of these patients were symptomatic. In the CT scan of the patients in our study (25%), there were findings consistent with COVID-19 (ground-glass opacities, local patch shadow). COVID-19 has mostly been diagnosed using nasal or pharyngeal swabs or blood specimens that were positive for 2019-nCoV nucleic acid using real-time, reverse transcriptase-polymerase chain reaction assays (RT-PCR). Alternative diagnostics have included genetic sequencing of specimens from the respiratory tract or blood consistent with SARS-CoV2. CXR and CT scan pictures in moderate to severe illness are suggestive of diffuse bilateral involvement of lungs.[28] Diagnosis of all patients was confirmed by RT-PCR test of nasal and oropharyngeal specimens.

Typical abnormal laboratory findings were reported such as lymphopenia (31%), leucopenia (19%), and elevated creatine kinase- MB (31%) and procalcitonin (17%) levels in the cohort of pediatric patients with COVID-19.8 Xia W et al.[25] showed the laboratory findings in pediatric patients with COVID-19, including lymphopenia (35%) and elevated ALT (25%), creatine kinase-MA (75%), CRP (45%), and procalcitonin (80%) levels. Yasuhara et al.[27] found similar laboratory findings such as lymphopenia and elevated CRP, ALT, and AST levels in children with COVID-19. The significance of blood inflammatory markers remains controversial, particularly in children. In a study found that over two-third (68.7%, n=57) of cases had a normal

WBC and a normal CRP in 70.1% (n=47/67) of cases.[12] Henry et al.[29] summarized the findings from 12 studies on 66 children and reported normal leucocyte counts (69.2%), neutropenia (6.0%), neutrophilia (4.6%) and lymphopenia (3.0%). CRP and PCT were high only in 13.6% and 10.6% of cases, respectively. Similar to the literature, we found 5.1% leukopenia, 8.9% neutropenia, 16.4% lymphopenia, 0.5% thrombocytopenia, 18.7% elevated CRP and 17.9% elevated PCT in our study. Symptomatic patients had higher lymphopenia rate, CRP and PCT values.The rate of neutropenia and leukopenia were higher in asymptomatic patients than in symptomatic patients. There was no significant difference between the symptomatic and asymptomatic groups in terms of leukocyte count, eosinophil count, platelet count, and mean platelet volume.

Current WHO recommendation for all patients with mild symptoms include antipyretics and self-isolation at the patient's home. The general strategies include resting and supportive treatments, sufficient calorie, and water intake, maintaining waterelectrolyte balance, and homeostasis.[18,30] Patients and household members should be educated about personal hygiene, infection control measures to prevent the infection from spreading to household contacts. Paracetamol (10–15 mg/kg every 4–6 h) can prefer in case of fever >38.5 °C. Avoid ibuprofen in case of dehydration, vomiting and diarrhea, as it is associated with an increased risk of kidney failure.[31] There is no need for antibiotic treatment routinely. If there is clinical or laboratory evidence of secondary bacterial infection, appropriate antibiotics should be used appropriately.[18]

Management of Hospitalized Cases: Oxygen supplementation to maintain SpO_2 >92%. Symptomatic treatment: Paracetamol for fever, Blood culture sample should be sent at time of admission before starting anti-microbials. Empirical antimicrobials (e.g., Ceftriaxone) within 1 h of admission in case of suspected sepsis and septic shock. Oseltamivir may be considered after sending appropriate investigation if influenza is suspected. Systemic corticosteroids are not recommended, unless indicated for any other reason.[32] No specific antivirals have been proven to be effective as per currently available data. Hydroxychloroquine and chloroquine have been demonstrated to have anti-SARSCoV-2 activity in in-vitro studies. Mechanisms for anti-viral activity of hydroxychloroquine include inhibiting membrane fusion by increasing pH of endosome/lysosome, inhibiting virus entry by changing glycosylation of ACE2 receptor and spike protein, and immune-modulation.[33,34] Similar to the literature, we did not prescribe any treatment to 71.8% of our patients but 8.5% only oral paracetamol, 15.5% antibiotic and paracetamol, 4.2% antibiotic, paracetamol and hydroxychloroquine treatment. Appropriate antibiotics were used appropriately for patients with clinical or laboratory evidence of secondary bacterial infection. There were several limitations to our study. Our study was single centered. All patients in our study did not have liver and kidney function tests, and coagulation panel.

