KAYSERI CHILD HEALTH ASSOCIATION

JP

The Journal of PEDIATRIC ACADEMY

Year 2020
Volume 01 | Issue 3

e-ISSN: 2718-0875

Journal Editorial Board

Publisher
Kayseri Child Health Association

Graphics, Design
MediHealth Academy
Fatih Şamil ULUDAĞ

Contact
The Journal of Pediatric Academy Office,
Kayseri Chamber of Medicine,
Seyitgazi Mah. Nuh Naci Yazgan Cad. Geriatri Merkezi Binası K:1 N:4, Melikgazi, Kayseri, Türkiye
Phone: +90.352.2076666 (int) 25373
jpediatracad@gmail.com

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

Information About the Journal

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been previously published or be currently under consideration for publication any place else and should report original unpublished research results.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

Journal Name	Journal Short Name	Publishing Language	Broadcast Period	ISSN/E-ISSN
The Journal of Pediatric Academy	J. Pediatr. Acad. (JPA)	English	3	-

Starting Date	Publication Type	Indexed	Journal Concessions
2020	Periodicals (Online)	-	Kayseri Child Health Association

Journal Management Location and Address

The Journal of Pediatric Academy Office,
Kayseri Chamber of Medicine,
Seyitgazi Mah. Nuh Naci Yazgan Cad. Geriatri Merkezi Binası K:1 N:4, Melikgazi, Kayseri - Türkiye
Phone: +90.352.2076666 (int) 25373

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

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

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Manuscript Types

JPA publishes the types of articles briefly described below.

Editorial Comment:

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

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

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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
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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).

Figures and Tables

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

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

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Journal of Pediatric Academy

Invited Review

Year: 2020 Volume: 1 Issue: 3
Doi: 10.38092/JPA-2020-849794

SARS-CoV-2 Infection in Children; What Do We Know So Far?

Author(s)

Benhur Şirvan Çetin

Affiliation(s)

Erciyes University, Faculty of Medicine, Department of Child Health and Diseases, Pediatric Infectious Diseases Unit, Kayseri, Turkey

Article Information

Article Type: Invited Review
Article Group: Pediatric Infectious Diseases

Received: 24.11.2020
Accepted: 17.12.2020
Aviable Online: 27.12.2020

Cite this article as: *Çetin BŞ. SARS-CoV-2 Infection in Children; What Do We Know So Far? J Pediatr Acad 2020; 1: 76-85.*

Abstract

After Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), SARS-CoV-2 is the newest member of the family of coronaviruses that are pathogenic to humans. The disease which occurs with SARS-CoV-2 is called coronavirus disease 2019 (COVID-19). COVID-19 was first described in December 2019 and has caused millions of people to get sick and hundreds of thousands of deaths over the past year. In this review, the epidemiology, diagnosis, clinical and laboratory features, radiological findings, treatment, and management of the disease are all reviewed from a pediatrician's perspective. Post-infectious complications, the impact of COVID-19 on global child health, and vaccine developments were also discussed in this review.

Keywords: SARS-CoV-2, COVID-19, MIS-C, children, infection

Introduction

Coronaviruses are single-stranded RNA viruses that cause a number of infections in animals and humans. After Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), SARS-CoV-2 is the newest member of the family of coronaviruses that are pathogenic to humans. The other family members of coronaviruses (229E, NL63, OC43, and HKU1) have been associated with usually mild clinical symptoms.[1] The disease which occurs with SARS-CoV-2 is called coronavirus disease 2019 (COVID-19). In early December 2019, the outbreak of COVID-19 started in Wuhan City, Hubei Province, China. On the 30th of January, 2020, the World Health Organization (WHO) declared the outbreak as a Public Health Emergency of International Concern. On the 11th of March, 2020, the WHO declared COVID-19 as a pandemic disease.[2] SARS-CoV-2 has, up to the 15th of November,

Correspondence: Benhur Şirvan Çetin, Erciyes University, Faculty of Medicine, Department of Child Health and Diseases, Pediatric Infectious Diseases Unit, Kayseri, Turkey
E-mail: benhurcetin@gmail.com

2020, caused nearly 54 million infections and 1.300.000 deaths worldwide.[3] Among 8.198.609 cases reported to the Centers for Disease Control and Prevention (CDC) in the United States (US), 9.4% were children.[4] In this review, evidences, theories, and questions about COVID-19 will be discussed from a pediatrician's perspective.

Epidemiology of COVID-19 in children

SARS-CoV- 2 is carried in the respiratory tract of infected people from nose to lungs and spread during speaking and coughing especially. Respiratory droplets, direct contact, and aerosol transmission are the primary infection routes in both children and adults.[5] SARS-CoV-2 actively infects gastric, duodenal, and rectal glandular epithelial cells. The fecal-oral route has also been evaluated in the pediatric population as a potential route of transmission. Nevertheless, it has not been accepted as a major transmission route for children or adults.[6–8]

Highlights

- Infected children generally had mild symptoms and were less likely than adults to report lower respiratory tract symptoms. Radiological imaging indications remain as they were before the pandemic.
- Corticosteroids may be beneficial in critical pediatric COVID-19 patients.
- MIS-C management should include a multidisciplinary care team, and pediatricians should have a high awareness of this post-infectious phenomenon.

Infectiousness starts two days before symptom onset, peaks 0.7 days before symptom onset, and declines within seven days.9 Both symptomatic persons and asymptomatic carriers can transmit disease. Furthermore, each patient can transmit the infection to 1.5-7 individuals.[10]

Worldwide, during lockdown periods, children constituted only 2% of recorded infections.[11] But, after the school openings and ending of the lockdowns, the number of pediatric cases increased dramatically. In the US, pediatric cases were 1.7% of all cases in the first months of the pandemic, but this ratio increased to 11.5% nowadays.[4,12,13] The recent report from the US, the overall rate of COVID-19 is 1,381 cases per 100,000 children in the population. Between two weeks (10/29 – 11/12), the rate of the increase in childhood cases was reported as 22%.[13] Early studies during the lockdowns showed that most children appeared to acquire infection from positive adults, especially within the family. On the other hand, when children have had contact with people infected with COVID-19, they are probably less likely to contract the infection than adults. Having an infected parent was associated with a marked increase in risk for secondary infection in a child.

Recent meta-analyses suggest that children's overall susceptibility is approximately half of adults, with the most significant effect on younger children.[14,15] Numerous large-scale studies have indicated that children, particularly children <10 years, have much lower infection rates than adults.[16,17] Schools or child care facilities are other potential areas for outbreaks. In countries with strict mitigation regulations like Ireland, Australia, Singapore, and Germany, there were reported no to the little facility-based transmission of SARS-CoV-2 by children despite the presence of infected children.[18–21] However, in areas with widespread community transmission or less strict mitigation procedures, large outbreaks have occurred.[22–24] These outbreaks reveal that infected adults are typically responsible for introducing viruses into these settings.

Infected children generally had mild symptoms and were less likely than adults to report lower respiratory tract symptoms or loss of taste or smell. Asymptomatic, mild, and moderate cases account for 98% of childhood cases.[25] Mortality rate is also much lower than that in adults. In the US, from the beginning of the pandemic, mortality in children (<18 years of age) accounts for <0.41% of all deaths.[4] The differences in clinical outcomes between children and adults with COVID-19 suggest that age-dependent host features are important contributors to the disease's pathophysiology. There are some possible answers to this question with the studies done so far. Children are more likely to have other viruses in their upper respiratory tract, and associations and competition of these viruses with SARS-CoV-2 can hinder their ability to cause infection.[11] SARS-CoV-2 enters into host cells by Angiotensin-Converting Enzyme 2 receptors (ACE2-r). These receptors are expressed in various tissues, especially alveolar epithelial cells, nasal and intestinal epithelium. Different from adults, children have significantly lower levels of ACE2-r in their nasal epithelium. This difference may make them less susceptible to infection.[26] Additionally, previous exposure to other seasonal human coronaviruses may also provide a level of protection through cross-reactive T-cells against SARS-CoV-2.[27] Differences in immune responses of children and adults to SARS-CoV-2 are another main reason why the clinical course of COVID-19 is different in children and adults. New findings suggest that children with COVID-19 do better than adults because their stronger innate immunity protects them against SARS-CoV-2 related complications like acute respiratory distress syndrome (ARDS), while adult patients respond to infection with an over-vigorous adaptive immune response that may promote the inflammation associated with ARDS.[28] The low mortality rates and the mild course of the disease are also frequently debated whether childhood vaccines will have a role. There may be a possibility that heterologous immunity developed against traditional childhood vaccines may positively affect COVID-19 infections in children. In this context, especially Bacillus Calmette-Guerin (BCG) and measles, mumps, and rubella (MMR) vaccines have been the subject of some studies, but there has not been sufficient evidence that childhood vaccines are protective against COVID-19. There are still unexplained points regarding the different epidemiological and clinical features of COVID-19 between children and adults. Therefore, it will remain important to explain the mechanisms responsible for differences in symptomatology, sensitivity, and infectivity between adults and children.

Virologic Diagnostic Tests

For the diagnosis of acute infection, detecting SARS-CoV-2 RNA from the nose and oropharynx is crucial. Real-time RT-PCR–based testing from the nasal and oropharyngeal swab is recommended. RT-PCR tests can also be used for other respiratory samples like endotracheal aspirate or bronchoalveolar lavage. Many factors affect the accuracy of testing include the quality of the sample, the material used for sampling, stage of the disease, and viral load in the patient. In clinical settings, the false-negative test rates have been reported between 10% to 40%.[29] When the clinical suspicion is high, the tests should be repeated. Overall, RT-PCR for SARS-CoV-2 has a high specificity of 95% but a lower sensitivity of approximately 70%.[30] Most studies on contagiousness are depended on viral RNA detection from respiratory specimens. Viral replication stops 5 to 7 days after the onset of symptoms, but patients can remain RNA-positive for days and weeks. It is essential to remind that prolonged viral RNA detection following illness resolution does not necessarily indicate infectiousness.[7,10,25,30–32] Saliva specimens may be an alternative diagnostic sample for RT-PCR based tests. These tests may be more comfortable and safer during the sample collection. Studies from the US and Canada suggest that saliva testing is as sensitive as nasopharyngeal swab testing in high-risk populations.[33,34]

Serological testing for SARS-CoV-2 (IgM and IgG) can detect recent or previous infection. The tests' sensitivity and specificity vary depending on the type, timing, and manufacturer of the test. While the specificity rates vary between 96.6% to 99.7%, sensitivity rates are between 66% to 97.8%. The tests that have no authorization from the United States Food and Drug Administration (FDA) or the European Medicines Agency (EMA) should not be used.