Conclusion

According to our study COVID-19 is asymptomatic or mildly severe in children. Lymphopenia, CRP and PCT elevation, ground-glass opacities on chest CT were important findings of COVID-19 disease. Most of the children recover without hospitalization and without any treatment. In those with underlying diseases (obesity, asthma, prematurity history, etc.) COVID-19 can be severe and need ICU.

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Resistant Chorea Successfully Treated with Intravenous Immunoglobulin: A Case Report

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Abstract

Sydenham's chorea (SC) is common cause of acquired chorea in childhood. SC occurs mainly in children with untreated streptococcal infections. An effective list of therapeutic options has been used to treat this disorder: antiepileptic drugs (valproic acid, carbamazepine etc.), haloperidol, chlorpromazine, amphetamines, steroids, plasma exchange and intravenous immunoglobulins (IVIG). We report a 12-year-old girl with carditis and severely generalized chorea and successfully treated with IVIG. This case report shows that IVIG is an effective treatment for the chorea cases resistant to anticonvulsants, dopamine antagonists and steroids, although larger studies are needed to confirm this conclusion.

Keywords: Antiepileptic drugs, dopamine antagonist, intravenous immunoglobulins, Sydenham chorea

Introduction

Sydenham's chorea (SC) is the most common acquired chorea of childhood.[1,2] SC occurs in about 10-15% of patients with acute rheumatic fever (ARF), in primarily ones with untreated streptococcal infections and usually presents as an isolated, frequently subtle, neurologic behavior disorder.[2] Treatment of SC is typically limited to supportive care and palliative medications. An impressive list of therapeutic options has been used to treat this disorder: dopamine receptor blockers (e.g. haloperidol, chlorpromazine), antiepileptic drugs [e.g. valproic acid (VPA), carbamazepine (CBZ)], and immune modulating therapy by means of prednisone, plasma exchange and intravenous immunoglobulins (IVIG). Curative treatment is still in the experimental stage.[3,4]

In this case, we describe a 12-years old girl, who presented with SC with severe disabilities in her daily life and we advocate the use of IVIG as a treatment option for SC.

Case Report

A 12-year-old girl, was admitted to our pediatric emergency department with complaint of intermittent swelling, redness, pain in the joints (migratory polyarthritis) for 2 weeks and, palpitations, involuntary movements and imbalance for several days.

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Her admittance vital parameters were as follows; blood pressure 120/60 mmHg, heart rate 104 beats/minute, respiratory rate 24 breaths/minute and temperature 37.9°C. She had intermittant, irregular, uncontrolled movements of the upper and lower extremities and to some extend also of the head and trunk. She exhibited darting tongue and milkmaid's grip with pronator sign and choreic hand. There were no further neurological abnormalities. Her cardiovascular examination presented a grade III-IV/VI° holosystolic regurgitant heart murmur on apical focus.

Complete blood cell count and the routine biochemical examination were normal; but erythrocyte sedimentation rate (ESR) was 23 mm/h, C-reactive protein (CRP) was 32.1 mg/L (N: <8 mg/L) and antistreptolysin O (ASO) titre was 371 Todd U/mL (N: 0-333 Todd U/mL). Rheumatoid factor, antinuclear antibody, anti-ds DNA antibody and anticardiolipin antibody were negative. Thyroid function test was also normal. In the throat culture no pathogens were isolated. PR interval was 0.16 second on electrocardiography and echocardiographic evaluation showed 3-4th degree mitral insufficiency, previous rheumatic heart disease (RHD; mitral valve echogenicity increased, mitral valve leaflet thickness: 6 mm). Brain magnetic resonance imaging (MRI) and electroencephalography were also normal.

The patient was hospitalized with the diagnosis ARF (migratory polyarthritis, active carditis and severe SC) and intramuscular benzathine penicillin G (1.2 milyon Unite), oral prednisolone (2 mg/kg/day, max 60 mg/day) and VPA therapy were started. On 10th day of hospitalization, patient's clinical status was worsened (she had incomprehensive speech with sucking and swallowing movements at rest, mood disorder with severe hypotonia, feeding, dressing and walking incapability); she also had periods of uncontrollable crying and extreme mood swings so we haloperidol added to VPA. Her clinical findings did not improve despite haloperidol and VPA treatment. Therefore, we started IVIG (0.5 g/kg/day for 4 days) on the 14th day of hospitalization. In addition, it was discontinued on the same day (before starting IVIG therapy) because of an extrapyramidal side effect related to haloperidol. We completed the steroid therapy to 6 weeks because of the active carditis. So we gave the IVIG in combination with steroids. After 48 hours of the last dose of IVIG, clinical findings including choreic movements and mood disorder were significantly improved. We continued VPA treatment for 3 more months. Her active carditis findings had improved in 1 month after discharge.

The patient has still been followed up without medication for 6 months without any problems.

Discussion

Acute rheumatic fever is still one of the most important causes of acquired heart disease all over the world and especially in developing countries. The diagnosis of this disease is made using the Jones criteria, revised by the American Heart Association in 2015. The revised Jones criteria were evaluated in 2 main categories according to the annual incidence of ARF as low risk (ARF incidence ≤2 per 100.000 school-aged children or all-age RHD prevalence of ≤1 per 1000 population per year) and moderate-high risk groups.[5] In the most recent wide-based study from Turkey, the annual incidence was reported to be 8.84/100.000 in the moderate risk group.[6] The revised Jones criteria include major and minor criteria. The major criteria consisting of carditis, arthritis (polyarthritis only in low-risk population and monoarthritis or polyarthritis in moderate- and high-risk populations), chorea, erythema marginatum and subcutaneous nodules. The minor criteria consisting of arthralgia, fever (≥38°C), ESR ≥30 mm/h and/or CRP ≥3.0 mg/dL, prolonged PR interval (after accounting for age variability (unless carditis is a major criterion). According to these criteria, the diagnosis of ARF was made in patients with recurrent ARF who had 2 major or 1 major and 2 minor or 3 minor criteria in addition to evidence of previous group A β-hemolytic streptococcal (GABHS) infection.5 In our case had a high ASO value and had previous RHD and active carditis findings in her echocardiography. In addition, the major criteria were migratory polyarthritis and chorea, and the minor criteria were levels of ESR and CRP elevation. We diagnosed ARF in our case who met 3 major and 1 minor criteria according to the revised Jones criteria.

SC is an antineuronal antibody-mediated neuropsychiatric disorder caused by a poststreptococcal, autoimmune condition affecting control of movement, mood, behaviour and is a major diagnostic criteria of ARF.[7] The age of onset of SC is 5-15 years old and it is more common in girls. SC is usually one of the late manifestations of ARF compared to the other major criteria of revised Jones criteria (arthritis and carditis). Chorea usually occurs weeks or months after GABHS pharyngitis. Generally, chorea in SC is generalized; however, hemichorea occurs in about 25% of patients. Although symptoms of SC is a benign and self-limiting disease, in rare cases the associated severe hypotonia as to be completely disabling, a variant known as severe chorea or chorea paralytica. Neuropsychiatric symptoms, including emotional lability, personality changes, obsessive compulsive behaviors, irritability, anxiety, and anorexia, are common and mostly predate the appearance of SC.[8] In a recent article from Italy, reported 171 children with SC under the age of 18. They declared 66% had generalized chorea, 34% had hemichorea, and 51% had neuropsychiatric findings.[9] In the differential diagnosis of SC included that drug intoxication, tic disorder, choreoathetoid cerebral palsy, encephalitis, intracranial tumor, hyperthyroidism, antiphospholipid antibody syndrome, autoimmune (systemic lupus erythematosus-SLE, systemic vasculitis) and metabolic diseases (e.g. Huntington disease, Wilson's disease).[5] In our case, there was no history of intoxication, hypoxic delivery or hyperbilirubinemia requiring exchange transfusion at the newborn. In addition, diagnoses of encephalitis, antiphospholipid antibody syndrome, SLE, hyperthyroidism, intracranial mass, Wilson's disease and Huntington's disease were excluded due to physical examination, laboratory findings and normal brain MRI. Also, this case had severe generalized chorea that