Antigen tests are another alternative for diagnosing acute infection rapidly. Most commercially available antigen tests detect the nucleocapsid (N) or spike (S) proteins of the virus by using enzyme-linked immunosorbent assay. Despite the lower price and easy usage of these tests, their sensitivity is less than that of nucleic acid amplification tests typically.[35]

Clinical and Laboratory Features

Children of all age groups can be infected with COVID-19. From the studies, there is no age or sex preponderance.[25] The incubation period is usually between 5-6 days but may reach up to 14 days. In COVID-19, the spectrum of the clinical features in children varies from asymptomatic to critical illness. The commonest presenting features in children are fever, coryzal symptoms, cough, lethargy, and shortness of breath. Respiratory symptoms are not the only features of COVID-19 in children. Abdominal pain, vomiting, and diarrhea are common gastrointestinal symptoms present with or without respiratory symptoms. Unlike adults, dermatologic lesions are more common in children and can be seen in up to 20% of patients. The common manifestations are maculopapular rash, urticarial eruptions, and transient livedo reticularis and pernio (chilblain)–like acral lesion.[36] Dermatological lesions can be easily misinterpreted and confused with other viral infections or non-infectious diseases. Around 10% of hospitalized children with COVID-19 have additional infectious diseases such as urinary tract infection, appendicitis, and sepsis.[11]

Patients with COVID-19 may be grouped in 5 clinical pictures: Asymptomatic infection, mild, moderate, severe, and critically severe infection. Severely ill cases are defined as those with central cyanosis and pneumonia, and critically ill cases develop acute respiratory distress syndrome that necessitates mechanical ventilation. Between 15% and 20% of virologically positive cases remain asymptomatic during the disease course in children. Meanwhile, most of the symptomatic cases often have mild to moderate symptoms in severity and can be cared for in the home.[37,38] As noted, the disease is more likely to be mild in children than adults. In a review in which 2228 children were evaluated, severe disease rate also reported that only 6% of infected patients.[39] Mortality rates are also very low in children compared to adults. The overall death rate in adults appears to be 2% to 3%.[40] In contrast, only two deaths (0.09%) were reported in the recent review of 2228 children.[39] Although children represent a growing percentage of total cases, hospitalization, and death due to COVID-19 are still uncommon in all countries. In the US, children were 1.2-3.3% of total reported hospitalizations, and between 0.5%-6.1% of all child, COVID-19 cases resulted in hospitalization. The rates are varying between states. Mortality rates also varied between the states, and 16 states reported zero child deaths in the US. As the last reports from the US, 0.00%-0.15% of all child COVID-19 cases resulted in death, and children made up 0.07% of total deaths.[13,41]

The laboratory characteristics of acute COVID-19 are variable in children, and a large proportion of them have normal values.[11] In adults, lymphopenia is the most common abnormality in complete blood count.[42] Limited studies in children describe relatively lower rates of lymphopenia. Additional to lymphopenia, elevated inflammatory markers, including C Reactive Protein (CRP) and procalcitonin, have been documented in children but are by no means universal.[43,44] Acute phase reactants like CRP, procalcitonin, erythrocyte sedimentation rate, ferritin, D-dimer, fibrinogen, and interleukin-6 are the most studied laboratory markers in COVID-19. An elevated marker of inflammation should point toward more severe disease and alert the clinician about the possibility of the multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 which is discussed in another section.[7]

Radiological Findings

Chest x-ray findings in COVID-19 are usually non-specific, and bilateral infiltrates like any other viral infections can be seen. Pleural effusion is an uncommon finding.[45] When chest radiography has been performed in children with COVID-19, no specific features are found to be diagnostic. Therefore, chest X-ray indications remain as they were before the pandemic. It should be remembered that X-ray findings may be normal in the early phases of the disease.[46] Computed tomography (CT) can show early changes in the lungs independent from the clinical symptoms. The radiological findings of subpleural lesions, bilateral peripherally distributed ground-glass opacities

(GGOS), and patchy alveolar infiltrations with lower lobe predominance are common findings in children in COVID-19 (**Figure 1**).[46,47] In addition to the GGOs and patchy alveolar infiltrations, the reversed halo sign can also be noted in children.[48] The critical point about imaging is performing a CT did not alter the management of the majority of these children.[47] It should be reminded that radiologic findings may not always be consistent with the clinical picture and may continue to persist for weeks even after the resolution of clinical symptoms.[7] Children with COVID-19 who have radiological evidence of pneumonia are significantly more likely to require intensive care unit (ICU) admission.[11,38]

Special patient groups

In adults, certain comorbidities like hypertension, chronic respiratory and cardiovascular diseases, obesity, diabetes, immune-compromised status, chronic kidney disease, smoking, and obesity have all been identified as an important risk factor for poor prognosis.[7] In the first international multicentric pediatric COVID-19 studies in Europe, significant risk factors found for requiring ICU admission were being younger than one month, male sex, pre-existing medical conditions, and presence of lower respiratory tract infection signs or symptoms at presentation.38 However, in children and adolescents, there is a need for more data to understand how pre-existing conditions can influence the course of COVID-19.

Neonates have been reported to have COVID-19 but rare. Evidences for transmission of the SARS-CoV-2 virus through the placenta or viral transmission through the birth canal during the labor is not clear. The majority of infected neonates are believed to have contracted COVID-19 after birth. Although compared to all children, age under one month is a risk factor for ICU admission in COVID-19, neonates have not usually required ICU admission.[38] In a systemic review, we see that most neonates with SARS-CoV-2 infection are asymptomatic or presented mild symptoms, generally have a good prognosis after a median of 10 days of hospitalization.[49] With current findings, neonatal guidelines do not recommend against breastfeeding for mothers with COVID-19. No replicable virus has been identified in breast milk yet.[50] During the breastfeeding period, contact precautions, use of maternal masks, hand hygiene before and after touching baby, social distancing from other individuals, limiting all contacts must be followed meticulously.[51]

Although recent studies have found that adults with cancer and COVID-19 have a higher death rate, this does not appear to hold for pediatric cancer patients. Boulad et al.[52] find that the overall morbidity of COVID-19 in pediatric patients with cancer is low, with only 5% requiring hospitalization for symptoms of COVID-19. Additionally, they showed that the rate of SARS-CoV-2 infection among asymptomatic pediatric patients was very low compared with their asymptomatic caregivers (2.5% and 14.7%, respectively).

As in adults, children with the following conditions might be at increased risk for severe illness: obesity, medical complexity, severe genetic disorders, severe neurologic disorders, inherited metabolic disorders, sickle cell disease, congenital (since birth) heart disease, diabetes, chronic kidney disease, asthma and other chronic lung diseases, and immune-weakening medications.[2,32,38,53,54] Several other aspects could be implicated in the severity of COVID-19 in children, such as coinfection with RSV, the immune system's responsiveness, vaccination history, and levels of vitamin D, and genetic polymorphisms. However, the present paucity of data limits the ability to draw such conclusions.[32]

Clinical management and treatment options

Most children with COVID-19 require only supportive therapy (e.g., acetaminophen and hydration for fever and lessen fluid uptake), with less than 25% of hospitalized children requiring oxygen and far fewer requiring ventilatory support.[11] Difficulty in breathing, cyanosis, undefined chest pain, altering mental status, poor feeding, and decreased urine out are the clinicians' main alarming points. Patients with underlying medical conditions and those who present with severe and life-threatening clinical features require hospital admission. Patients should be monitored for clinical deterioration. Supportive care is the primary treatment for these patients. Fever control, respiratory support (oxygen supplementation, non-invasive, and invasive ventilation), adequate nutrition, and fluid replacement are the main supportive care approaches. In more severe cases, renal replacement therapy and extracorporeal membrane oxygenation may be needed. In children receiving immunosuppression therapy, the risk and benefit of reducing immune suppression must be evaulated.[55]

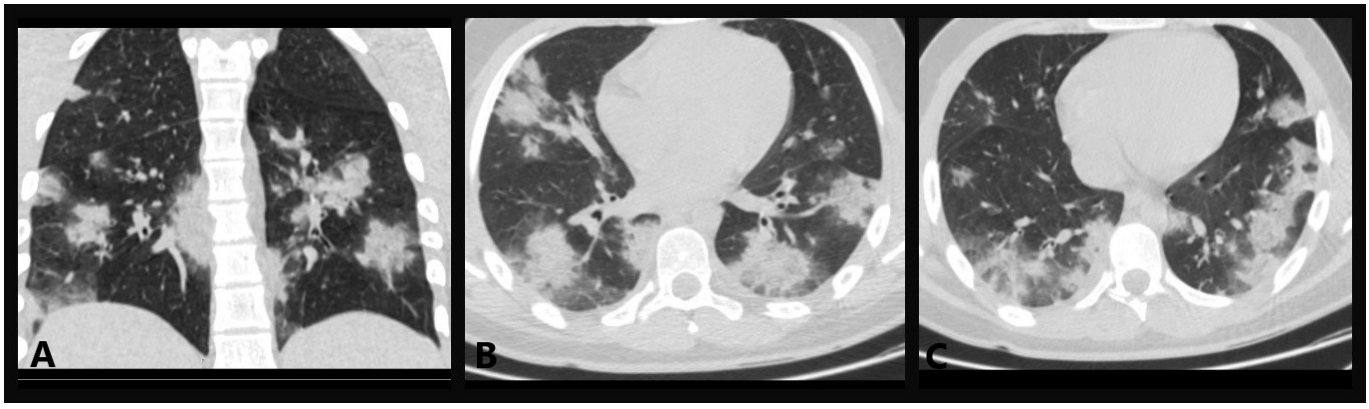

Figure 1. Computed chest tomography findings of a child with COVID-19; subpleural lesions, bilateral peripherally distributed ground-glass opacities, and patchy alveolar infiltrations, especially in lower lobes (A: Coronal reconstruction plane, B and C: horizontal planes).

Corticosteroids: Current literature shows that the most effective agent for reducing mortality in critically unwell adults with COVID-19 is dexamethasone.[56] The safety and effectiveness of corticosteroids have not been sufficiently evaluated in pediatric COVID-19 patients. Dexamethasone or another corticosteroid is not recommended for mild pediatric patients who require low levels of oxygen support. As in the adult studies, corticosteroids may be beneficial in critical pediatric COVID-19 patients with respiratory disease who require mechanical ventilation.[57]

Remdesivir: Remdesivir is a nucleotide analog that inhibits RNA-dependent RNA polymerase. It was first developed for Ebola therapy in 2017 by Gilead and has been found to have in vitro activity against coronaviruses. At the beginning of the pandemic, studies showed in vitro activity of remdesivir against SARS-CoV- 2. In April 2020, the American Pediatric Infectious Diseases Society suggested remdesivir for COVID-19 treatment in children if an antiviral is used.[58] Meanwhile, the drug has received emergency authorization by the FDA for emergency use in both children and adults with severe COVID-19 disease in May 2020.[59] The current dose of remdesivir in pediatrics is 5 mg/kg (maximum dose 200 mg) IV loading dose on day 1, followed by 2.5 mg/kg (maximum dose 100 mg) IV every 24 hours for 5 to 10 days.[59] Based on the results of recent multicenter studies, on 20th of November, WHO has issued a conditional recommendation against the use of remdesivir in hospitalized patients, regardless of disease severity, as there is currently no evidence that remdesivir improves survival and other outcomes in these patients.[60]

Favipiravir: Favipiravir is a guanine analog that inhibits RNA polymerase. It is approved for the treatment of influenza virus infection in Japan previously. None of the European, US, and WHO guidelines recommend favipiravir for the treatment of COVID-19 for now.[57,60,61] The potential of this drug remains unclear and requires additional clinical studies before any recommendations can be offered.