caused complete disability and neuropsychiatric findings. We diagnosed ARF in our case who met 3 major and 1 minor criteria according to the revised Jones criteria.

The most common of major manifestation in ARF is carditis (clinical and subclinical carditis). In a national ARF study from Turkey, they had been reported incidence of clinical carditis, subclinical carditis, polyarthritis, aseptic monoarthritis, polyarthralgia and SC had 53.5%, 29.1%, 52.8%, 10.3%, 18.6% and 7.9%, respectively.[6] Also, the patients with SC frequently have clinical or subclinical carditis. Orsini et al. reported carditis in 81% (subclinical in 65%),[9] and Gürses et al. in 93% of of children with SC.[6] In our case had active carditis, SC and migratory polyarthritis. She also had RHD on her echocardiography. Possibly she had a previous episode of ARF. Therefore, we have seen these 3 major criteria together.

The mainstay treatment of SC includes dopamine receptor blockers (eg, haloperidol, chlorpromazine) and certain antiepileptic medications like VPA and CBZ. VPA is recommended as the first-line agent in the treatment of SC,[3,10] especially in severe cases of SC where trials with haloperidol and diazepam have failed.[11] CBZ is used in some institutions to treat SC. A comparative study from Turkey compared the effectiveness of VPA with CBZ on SC patients and revealed no significant difference between the groups with respect to time of clinical improvement and time to complete remission, duration of therapy and the recurrence rates.[12]

Because SC is an immune-mediated disease, it has been hypothesized that steroids in an immunomodulatory dose may ameliorate the symptoms of SC that are refractory to neuroleptic and antiepileptic drugs. Indeed, immune modulating therapy, like corticosteroids or immunoglobulin infusion, was found to improve SC.[4,7,13-15] Several studies (case reports or retrospective cohorts) demonstrated that prednisone had improved the course of the disease.[4] However, many of these reports noted a rapid relapse of symptoms or the development of important side effects. We completed the steroid therapy to 6 weeks because of the active carditis. So we gave the IVIG in combination with steroids.

Van Immerzeel et al reported a successful outcome of two patients treated with IVIG 400 mg/kg/day for 5 days.[13] Garvey et al reported the comparison of plasma exchange and IVIG with prednisone. The results were not statistically significant but clinical improvement appeared to be more rapid and robust in the plasma exchange and IVIG groups.[4]

A novel randomized study made by Walker et al. compared the outcomes of 10 children treated with standard management alone with 10 who received additional IVIG.[7] The outcomes were assessed using a clinical rating scale, brain singlephoton emission computed tomography, and the duration of symptomatic treatment. All three outcome measurement tools found to be improved in the IVIG group.

Although there are different treatment options in SC, there is no internationally accepted consensus for its treatment.[16] Boersma et al.[15] also administered their treatment similar to our case. Since our patient had severe chorea, we initially given VPA, after added haloperidol. On the 14th day of hospitalization, we discontinued it because of an extrapyramidal side effect related to haloperidol. We started additional IVIG therapy to on-going 2 mg/kg/day prednisolone therapy after the fail of 14-day VPA therapy and 4-day haloperidol therapy to our patient and observed clinical improvement (chorea and carditis) 48 hours after the last dose of IVIG. We continued VPA treatment for 3 more months. Her active carditis findings had improved in 1 month after discharge. Our findings are correlated with the results of previous studies.