Convalescent Plasma: In phase II, randomized controlled trial in India (PLACID trial), investigators found no net benefit associated with convalescent plasma in patients admitted to hospital with moderate COVID-19. Using convalescent plasma was not associated with a reduction in progression to severe covid-19 or all-cause mortality. Small beneficial effects were found for the resolution of shortness of breath and fatigue.[62] We have not sufficient data to recommend either for or against the use of convalescent plasma to treat COVID-19 in adults yet. Additionally, the safety and effectiveness of convalescent plasma have not been evaluated in pediatric patients. Clinical trials of convalescent plasma in COVID-19 treatment in children are ongoing.[57]

Venous thromboembolism prophylaxis: COVID-19 seems to be associated in adults with an increased risk of disseminated intravascular coagulation and venous thromboembolism, but children have a much lower incidence of thrombotic complications than adults. Preventive anticoagulant therapy can be considered for neonates and adolescents in cases where severe inflammatory conditions and hyperactivation of the clotting process can occur. In these groups, the suggested treatment is with subcutaneous enoxaparin 100–200 U/kg/day, which can be increased to 150–300 U/kg/day in neonates.[61]

Other drugs and supplements: Currently, because of the lack of a strong rationale and the absence of evidence of certain effects in the treatment of COVID-19 patients, guidelines recommendations are against to use hydroxychloroquine, chloroquine, azithromycin, lopinavir/ritonavir, or ivermectin for the treatment in adults and children both in inpatient and outpatient settings.[57,60] Antibacterial and antifungal agents should be used only when an infection is suspected/confirmed. If it is needed, anti-infective agents should be used according to local guidelines and clinical/laboratory assessments.[7] In the management of COVID-19, the function of vitamin and mineral supplements such as vitamin C, vitamin D, vitamin A, and zinc remains uncertain. There is not yet a well-designed controlled study to evaluate their effects. Until more data become available, dietary supplements should be avoided if there is no documented deficiency.[62]

Vaccine studies

Many potential vaccines for COVID-19 are being studied, and several large clinical trials are ongoing. At the time of writing this article, 56 vaccines have been testing in clinical trials, and at least 200 vaccine candidates are under investigation in the pre-clinical stage. Currently, 11 vaccines are in the final stages of phase studies.[63] In China and Russia, some vaccines had received limited approval for use before the phase 3 trial results. The WHO is actively involved in the progress of vaccine discovery and development. The first preliminary data about effectiveness from phase 3 trials came in November 2020. Firstly, Pfizer and BioNTech announced that their coronavirus vaccine is 95% effective on the 9th of November. A week later, Moderna, another company that works with the National Institutes of Health in the US, announced that their vaccine is 94.5% effective. On the 20th of November, a request for an emergency use authorization to FDA was submitted by Pfizer.[64] The Moderna's and Pfizer's vaccines are based on messenger RNA (mRNA) technology.

Meanwhile, many other phase 3 clinical trials with different vaccines are ongoing. The two vaccines from the Johnson & Johnson/Beth Israel Deaconess Medical Center collaboration and the AstraZeneca/University of Oxford collaboration are both viral vector vaccines. Phase 3 studies of both are ongoing. At the time of this review, AstraZeneca was the last company to share its phase 3 trial results. On the 23rd of November, AstraZeneca and Oxford announced that their vaccine has an average 70% efficacy.[64] Johnson & Johnson phase 3 trial results have not been announced yet.[7,65] From China, CanSino Biologics's vaccine is a viral vector vaccine while Sinovac Biotech's and Sinopharm's vaccines are inactivated vaccines. All these three vaccines are in the phase 3 stage and received approval for limited use in China. Gamaleya Research Institute and Vector Institute developed two different vaccines that received approval before a phase 3 trial from Russia. The results of phase 3 trials of the Russian vaccines are pending.[63,64] In early

2021, at least one vaccine is expected to be available for use in Europe and the US. Because of the benign nature of the disease and limited resources, the use of a COVID-19 vaccine in healthy children will remain controversial. With the results of future phase studies in children, the need for vaccination can be determined by clinical evaluation on a case-by-case basis.

Multisystem inflammatory syndrome in children (MIS-C)

MIS-C is an emerging phenotype of illness that is consistent with inflammation and organ dysfunction in the absence of another apparent cause. This phenomenon is a rare complication of COVID-19 in children; however, the presentation can overlap with acute COVID-19 illness or be a delayed response up to six weeks.[11] In the study from the New York State, the estimated incidence of MIS-C was 2 per 100,000, but the incidence of MIS-C is not known exactly yet.[66] While this syndrome is named as MIS-C by the National Institutes of Health in the US, and it has also been named in different institutions as pediatric inflammatory, multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS).[7] Children usually present with persistent fever, but the presentation of MIS-C is varied. Skin and mucous membrane changes like a polymorphic rash, non-purulent conjunctivitis, and cracked lips (**Figure 2**), hand and foot swelling, and gastrointestinal disturbance are the other common findings.[67] Abdominal pain is present in over 50% of children. Children can be presented acutely unwell with vasodilatory shock features or features consistent with complete or incomplete Kawasaki Disease (KD). In contrast, others may have more non-specific features.[68] MIS-C is thought to be a post-infectious phenomenon triggered by an abnormal immune response after the acute infection. Laboratory findings in these children are characterized by lymphopenia, anemia, thrombocytopenia, and elevated inflammatory markers. The inflammatory markers studied mainly in MIS-C are CRP, procalcitonin, B-type natriuretic peptide (BNP), erythrocyte sedimentation rate, ferritin, fibrinogen, D-dimer, interleukin-6, and interleukin-8. Increased levels of CRP, BNP, troponin were reported in most of the studies.[69] Echocardiography can demonstrate decreased left ventricular ejection fraction, myocarditis, pericardial effusion, and a coronary artery abnormality, including dilation or aneurysm. The rates of cardiac involvement differ from 25% to 70% in studies.[66,68,69] The diagnosis relies on the CDC or WHO case definition criteria (**Table 1**).[68,70]

Management of MIS-C should involve a multidisciplinary care team with pediatric infectious diseases, intensive care, pediatric cardiology, and rheumatology specialists. American College of Rheumatology has published clinical guidance for diagnostic and therapeutic management for MIS-C recently.[71] Treatment involves supportive care, management of shock and left ventricular dysfunction, and other critical care support.[7,68] Intravenous immunoglobulin (IVIG) and glucocorticoids are the main backbones of the therapy in MIS-C. If the inflammation persists despite IVIG and glucocorticoid therapy, other drugs that could be a choice include anakinra, tocilizumab, and infliximab, used to manage other cytokine release syndromes.[7,68-72] Anakinra targets IL-1ß, and it has been widely used in many other inflammatory conditions like rheumatoid arthritis, juvenile idiopathic arthritis. Tocilizumab, another immunomodulator, targets IL-6, and it has been mainly studied in adults to date. Anakinra has some advantages from tocilizumab. Anakinra has a short half-life, whereas tocilizumab has a one-month half-life, so anakinra can be discontinued rapidly if it is not effective or has side effects. We have experience with anakinra's effects on children. However, pediatricians do not have much experience with tocilizumab in the setting of severe infections. Antibiotics should be given for suspected or confirmed concurrent bacterial infection. Due to the post-infectious nature of the disease and the negative PCR tests for SARS-CoV-2 in most cases, it is thought that remdesivir would not be effective in treatment.[67] In children who meet KD's criteria, IVIG and aspirin should be started as the standard KD therapy.[68] Because of the risk of coronary artery aneurysms, echocardiographic follow-up is essential in all MIS-C patients.[69] Duration of hospitalization ranged from 4 to 13 days, and favorable outcomes are reported with a mortality rate between 1.4–1.7%.[69]

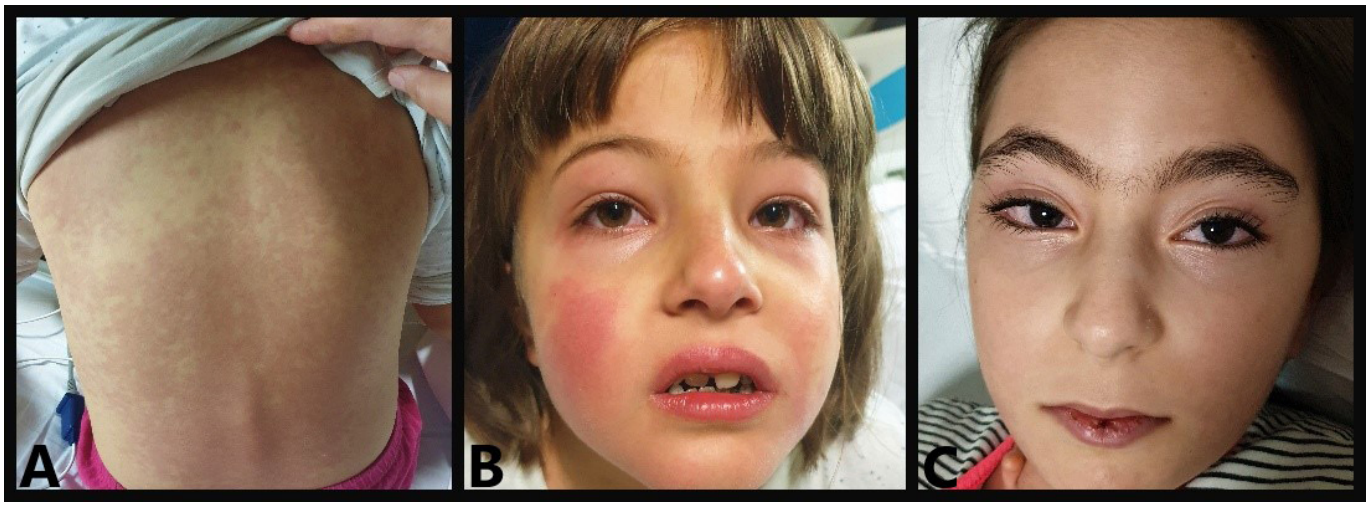

Figure 2. Examples of mucocutaneous manifestations of MIS-C. A child with an erythematous polymorphic rash on the back (A) and her face with cracked lips (B). Characteristic non-purulent conjunctivitis in another child (C).
Written consent form obtained from the patient and parents for the photos.

Table 1.
CDC and WHO case definitions of multisystem inflammatory syndrome in children

CDC case definition	WHO case definition
All 4 criteria must be met:	**All 6 criteria must be met:**
1. Age <21 years	1. Age 0 to 19 years
2. Clinical presentation consistent with MIS-C, including **all** of the following: ►Fever: ♦ Documented fever >38.0°C (100.4°F) for ≥24 hours **or** ♦ Report of subjective fever lasting ≥24 hours ►Laboratory evidence of inflammation ♦ Including, but not limited to, **any** of the following: • Elevated CRP • Elevated ESR • Elevated fibrinogen • Elevated procalcitonin • Elevated D-dimer • Elevated ferritin • Elevated LDH • Elevated IL-6 level • Neutrophilia • Lymphocytopenia • Hypoalbuminemia ►Multisystem involvement ♦ **2 or more** organ systems involved: • Cardiovascular (eg, shock, elevated troponin, elevated BNP, abnormal echocardiogram, arrhythmia) • Respiratory (eg, pneumonia, ARDS, pulmonary embolism) • Renal (eg, AKI, renal failure) • Neurologic (eg, seizure, stroke, aseptic meningitis) • Hematologic (eg, coagulopathy) • Gastrointestinal (eg, abdominal pain, vomiting, diarrhea, elevated liver enzymes, ileus, gastrointestinal bleeding) • Dermatologic (eg, erythroderma, mucositis, other rash) ►Severe illness requiring hospitalization	2. Fever for ≥3 days 3. Clinical signs of multisystem involvement (**at least 2** of the following): • Rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet) • Hypotension or shock • Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/BNP) • Evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer) • Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain) 4. Elevated markers of inflammation (eg, ESR, CRP, or procalcitonin)
3. No alternative plausible diagnoses	5. No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal/streptococcal toxic shock syndromes
4. Recent or current SARS-CoV-2 infection or exposure ►**Any** of the following: • Positive SARS-CoV-2 RT-PCR • Positive serology • Positive antigen test • COVID-19 exposure within the 4 weeks prior to the onset of symptoms	6. Evidence of SARS-CoV-2 infection ►Any of the following: • Positive SARS-CoV-2 RT-PCR • Positive serology • Positive antigen test • Contact with an individual with COVID-19

CDC: Centers for Disease Control and Prevention; WHO: World Health Organization; MIS-C: multisystem inflammatory syndrome in children; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase; IL-6: interleukin-6; BNP: brain natriuretic peptide; ARDS: acute respiratory distress syndrome; AKI: acute kidney injury; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; RT-PCR: real-time polymerase chain reaction; COVID-19: coronavirus disease 2019; PT: prothrombin time; PTT: partial prothrombin time.

Impact of COVID-19 on child health

In many places, especially in low-and middle-income countries (LMICs), the impact of COVID-19 on children will be more significant than the impact of the virus itself. Many major causes of poor health and mortality in children are expected to increase due to the pandemic and the response.[73] The economic impact of enforced lockdown and social distancing can increase violence and addictive behaviors (e.g., alcohol, junk food, and other substances). Since the beginning of the COVID-19 pandemic, violence against women and girls has increased in different countries.[11,74] The spread and severity of COVID-19 are also expected to be further exacerbated in LMICs because of the inadequate sanitation facilities, crowded living conditions, and difficult access to healthcare. Healthcare services are now severely compromised due to closures, lack of personal protective equipment, and fear of attending health facilities.

During the pandemic, well-child care visits should not be deferred because of COVID-19 disease; growth and development of infants should be followed up regularly according to the local guidelines. Telemedicine can be an option during the lockdowns and in high-risk situations. All childhood vaccines should be given in accordance with the recommendations of the WHO or the Ministry of Health. Due to COVID-19 measures, approximately 80 million children under the age of 1 in at least 68 countries may miss receiving life-saving vaccines.[75] Vaccination activities have been delayed or suspended in at least 27 countries to prevent the spread of COVID-19, despite several having ongoing measles epidemics.[73] Childhood malaria deaths are also predicted to double this year due to the downscaling of prevention and treatment.[76] The World Food Programme predicts a doubling of malnutrition, disproportionately affecting children.[77] In a modeling study, Roberton T et al.[78] showed that if routine health care is disrupted and

access to food is decreased over six months, it would result in nearly 1 million excess child deaths in 118 low-income and middle-income countries.

Children's teaching in schools were in crisis in many countries, and the pandemic has sharpened inequities, especially in poorer countries. Many schools lack the resources to invest in digital learning, and many children from poorer households do not have internet access. Unicef reported that at least 463 million–or 31 percent–of schoolchildren worldwide could not be reached by digital and broadcast remote learning programs.[75] We know from the history that school closures have secondary effects on increasing in child marriage and child labor. These often prevent children from continuing their education and effects negatively on their health status. We can see the secondary effects of COVID-19 for years, and the wounds of the pandemic in children may take much longer to heal.

Conclusion

In summary, children at any age may be infected with SARS-CoV-2, with reduced frequency and severity compared with adults. Infected children are mainly asymptomatic or develop only mild symptoms. Most children with COVID-19 can be managed symptomatically without hospitalization. The treatment of severe disease is essentially supportive. We still need evidence-based diagnostic and treatment guidelines for children. On the other hand, the recently identified MIS-C may pose an additional threat. The treatment of this rare phenomenon involves the use of immunomodulators, as well as supportive care. Data on the outcome of antiviral treatments, the safety and immunogenicity of vaccinations, and better specification of high-risk patients in the pediatric population are still needed. COVID-19 is a new disease, and the pandemic continues to evolve. The mid- and long-term effects of this pandemic on child health need to be evaluated by medical and social aspects. Further studies will help to understand the complete picture of the COVID-19 in the pediatric population.

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

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

Informed Consent: Written consent form obtained from the patient and parents for the photos.

Peer-review: Externally peer-reviewed.

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Journal of Pediatric Academy

Original Article

Year: 2020 Volume: 1 Issue: 3
Doi: 10.38092/JPA-2020-507455

Risk Factors for Renal Function Impairment in Children with Meningomyelocele; a Single Center Study

Author(s)

Hülya Nalçacıoğlu[1], Demet Tekcan[1], Özlem Aydoğ[1]

Affiliation(s)

[1]Ondokuz Mayis University Faculty of Medicine, Pediatric Nephrology Department, Samsun, Turkey

Article Information

Article Type: Original Articles
Article Group: Pediatric Nephrology

Received: 30.10.2020
Accepted: 14.11.2020
Available Online: 27.12.2020

Cite this article as: *Nalçacıoğlu H, Tekcan D, Aydoğ Ö. Risk Factors for Renal Function Impairment in Children with Meningomyelocele; a Single Center Study. J Pediatr Acad 2020; 1: 86-89.*

Abstract

Chronic kidney disease and its complications are among the most frequent cause of morbidity and mortality in patients with meningomyelocele. In this study, we aimed to determine the risk factors leading to chronic kidney disease progression in these patients.Fifty patients with meningomyelocele were analyzed retrospectively. Age, gender, follow-up period, serum creatinine, glomerular filtration rate, vesicoureteral reflux (VUR), initial urodynamic findings and initiation time of clean intermittent catheterization (CIC) were noted. The progression of Chronic kidney disease (CKD) was evaluated by DMSA renal scintigraphy, changes in serum creatinine (Screa), and glomerular filtration rate (GFR). 30 of the 50 patients were included in the study. VUR was detected in 63% of the patients, and scar was detected in 83% by renal scintigraphy. The median value of Screa was 0.5 mg/dl in admission, while the median Screa was 1.02 mg/dl (min-max: 0.27-5) at the last visit and the difference was statistically significant (p=0.001). A statistically significant was found between CKD progression and GFR in admission (p=0.001), CIC onset age (p=0.03), degree of VUR (p=0.046), presence of renal scar (p=0.002). It was shown that delay in admission (p=0.011; OR 1.36; CI 1.07-1.73) and low GFR in admission (p=0.036 OR 0.915 CI 0.842-0.994) were the most important risk factors. In our study, it was shown that delay in neurogenic bladder treatment, delay in the initiation of CIC, and low GFR at admission were important risk factors for the progression of CKD in children with meningomyelocele. Therefore, we aimed to emphasize the importance of regular follow-up of these children in Pediatric Nephrology Clinics from the neonatal period.

Keywords: Meningomyelocele, chronic kidney disease, risk factors

Correspondence: Hülya Nalçacıoğlu, Ondokuz Mayis University Faculty of Medicine, Pediatric Nephrology Department, Samsun, Turkey
E-mail: hulyanalcacoglu@hotmail.com

Introduction

Neural tube defects are the most common pathology in the neurogenic bladder etiology in children and are responsible for 90% of cases.[1-2] Spinal cord injury is a dynamic process that starts from the antenatal period and continues in postnatal life and is affected by many factors. All these problems result from the bladder's inability to perform its storage and emptying function properly, secondary to the deterioration of bladder innervation. In the urodynamic evaluation, an increase in detrusor filling pressures, detrusor sphincter dyssynergia, and high discharge or leakage pressures are determined. Upper urinary system dysfunction may develop over time in more than half of the children who are not treated.[1-5]

Highlights

- Spina bifida is the most common cause of neuropathic bladder dysfunction in children.
- Early diagnosis and correct treatment of these patients prevent negative outcome of neurogenic bladder and improve both the survival and quality of life of the patients.

Children with meningomyelocele are generally born with normal upper urinary tract, but are at a high risk of chronic kidney disease (CKD) secondary to poor bladder dynamics.[2-4] Only 5% of cases can urinate spontaneously. Therefore, almost all patients should be evaluated by predicting that they have a neurogenic bladder. The most common complications in patients with meningomyelocele are vesicoureteral reflux (VUR) secondary to neurogenic bladder, the development and progression of CKD with the development of renal parenchymal damage.[4-7] Early detection of and prevention of renal scar with correct treatment result in renal preservation and a safe method of management.[7-9]

In this study, we aimed to determine the risk factors leading to CKD progression in children with meningomyelocele.

Material and Method

Fifty patients diagnosed with meningomyelocele were included in this study. A detailed history was taken from all patients, and physical examinations, including neurological examination were performed. Age, gender, time of follow-up, serum creatinine and GFR both at admission and last visit, urinary Ultrasonography (USG), Voiding Cystourethrogram (VCUG), DMSA renal scintigraphy and urodynamics reports, initiation time of clean intermittent catheterization (CIC) were recorded. Renal function was evaluated by urinary USG, Screa with creatinine clearance calculated by the Schwartz formula[10], and DMSA scan.

The Ethical Committee of Ondokuz Mayis University, Faculty of Medicine, approved this study (number: 220-664). All the procedures in this work were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Statistical Analysis

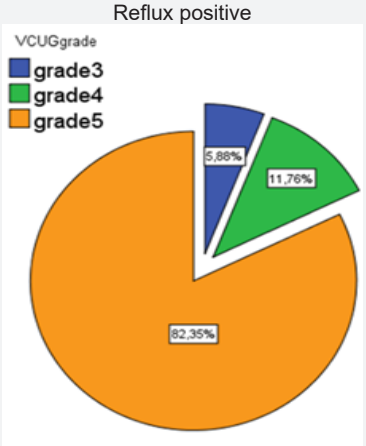
Statistical Packages for the Social Sciences (SPSS) version 24 was used for statistical analysis. Mean, standard deviation, lowest, highest, median, ratio, and frequency values were used in the data's descriptive statistics. The distribution of variables was checked with the Kolmogorov Smirnov test. In quantitative data analysis, the t-test was used for parametric distributed data, and the Many-Whitney U test was used for non-parametric data. A Chi-square test was used to analyze qualitative data, and the Fischer test was used when test conditions were not provided. Pearson and Spearman correlation analysis was used for correlation analysis.

Results

Of the 50 patients examined, those with incomplete data were excluded, and 30 were included in the study. 13 of the patients were male, 17 of them were girls, and their mean age was 10.5±4.83 years (min-max: 3-17 years); The median value of the follow-up period was 5.83 years (min-max: 1 month-17 years). The patients' imaging results are given in **Table 1**. VUR was detected in 63% of the patients, and scar was detected in 83% by DMSA scan. 82.3% patients had bilateral grade V VUR. The median Screa was 0.5 mg/dl (min-max: 0.17-1.7) at time of admission, while the median Screa was 1.02 mg/dl (min-max: 0.27-5) at the last visit. The difference was statistically significant (p=0.001).