Conclusion

Sydenham's chorea is a infrequent presentation of ARF. Inadequate treatment of SC may result in severe functional disability. SC should be considered in the differential diagnosis in children aged 5-15 years with movement disorder. It has been reported that immunotherapy (especially IVIG and plasmapheresis) is beneficial in cases with severe chorea. Therefore, we conclude that IVIG therapy may help for improvement in severe SC and carditis patients whom didn't respond to classical medications such as VPA, dopamine receptor blockers and steroid.

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Allergic Reaction Following Implantation of a Blood Glucose Sensor

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Increasing incidence and onset at a younger age has changed the treatment strategy of diabetes mellitus (DM) towards prevention, delaying the onset, and minimizing disease complications. Self-monitoring blood glucose systems and continuous glucose monitoring systems are routinely preferred in diabetic children.[1] The FreeStyle® Libre™ Flash glucose monitoring system (Abbott Diabetes Care, Alameda, CA) has come as an entirely new concept in glucose monitoring by providing much greater data than blood glucose testing while being more affordable than the continuous glucose monitors. The FreeStyle Libre provides 'flash glucose monitoring' with glucose readings by scanning a sensor rather than pricking the patient's finger. The sensor measures interstitial tissue glucose levels every minute via a disposable round sensor with a small catheter inserted under the skin that can be worn for up to 14 days. The entire system's on-body sensor patch worn on the back of the upper arm is disposable. However, the mild erythema may occur on the skin and disappear spontaneously after 24 hours from the detachment of the sensor. Similar skin lesions were observed in diabetic patients, and there was moderate to severe itching in 0.5% of the cases and moderate erythema in 4% of cases.[2]

Our patient, a seven-year-old boy, was followed with the diagnosis of type 1 diabetes since six years old, and he was started to check his blood glucose levels via The FreeStyle Libre 10 days ago. However, he developed severe pruritis after implantation. After removing the sensor, skin irritation and a local cutaneous reaction, probably allergic reaction to the sensor containing the latex was detected. The patient did not report a history of allergy to medications or adhesive tapes. The sensor patch was removed, and dermatitis was resolved by the application of topical creams containing corticosteroids (**Figure 1**)

Although there is not enough experience in children, the FreeStyle Libre is often preferred by parents because of the lack of fingerstick measurement and the ability to check glucose levels frequently. We thought that allergic reactions would also be seen more frequently depending on the increase in the frequency of use. Application of topical products such as a blood glucose sensor can potentiate local or systemic hypersensitivity reactions. Because The FreeStyle Libre system is accessible for home use, health care providers need to be aware of its potential consequences.

The continuous glucose monitoring systems improves the quality of diabetic patients life and relieves them the burden of repeatedly measuring blood glucose. Local steroids generally recommended in reactions such as dermatitis. Additionally, there are alternative products that can be used for a period of 3-15 days.

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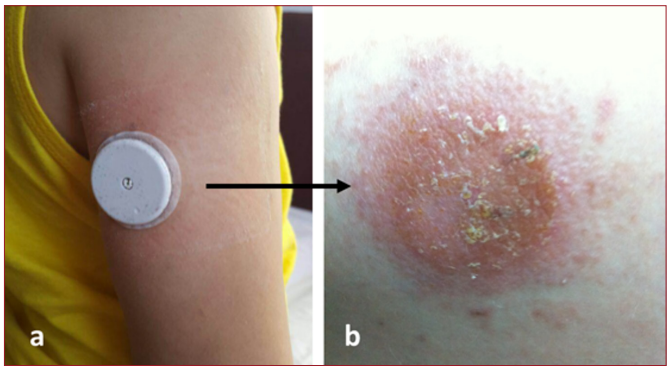

Figure 1. Allergic skin reaction was detected after the removal of the patch

Keywords: Flash glucose monitoring, type 1 diabetes, dermatitis

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