Table 1.
Imaging Results of the patients with meningomyelocele

Urinary System Ultrasonography (n, %)	Normal	4 (13.3%)
	Bilateral/unilateral hydroureteronephrosis	24 (80%)
	Solitary kidney	2 (6.6%)
	Increase in bladder wall thickness	15 (50%)
DMSA results (n, %)	Skar present	25 (83.3%)
VCUG Results (n, %)	Reflux positive	19 (63.3%)
Urodynamic findings	High pressure low bladder capacity	25 (83.3%)



The median GFR was 66 ml/min (min-max: 12-178 ml/min) at time of admission, the median GFR was 51 ml/min (min-max: 10-221 ml/min) at the last visit. There was no statistically significant (p=0.657). Laboratory results of the patients are given in **Table 2**. The median age at the initial time of CIC was four years (2 months-16 years).

Table 2.
Laboratory results of patients

	Admission	Last follow -up	p
Plasma Creatinine mg/dl	0.5 (min-max: 0.17-1.7)	1.02 (min-max: 0.27-5)	0.001
GFR (ml/min)	66 (min-max: 12-178)	51 (min-max: 10-221)	0.657
CKD, stage n (%)			
Stage I	6 (22.2)	10 (34.5)	0.284
Stage II	9 (33.3)	2 (6.9)	
Stage III	6 (22.2)	9 (31)	
Stage IV	5 (18.5)	5 (17.2)	
Stage V	1(3.7)	3 (10.3)	

There was statistically significant difference was found between CKD progression and admission GFR (p=0.001), initial age of CIC (p=0.03), VUR degree (p=0.046) and presence of renal scar in initial DMSA (p=0.002). There was no significance between recurrent UTI (p=0.98) and CKD progression (**Figure 1**) (**Figure 2**).

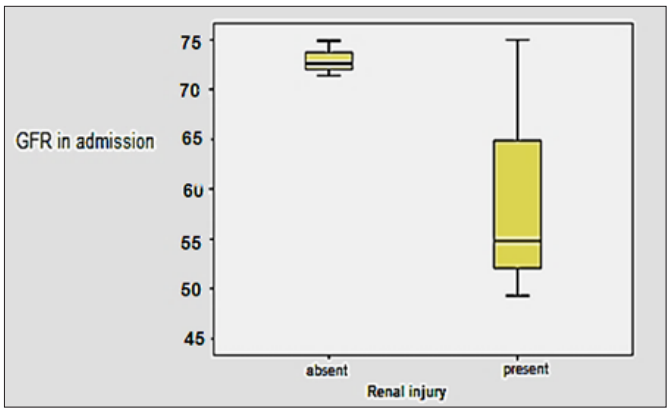


Figure 1. Relationship between chronic kidney injury and reference glomerular filtration rate

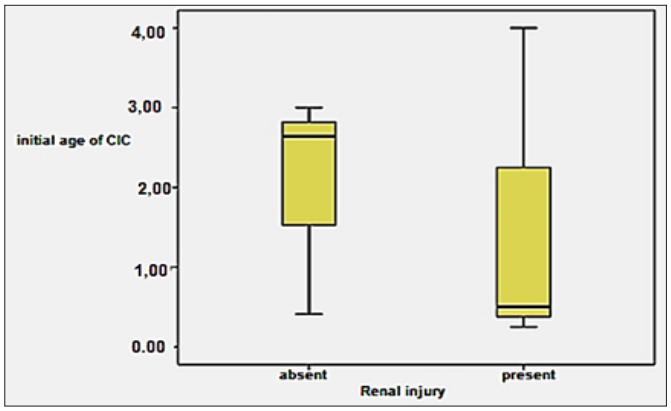


Figure 2. Relationship between chronic kidney injury and clean intermittent catheterization onset age

It was shown that delay in CIC (p=0.011; OR 1.36; CI 1.07-1.73) and low GFR at the time of admission (p=0.036 OR 0.915 CI 0.842-0.994) were the most important risk factors.

Discussion

The development of kidney damage is the most important problem affecting life in meningomyelocele cases. Most children with meningomyelocele are born with a normal upper urinary system.[11] However, it is expected that upper urinary system changes which start within the first six months of life due to the onset of bladder dysfunction. About 10–30% of children are born with the evidence of upper urinary tract pathology and increases to about 50% by the age of five.[12] Recent reports suggest that early detection of the pathology and follow-up with proper treatment result in excellent renal preservation and a safe method of management.[12-14]

Several factors may contribute to the severity of renal scarring. In this study, these factors included high-grade VUR, older age, low GFR at admission, late initial age of CIC. In our study, 25 (83.3%) of 30 children had renal parenchymal damage. The cause of higher incidence of renal damage in our study could be explained by the delay in proper management, poor socio-economic background resulting in non-compliance issues, or the lack of adequate medical follow-up or management, including early diagnosis and treatment could also have contributed to the worse outcome in these patients. We emphasized the necessity of early proper treatment and referral which is still a problem in some areas.

This study revealed that, 19 (63.3%) patients had VUR, and a significant relationship was found between the development of kidney damage and VUR. VUR was reported with a frequency of 15-50% in children with SD.[15] This finding is well defined to have negative effects on renal function in this patient group.[16,17]

Vesicoureteral reflux treatment is a controversial issue in meningomyelocele patients. Klose et al.[18] reported that 92% of VUR decreased with only CIC. According to Sillen et al.[19] no significant relationship was found between the regression of VUR in children with isolated high-grade reflux without spinal pathology and neurogenic bladder treatment in infancy. This suggests that reflux may not only be due to bladder dysfunction in cases with spinal pathology, and accompanying ureterovesical junction insufficiency may also play a role in VUR. This should be supported by larger and homogeneous patient groups. VUR treatment in children with the neurogenic bladder is so controversial in the literature because the groups are not homogeneous enough, and the number of patients in the series is insufficient to establish follow-up protocols. In our study group, we found a significant relationship between progression of kidney damage and high-grade reflux. As a result, we recommend that their kidney functions should follow up closely and choose the treatment in patients with high-grade reflux and congenital neuropathic bladder. Prediction of patients who are resistant to conservative management of VUR with CIC, anticholinergic drugs and surgery may also prevent prolonged risk of renal damage.

In children with meningomyelocele, urodynamic findings provide important information about lower urinary tract dysfunction. Although multiple parameters are obtained in urodynamics according to the findings of the detrusor muscle and external sphincter activities, detrusor leak

point pressure (DLPP) of 40 cmH_2O and above is the most important urodynamic parameter stated as a risk for upper urinary tract damage.[20] We found that delay in admission and low GFR at admission were the most important risk factors for kidney damage development. Early investigation and management of neurogenic bladder are crucial to protect the kidneys. Early CIC is one of the most important factors in preventing kidney damage. Özel et al.[21] reported that the risk of developing kidney damage increased when neurogenic bladder treatment was delayed. Dik et al.[22] reported that they could reduce the development of kidney damage to 2.1% with early CIC, antimuscarinic, and prophylaxis treatment immediately after birth in a study group of 144 patients.

Conclusion

In our study, in neurogenic bladder treatment, we found that delay in the initiation of CIC and low GFR at admission were important risk factors for the progression of CKD in children with meningomyelocele. There is a need for more awareness about the importance of starting proactive treatment to prevent renal damage of these children.

Acknowledgements: This study was accepted as a oral poster the 6th Anniversary Meeting of the EPA, February 27-29 2019, Kayseri

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

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

Ethics Committee Approval: The Ethical Committee of Ondokuz Mayis University, Faculty of Medicine, approved this study(number: 220-664).

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

Informed consent: Informed consent was obtained from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

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Journal of Pediatric Academy

Original Article

Year: 2020 Volume: 1 Issue: 3
Doi: 10.38092/JPA-2020-760856

The Evaluation of the Children with Renal Transplant: Single Centre Experience

Author(s)

Muhammed Mustafa Özdemir[1], Ayşe Seda Pınarbaşı[2], Neslihan Günay[2], Aynur Gencer Balaban[2], Sibel Yel[2], Muammer Hakan Poyrazoğlu[3], İsmail Dursun[2]

Affiliation(s)

[1]Health Ministry, Ciftlik State Hospital, Nigde, Turkey
[2]Department of Pediatric Nephrology, Erciyes University, Faculty of Medicine, Kayseri, Turkey
[3]Department of Pediatric Nephrology-Rheumatology, Erciyes University, Faculty of Medicine, Kayseri, Turkey

Article Information

Article Type: Original Articles
Article Group: Pediatric Nephrology

Received: 16.10.2020
Accepted: 18.11.2020
Available Online: 27.12.2020

Cite this article as: *Özdemir MM, Pınarbaşı AS, Günay N, Gencer Balaban A, Yel S, Poyrazoğlu MK, Dursun İ. The Evaluation of the Children with Renal Transplant: Single Centre Experience. J Pediatr Acad 2020; 1: 90-93.*

Abstract

This study aimed to evaluate patients with renal transplantation in terms of clinical and laboratory parameters. This study was performed retrospectively with records of 48 patients who underwent renal transplantation before 18 years of age, between June 2008 and July 2019.Congenital malformations of the urinary tract were the most common underlying causes of chronic kidney disease stage 5. Surgical complications occurred in 33.4% of the patients and BK viremia was the most common opportunistic viral infection during the follow-up. At the last clinic visit, 57.4% of our patients had CKD stage 1, hypertension and nephrotic range proteinuria were seen in eight and two patients, respectively.Although renal transplantation is the most ideal renal replacement therapy, patients may experience various complications during the follow-up. Therefore, they should be monitored regularly.

Keywords: Chronic kidney disease stage 5, kidney transplantation

Introduction

Although kidney transplantation is the most ideal treatment for adults and children who have reached the chronic kidney disease stage 5 (CKD5), long-term deterioration in graft functions may occur due to primary disease, surgical complications, rejection, and side effects of the immunosuppressive drugs. Although new surgical methods and medical treatments significantly improve graft survival and patient quality of life, some complications can be seen during the follow-up.[1] The surgical and urological complications, such as ureteral obstruction or urinary leakage, may result in morbidity and graft loss at the early period of transplantation.[2] Infections and rejection may deteriorate allograft functions during the course of transplant follow-up. In this retrospective study, we aimed to evaluate the patients with renal transplantation in terms of clinical and laboratory parameters.

Correspondence: Ismail Dursun, Department of Pediatric Nephrology, Erciyes University, Faculty of Medicine, 38200, Talas, Kayseri, Turkey
E-mail: drdursun@hotmail.com

Material and Method

We retrospectively reviewed the medical records of 53 children with kidney transplant who underwent kidney transplantation before the age of 18 and were followed up between June 2008 and July 2019 in the department of Pediatric Nephrology. Approval was obtained from the Local Ethics Committee on 09.05.2018/255

Medical records were reviewed for clinical data including gender, age, anthropometric measurements, underlying cause of CKD5, dialysis modality before transplantation, surgical complications during and after transplantation, induction and maintenance therapies, post-transplant medical problems (hypertension, proteinuria, infection, rejection, chronic kidney disease, etc.) and continuation of clean intermittent catheterization after transplant

The Schwartz formula was used for the calculation of estimated GFR (eGFR). The constant k was defined based on literature values: k=0.55 for children aged 2–12 or adolescent females and k=0.7 for adolescent males.[3]

Highlights

- Kidney transplantation is an important chronic disease.
- It can cause morbidity and mortality despite the all development treatment strategy.
- Opportunistic infections and malignity seen especially in patients given intensive immunosuppressive treatment.

The measurement of CMV, EBV and BKV viral loads were done using by a polymerase chain reaction (PCR). The measured value above 250 IU / mL was accepted as CMV viremia.[4] EBV and BK were accepted as viremia criteria according to the virology laboratory values of Erciyes University Hospital. The value above 26 copy/mL and 316 copy/mL was accepted as BK and EBV viremia, respectively.

Five patients were excluded from study because of lack of data and analysis was completed with 48 patients.

Statistical Analysis

SPSS Windows software was used for the statistical analysis. Whether the quantitative variables showed normal distribution was tested with the Shapiro Wilk normality test. Descriptive statistics were shown as mean±standard deviation for variables with normal distribution, as median (min-max) for variables with non-normal distribution, and several cases and (%) for nominal variables.

When the number of groups was two, the significance of the difference between the groups in terms of means was investigated with the t-test and the Mann Whitney-U test. Nominal variables were evaluated using Pearson Chi-Square or Fisher's exact test. A P-value of less than 0.05 was considered statistically significant.

Results

In our study, the patient group consisted of 30 boys and 18 girls (ratio 1.7:1). Peritoneal dialysis was used as renal replacement therapy in 18 (72%). The mean age at the time of transplantation was 9.8 years and follow-up duration was 55, 8±33, 5 months. The duration of graft survival was 56, 3±34, 2 months. Kidney transplantation was performed from living donors in 38 patients (79.2%) and cadaver in 10 patients (20.8%). Preemptive kidney transplant was done in 23 patients (47.9%). The leading resource in living donors was the mother with 65%. Congenital Malformations of the Kidney and Urinary Tract (CAKUT) is the most common cause of CKD5 (50 %), followed by glomerulonephritis (14.6%).

Graft loss was seen in four patients (8.3%). Two of them died during the follow-up, one from vascular thrombosis and another one from invasive aspergillus infection possibly due to treatment with intensive immunosuppressive therapy for the rejection. One patient had chronic allograft nephropathy and one patient had BK nephropathy.

Surgical complications developed in 33.4% of the patients (n: 16) and the most common surgical complication was found to be UV stenosis. In 87.5% (n: 14) of the patients who developed surgical complications, the complication was also surgically corrected.

While proteinuria was present in 6 (75%) of 8 patients with hypertension at the last control, proteinuria was detected in 23.5% of patients without hypertension. The difference between these two groups was statistically significant ($p<0.05$).

When the CKD staging at the last control was compared with proteinuria and hypertension, it was found that our patient, who was at stage 5, had both proteinuria and hypertension. The difference between CKD staging and hypertension at the last control was statistically significant ($p<0.05$) (**Table 1**).

Urinary tract infection was the most common infection seen in renal transplant recipients (62.5%). 18 (37.5%) of the patients had at least 2 or more urinary tract infections during their post-transplant follow-up. Besides, 10 patients experienced with pneumonia at follow-up. Patients' induction treatments and CMV, EBV, and BK viremia were compared, and a statistically significant difference was found between CMV viremia and induction therapies (**Table 2**). CMV viremia was more common in patients who used ATG than those patients who used Basiliximab

Table 1.
Comparison of CKD staging at last follow-up based on proteinuria and hypertension

		CKD Stage				
		Stage 1	Stage 2	Stage 3	Stage 5	P Value
Proteinuria	Nephrotic range	1	1	0	0	0.256
	Non- nephrotic range	9	1	1	2	
	No	17	8	4	0	
Hypertension	Yes	5	1	0	2	0.018
	No	21	8	5	0	

Table 2.
Relationship between induction therapies and the situation of CMV, EBV, and BK viremia

		ATG	Basiliximab	Total	P Value
CMV Viremia	Yes	6	9	15	0.05
	No	4	29	33	
EBV Viremia	Yes	5	8	13	0.108
	No	5	30	35	
BK Viremia	Yes	2	11	13	0.706
	No	8	27	35	

Discussion

Persistent proteinuria and hypertension are the risk factors for the progression of CKD and poor graft survival in transplanted patients.[5] In our study, the most of the patients with hypertension had proteinuria at last follow-up and patients having both hypertension and proteinuria had poor graft function.

Acute rejection attacks are an important factor affecting long-term kidney survival.[6] Considering the development of acute rejection and the last GFR of the patients in our study, it was found that the patients who had rejection had lower GFR. In our study, it was observed that only one of the seven patients who had stage III-V according to the CKD staging at the last follow-up did not experience acute rejection and the other six patients had rejection. In a study performed in Mexico, it was found that acute rejection was a negative predictor of graft survival, as seen in our study.[7]

Infections are an important complication that results in recurrent hospitalizations and poor graft survival in kidney transplant patients.[8] In our study, it was determined that 62.5% of the patients with kidney transplantation had at least one infection during their follow-up. Pourmand et al.[8] found that 54.2% of the patients had an infection attack at least once during a one-year follow-up. In our study, it was determined that the most common infection was urinary system infection, followed by BK viremia. In our study, the rate of urinary tract infection in the first year was found to be 37.5%. This rate is between 35 and 80% in the literature, and is similar to our study.[8] As previously shown in adult transplant recipients, urinary tract infections did not increase the risk of rejection.[9] However, urinary tract infections, transplantation procedures, prevention of rejection development and immunosuppression treatments used in rejection have been found to increase the risk of infection.[10] Recurrent urinary tract infections were found in four of our patients in our study. Recurrent urinary tract infection of three of these patients started after the first year and two of them had GFR rates above stage III according to the CKD staging in the third year in their follow-up. None of these patients experienced graft loss.

In the literature, the frequency of BK viremia varies between 15.4% and 39.7%.[11,12] It was seen 33.3% of patients in our study. Although there was no significant relationship between BK viremia and graft survival, BK viremia may cause nephropathy and graft loss in the transplanted kidney in the literature.[12] One patient in our cohort experienced with BK virus nephropathy at 4th months of transplant. We switched MMF with leflunomide and decreased target level of tacrolimus, and additionally gave him cidefovir and IVIG. He did not give response to management and reached at CKD5 at 12th months of transplant.

The induction regimen may increase susceptibility to infections in kidney transplant patients. Luan et al.[13] evaluated the impact of various antibody induction regimens on CMV infection in adult kidney and/or pancreas transplant patients. They showed that the use of rATG but not basiliximab was found to be associated with an increased risk for CMV infection. In another study, Bayraktar et al.[14] investigated the role of induction therapy on the onset of CMV disease in 257 adult kidney transplant patients and showed that a higher dosage of ATG was associated with an increased risk of CMV disease. In line with these, the use of ATG as induction therapy resulted in increased number of CMV infection in our study. Although EBV infection is less common than CMV or BK virus infection, it may negatively affect graft survival in solid organ transplants, if it is complicated with post-transplant lymphoproliferative disease (PTLH) which is a potentially fatal complication after transplantation.[15,16] The incidence of EBV infection ranges from 30 to 44% in pediatric transplant patients.[17,18] You et al.[17] monitored pediatric kidney transplant patients in term of EBV infection and PTLD. They demonstrated that 21 patients of 70 renal transplant recipients had EBV infection and six of them developed PTLD and the mortality rate in those patients was 16.6%. In our study, PTLH developed in 1 of 9 patients with EBV infection at the 6th year of kidney transplantation. His immunosuppression was decreased and rituximab based chemotherapy was given. With this, PTLD resolved without any rejection.

Conclusion

Kidney transplantation is an important chronic disease that can cause morbidity and mortality despite the all development treatment strategy. Especially, patients should be closely monitored for opportunistic infections and PTLD.

Acknowledgements: This study was accepted as a oral poster the 6th Anniversary Meeting of the EPA, February 27-29 2019, Kayseri

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: All the authors declare that they have not received any financial support or other benefits from commercial sources for the work described in this paper. They also declare that they have no other financial interests that could create a potential conflict of interest or the appearance of a conflict of interest with regard to this work.

Ethics Committee Approval: Local ethics committee was approved this study with the number of 09.05.2018-255.

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

Informed Consent: Written Informed consent was obtained from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

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Journal of Pediatric Academy

Original Article

Year: 2020 Volume: 1 Issue: 3
Doi: 10.38092/JPA-2020-909489

The Treatment Outcomes in Children with Medulloblastoma

Author(s)

Buket Kara[1], Hilal Akbas[2], Mürsel Düzova[3], Hakan Karabağlı[4], Yavuz Köksal[1]

Affiliation(s)

[1]Department of Pediatric Hematology and Oncology, Selcuk University, Faculty of Medicine, Konya, Turkey
[2]Department of Pediatric Hematology and Oncology, Saglik Bilimleri University, Hamidiye, Turkey - Faculty of Medicine, Ministry of Health Konya City Hospital, Konya, Turkey
[3]Department of Radiation Oncology, Selcuk University, Faculty of Medicine, Konya, Turkey
[4]Department of Neurosurgery, Selcuk University, Faculty of Medicine, Konya, Turkey

Article Information

Article Type: Original Articles
Article Group: Pediatric Hematology-Oncology

Received: 16.11.2020
Accepted: 08.12.2020
Available Online: 27.12.2020

Cite this article as: *Kara B, Akbas H, Düzova M, Karabağlı H, Koksal Y. The Treatment Outcomes in Children with Medulloblastoma. J Pediatr Acad 2020; 1: 94-98.*

Abstract

Medulloblastoma is the most common central nervous system tumor in childhood. This study aims to evaluate the clinical features, treatments, and outcomes of pediatric patients diagnosed with medulloblastomaBetween 2006 and 2019, the medical records of children with medulloblastoma were reviewed retrospectively. Patients who died after surgery, before chemotherapy or radiotherapy were not included in the survival analysisDuring the study period, 38 children were diagnosed with medulloblastoma. Twenty-one of the patients were male (55.3%) and 17 were female (44.7%). The ages of the children ranged from 3 months to 17 years (median age 8 years). The ages of five patients were under 3 years (13.1%). The most common complaints were headache (n: 26, 68.4%), imbalance (n: 21, 55.3%), and vomiting (n: 20, 52.6%). The mass sizes ranged between 3 and 6 cm in 32 patients (84.2%). At the time of diagnosis, 5 patients had seeding metastasis (13.1%). The most commonlyused chemotherapy protocol included vincristine, cisplatin, etoposide (60.5%). Five patients died after surgery without any chemotherapy or radiotherapy. Of the 33 patients included in the life analysis, 12 died (36.4%). Follow-up times ranged from 2 months to 14 years (median, 44 months). The overall survival rate was 59.1%. Eight patients had relapsed (24.2%). Late relapse was detected in 3 of the relapsed patients (relapse times were the 91st, 69th, and 72nd months).It is possible to achieve satisfactory treatment results in children with medulloblastoma using international treatment guidelines and recommendations, with an experienced professional team dedicated to pediatric neurooncology.

Keywords: Children, medulloblastoma, treatment

Correspondence: Buket Kara, Department of Pediatric Hematology and Oncology, Selcuk University, Faculty of Medicine, Konya, Turkey
E-mail: buketkara1001@gmail.com

Introduction

Medulloblastoma generally locates in the posterior fossa, is the most common central nervous system (CNS) tumor in childhood, nearly 20% of all childhood CNS tumors.[1,2] Generally, the metastasis is seen as seeding to the subarachnoid space, extra-neural metastasis can rarely be seen.[3,4] The morphological variants of medulloblastoma are classic, large cell/anaplastic, desmoplastic/nodular medulloblastomas, and medulloblastoma with extensive nodularity. Together with molecular genetic studies, the World Health Organization made a new classification as Wingless (WNT)-activated, Sonic hedgehog (SHH)-activated, Group 3, and Group 4 in medulloblastoma in 2016.[2]

Highlights

- Medulloblastoma is the most common CNS tumor in children.
- The overall survival rate of the included children with medulloblastoma was 59.1%.
- The event-free survival was 40.6%.
- Satisfactory resultsof medulloblastoma require an experienced neuro-oncology team.

The treatment approach in patients with medulloblastoma is surgery, radiotherapy, and chemotherapy, respectively. In recent years, the improvement in the overall survival rates with the use of chemotherapy as well as surgery and radiotherapy in medulloblastoma has been detected. Also, the risk categories in medulloblastoma have been defined recently and the researchers are trying to plan the treatment approaches according to these risk categories.[5] Survivals for patients with average- and high-risk were reported to be 82% and 45-50%, respectively.[1] In a large series from Hacettepe University, the overall survival rate was 43.1% in the whole group.[6]

In this study, from 2006 to 2019, the clinical features, treatments, and outcomes of pediatric patients diagnosed with medulloblastoma were evaluated retrospectively.

Material and Method

Between 2006 and 2019, the oncology charts of patients diagnosed, treated, and followed up with the diagnosis of medulloblastoma in our center were retrospectively reviewed. This study was approved by the Local Ethics Committee of Selçuk University (date: 17.12.2020, number: 2020/540). Demographic characteristics, symptoms and signs, radiologic and surgical findings, treatment approaches, and treatment outcomes were noted from the patients' oncologic charts.

The ages of the patients were grouped as 0-5 years, 5-10 years, and >10 years.

All patients' complaints have been noted and physical and neurological examinations have been carefully recorded. The primary tumor and spinal extension have been evaluated by craniospinal magnetic resonance imaging (MRI). Tumor size on MRI was divided into three groups as <3 cm, 3-6 cm, and >6 cm. Also, the presence of spinal seeding was investigated by MRI. In cases in which spinal seeding is suspected, a cerebrospinal fluid cytological examination was performed.

According to the surgical findings, they were classified as (i) total resection, (ii) subtotal resection, and (iii) only biopsy.

After surgery, all patients were treated with craniospinal radiotherapy (except the patients under age 3 years) and chemotherapy. The chemotherapy protocols used in order of frequency are

i. Cisplatin (100 mg/m²/day, day 1 or 20 mg/m²/day, days 1-5), etoposide (100 mg/m²/day, days 1-3), vincristine (1.5 mg/m²/day, day 1) with a 4-week interval thereafter;

ii. On cycles 1, 4, and 7: cisplatin (20 mg/m²/day, days 1-5), etoposide (100 mg/m²/day, days 1-3);

On cycles 2, 5, and 8: vincristine (1.5 mg/m²/day, day 1), cyclophosphamide (900 mg/m²/day, days 1 and 2)

On cycles 3, 6, and 9: Carboplatin (150 mg/m²/day, days 1 and 15), vincristine (1.5 mg/m²/day, days 1 and 15).

iii. Chloroethylnitrosurea [(CCNU), 100 mg/m²/day, day 1], procarbazine (100 mg/m²/day, days 1-14), vincristine (1 mg/m²/day, days 1, 8, and 15), prednisolone (40 mg/m²/day, days 1-42 days, only the first cycle) with 6-week intervals

The patients who died early after surgery before chemotherapy or radiotherapy were excluded from the survival analysis.

Statistical analysis

SPSS-15 software (SPSS Inc., Chicago, Illinois, USA) was used for all statistical analyses. Frequency and percentage values were used for categorical data, and minimum and maximum values were used in addition to the median value for numerical data.

Kaplan–Meier survival analysis was used for survival analyses. The patient groups were compared in terms of survival duration using a log-rank test. Alpha value (p) <.05 was considered significant.

Results

Between 2006 and 2019, 38 pediatric patients were diagnosed with medulloblastoma. The patients' demographic and clinical features are in **Table 1**. Twenty-one of the patients were male (55.3%) and 17 were female (44.7%). The patients' ages ranged from 3 months to 17 years (median age 8 years). Five patients were under 3 years (13.1%).

The most common complaints were headache (n: 26, 68.4%), imbalance (n: 21, 55.3%), and vomiting (n: 20, 52.6%). The patients' mass sizes varied between 3 and 6 cm in 32 patients (84.2%). Seeding metastasis was present in 5 patients at the time of diagnosis (13.1%).

Table 1.
The patients' demographic and clinical features

	n (%)
Age, median (minimum-maximum)	8 years (3 months – 17 years)
Age group	
0-5 years	11, (28.9%)
5-10 years	15, (39.5%)
>10 years	12, (31.6%)
Gender	
Male	21, (55.3%)
Female	17, (44.7%)
Symptoms and signs	
Headache	26, (68.4%)
Vomiting	20, (52.6%)
Disturbances of gait and balance	17, (44.7%)
Strabismus	5, (13.2%)
Diplopia	5, (13.2%)
Head tilt	5, (13.2%)
Mental disturbances	1, (2.6%)
Mass size	
<3 cm	3, (7.9%)
cm	32, (84.2%)
>6 cm	3, (7.9%)
Seeding	5, (13.2%)
Surgery	
Total	31, (81.5%)
Subtotal	5, (13.2%)
Only biopsy	2, (5.3%)
Pathology	
Classic	35, (92.1)
Nodular	2, (5.3%)
Desmoplastic	1, (2,6%)

The most commonly used chemotherapy protocol included vincristine, cisplatin, etoposide (60.5%). Five patients died without any treatment (chemotherapy or radiotherapy) in the early period after surgery.

Twelve of the 33 patients included in the life analysis died (36.4%). Follow-up times ranged from 2 months to 14 years (median, 44 months). The overall survival (OS) and event-free survival (EFS) rates were 59.1% and 40.6%, respectively (**Figure 1**).

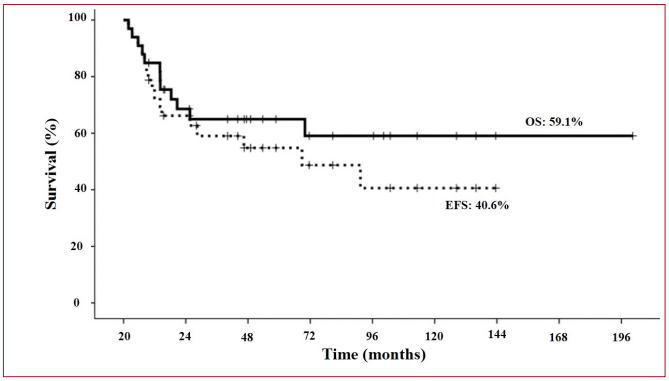

Figure 1. The rates of overall survival and event free survival of all patients

Eight patients had arelapse (24.2%). Late relapses were detected in 3 of the patients (relapse times were the 91st, 69th, and 72nd months).

Discusion

Medulloblastoma is the most common CNS tumor in childhood and constitutes approximately 20% of all CNS tumors in children aged 0-14 years. Although they are usually diagnosed in the first decade of life, it can be diagnosed in older children and even in adult age groups. It is more common in males than females. Although its etiology is not known exactly, its association with some inherited syndromes such as Gorlin-Goltz syndrome, Turcot syndrome, Li-Fraumeni syndrome, neurofibromatosis type 1 and 2, Rubinstein-Taybi syndromes, Fanconi anemia, and Nijmegen breakage syndrome have been reported.[1,2]

In this study, the clinical features, treatments and treatment outcomes of pediatric patients diagnosed with medulloblastoma were evaluated retrospectively.

Although the age of our patients ranged from three months to 17 years (median, 8 years), approximately two-thirds of the patients were under 10 years old. There was a slight male dominance in gender distribution. These demographic features were similar to the literature.

Medulloblastoma is generally located posterior fossa and associated with the fourth ventricle. Clinical findings include headache, vomiting, papillary edema, irritability, diplopia, nystagmus, and rapid growth of head circumference during infancy. These findings occur due to hydrocephalus and increased intracranial pressure secondary to tumor obstruction. The most common symptoms are vomiting and headache and they are present in 80% of patients.[1,2] The most common complaints in our patients were headache, vomiting, and disturbances of gait and balance. Other findings such as strabismus, diplopia, head tilt, and mental disturbances were less frequent.[7]

In medulloblastoma, theinitial treatment approach is surgery. The main purpose of surgery is total or near-total resection of the tumor and, if possible, remaining residual tumor less than 1.5 cm², and this is one of the main prognostic factors.[1,2,5,6] In our study, it was learned from the patients' charts that a significant portion of our patients underwent total or near-total resection. However, because our study was retrospective and some patients were referred from another center, we were unfortunately not informed about the residual tumor volume due to the lack of early radiological examination. This was one of the limitations of our study.

Another treatment that has a critical role in medulloblastoma is radiotherapy.Radiotherapy application is craniospinal radiotherapy. However, an important limitation in radiotherapy is radiotherapy-related side effects such as neurocognitive, endocrinological and growth side effects in children under three years of age.[1,2,5,6] In our patients, radiotherapy could not be applied in five patients younger than three years old. The others received appropriate radiotherapy for the risk group.

Chemotherapy is currently considered as a standard adjuvant treatment modality. Many chemotherapeutic agents, vincristine, cisplatin, etoposide and alkylating agents are used.[1,2,5,6] Cisplatin-based chemotherapy

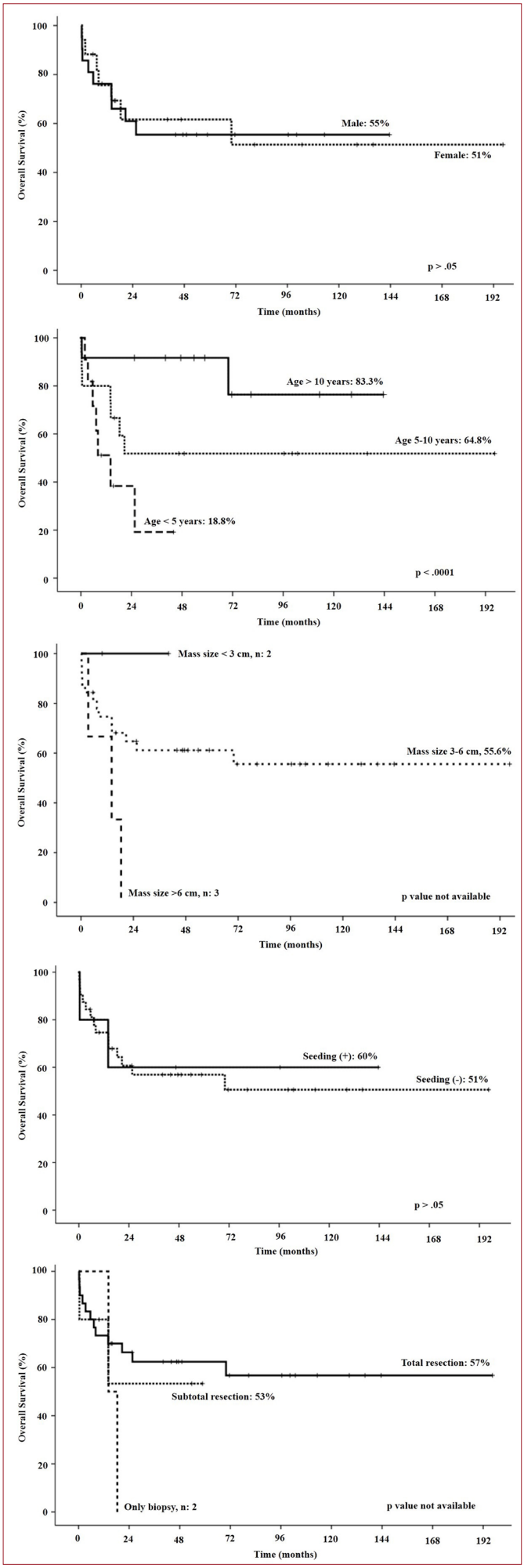

Figure 2. The factors affecting overall survival

protocols were mostly used in our patients. While the first applied chemotherapy scheme was vincristine, cisplatin, etoposide, alternating with cisplatin, etoposide (on the 1, 4, and 7. cycles), vincristine, cyclophosphamide (on the 2, 5, and 8. cycles), carboplatin, vincristine (on the 3, 6, and 9. cycles) chemotherapy schemes were used in the following years.

Medulloblastoma is divided into two as standard and high risk according to its prognostic factors. The standard risk group is >3 years old, no metastatic disease at diagnosis, tumor resected totally or nearly total, residual tumor size <1.5 cm². High-risk group is being younger than 3 years old, the presence of metastases at diagnosis, or determination of >1.5 cm² tumor mass after resection.Medulloblastoma has four molecular subgroups as WNT tumors, Sonic Hedgehog tumors, Group 3, and Group 4 tumors. Groups 3, and 4 medulloblastomas are considered as non-WNT, non-Sonic Hedgehog tumors. Retrospective studies have shown that this classification has important prognostic significance. While survival rates in patients with medulloblastoma in which the WNT pathway is activated are determined to be above 90%, Sonic Hedgehog tumors subtype and Group 4 tumors have a moderate survival rate (75%). Group 3 cases have the worst survival rates of 40-60%.[7] Another limitation of our study is that molecular subgroups could not be determined, especially since it was a retrospective study.

For standard and high-risk medulloblastoma, the overall survival rates are nearly 80% and 50%, respectively.[1] The overall survival rate was reported as 43.1% in the whole group from a big center.[6] In our study, the OS and EFS rates were 59.1% and 40.6%, respectively. It may contribute more positively to survival rates by determining a more reliable risk group and molecular subgroups.

Conclusion

In medulloblastoma, which is the most common CNS tumor of childhood, multidisciplinary approaches both at the diagnosis and treatment will have positive contributions to the treatment success of the disease

Acknowledgement: We would like to thank all patients and families for their participation in this study.

Author Contributions: YK conceived the study. YK and BK were involved in patient care, including the process of procedure and routine clinical follow-up. YK, BK, HA and MD performed the literature review and wrote the manuscript. YK also made statistical analysis. HA, MD and HK also made helpful suggestions to improve the manuscript.

Conflict of Interest Statement: The authors declared no potential conflicts of interest with respect to the research, authorship,and/or publication of this article.

Ethics Committee Approval: This study was approved by the Local Ethics Committee of Selçuk University (date: 17.12.2020, number: 2020/540).

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

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Peer-review: Externally peer-reviewed.

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Journal of Pediatric Academy

Original Article

Year: 2020 Volume: 1 Issue: 3
Doi: 10.38092/JPA-2020-48192

Can Phototherapy Requirements Be Predicted through Cord Blood Test Results in Newborns?

Author(s)

Berna Hekimoğlu

Affiliation(s)

Health Science University, Kanuni Education and Research Hospital, Trabzon, Turkey

Article Information

Article Type: Original Articles
Article Group: Newborn

Received: 17.10.2020
Accepted: 08.12.2020
Available Online: 27.12.2020

Cite this article as: *Hekimoğlu B. Can Phototherapy Requirements Be Predicted through Cord Blood Test Results in Newborns? J Pediatr Acad 2020; 1: 99-102.*

Abstract

Hyperbilirubinemia is one of the common problems in newborns. If not diagnosed and treated in time, high bilirubin levels can cause kernicterus and permanent brain damage. Therefore, early detection of hyperbilirubinemia development risk in newborns is important. In this study, we aimed to investigate whether the direct Coomb'test and cord blood bilirubin level (UCB) could be used to predict newborns at a high risk of developing hyperbilirubinemia.A total of 300 newborns born between January-June 2014 with a birth weight ≥ 2500g and gestational week ≥37 weeks were included in the study. The results of direct Coombs'test, UCB, maternal and infant blood groups and serum total bilirubin levels were analyzed retrospectively.Phototherapy was given to 35 (11.7%) of 300 newborns and 25 (8.3%) had positive direct Coombs'test. ABO incompatibility was found in the etiology of 51.5% of the cases with hyperbilirubinemia. It has been observed that patients with positive direct Coombs'test have a high rate of hospitalization ($p<0.001$). The UCB levels were found to be statistically higher in cases who received phototherapy (2.7±1.0 and 1.8±0.6, respectively, $p<0.01$). The cutoff value of UCB for predicting the occurrence of significant hyperbilirubinemia requiring phototherapy was 2.0 mg/dL, with a sensitivity of 77% and specificity of 77% and negative predictive value was 96%.The UCB and direct Coombs'test could be useful in predicting the possibility of significant hyperbilirubinemia and hospitalization in newborns. Thus, detection of newborns at risk of hyperbilirubinemia with a noninvasive method within a few hours after birth will prevent early discharge and provide close follow-up and early treatment.

Keywords: Cord blood bilirubin, direct Coombs'test, hyperbilirubinemia, newborn

Correspondence: Berna Hekimoglu, Department of Neonatology, Health Science University, Kanuni Education and Research Hospital, Trabzon, Turkey
E-mail: dr.bernasygn@gmail.com

Introduction

Hyperbilirubinemia is one of the common problems in newborns. If not diagnosed and treated in time, high bilirubin levels can cause kernicterus and permanent brain damage.[1] Therefore, early detection of hyperbilirubinemia development risk in newborns is important. In developed countries, the incidence of neonatal hyperbilirubinemia has been reported as 17–45 and 2–36 cases per 100,000 live births for serum bilirubin levels >25 mg/dl and 30 mg/dl, respectively.[2,3] In our country, in a multicenter study published in 2018, the incidence of severe hyperbilirubinemia (>25mg/dl) and bilirubin encephalopathy has been reported as 6.4% and 2.3%, respectively.[4] The gold standard to measure hyperbilirubinemia continues to be only total serum bilirubin. This technique is painful and can cause anemia if applied frequently. Therefore, we aimed to investigate whether the direct Coomb'test and cord blood bilirubin level (UCB) could be used to predict newborns at a high risk of developing hyperbilirubinemia.

Highlights

- Hyperbilirubinemia is one of the common problems in newborns.
- Cord blood bilirubin levels and direct Coombs test are useful tools for the detecting of severe indirect hyperbilirubinemia and predicting the possibility of hospitalization.
- Using this approach will prevent the early discharge of newborns and provide a close follow-up and early treatment.

Material and Method

This study was conducted by retrospective analysis of clinical and laboratory data in Ordu University Medical Faculty, Clinic of Obstetrics and Gynecology and medical records of the infants admitted to the neonatal intensive care unit between January and June 2014. A total of 300 babies with a birth weight ≥2500 g and gestational week ≥37 weeks were included in the study. In accordance with the policy of our hospital, total bilirubin levels, blood groups and direct Coombs'test are routinely studied from umbilical cord blood in order to evaluate the risk of blood group incompatibility in all infants who are born in our hospital. In addition, serum total bilirubin levels of those who were hospitalized for phototherapy treatment in the first 24 hours were recorded retrospectively. The infants who received phototherapy treatment in the first 24 hours of life were considered as Group 1, and those who were not given phototherapy treatment were considered as Group 2. Phototherapy indication was evaluated in accordance with the recommendations of the American Academy of Pediatrics (AAP).[5] Prematurity, those with 1 and 5 minutes of Apgar score <7, those with congenital anomalies, cases with complications that aggravate the development of hyperbilirubinemia such as sepsis or hematoma were not included in the study.

Demographic features, UCB and direct Coombs' test values were compared between the two groups. The UCB levels were determined using the Beckman Coulter Au2700. Direct Coombs'test was performed through full automatic gel centrifugation method. Total serum bilirubin levels were determined on heel stick (capillary) samples using bedside BR 5000N Apel bilirubinometer. This study was approved by Local ethics committee was approved this study with the number of 15.05.2016-120.

Statistical analysis

Statistical analysis was performed using SPSS version 13.0 package software (SPSS for Windows Version 13.0. SPSS Inc. Chicago, USA, Released 2005). Descriptive statistical analysis was carried out for all variables. The results are expressed as mean ±standard deviation. Chi-square test was used in the comparison of categorical variables. Normality of the variables was tested using Kolmogorov-Smirnov and Shapiro-Wilk tests. Nonnormally distributed variables between two groups were analyzed using Mann–Whitney U test. ROC curve test was used to determine cutoff values of UCB in infants who required phototherapy. Sensitivity, specificity, negative predictive value and positive predictive value were calculated.

Results

A total of 300 newborns were included in the study. There were 35 (11.7%) cases in Group 1 and 275 cases in Group 2 (88.3%). Direct Coombs'test was positive in 25 (8.3%) of all cases.

Demographic features, direct Coombs'test and UCB values were compared between the two groups (**Table 1**).

Table 1
Demographic characteristics of the groups included in the study.

	Grup 1	Grup 2	P
Gestationalage (weeks)	39.2±0.9	38.9±1.2	0.12
Birth weight (g)	3364.7±359.5	3251.1±401.7	0.09
Male gender [%, (n)]	46 (16)	50 (133)	0.62
Vaginal delivery [%, (n)]	40 (14)	50 (133)	0.26
Blood type incompatibility [%, (n)]	83 (29)	23 (60)	0.62
ABO inconsistency [%, (n)]	52 (18)	14 (36)	<0.001
Rh inconsistency [%, (n)]	20 (7)	8 (21)	<0.001
ABO+Rh inconsistency [%, (n)]	11 (4)	1 (3)	<0.001
Direct Coombs test [%, (n)]	57 (20)	2 (5)	<0.001
UCB levels (mg/dl)*	2.7±1.0	1.8±0.6	<0.001

*UCB: Umblical cord bilirubin
Continuous variables are expressed as mean±standard deviation and groups were compared using the Mann Whitney U test. Categorical variables were expressed as frequency (percentage) and were compared using the chi-square test. Statistically significant at p<0.05.

In the etiology of the cases with direct Coombs'test results; ABO incompatibility, Rh incompatibility, both ABO and Rh incompatibility were found in 52% (n:13), 20% (n: 5), 8% (n:2) respectively, while the cause could not be determined in 20% of the cases. The mean bilirubin level of the patients was 8.6±2.4 mg/dl. Intravenous immunoglobulin was given to 2 cases (5.7%) since bilirubin values were close to the blood exchange limit.

The rate of hospitalization and early phototherapy initiation rate were found to be statistically significantly higher in cases with positive direct Coombs'test compared to negative ones (p<0.001). In 20 of 25 patients who were positive for direct Coombs'test in the first 24 hours, phototherapy was initiated by finding serum bilirubin levels above the 95th percentile according to the bilirubin normogram for age. It was found that UCB levels had higher in Group 1 compared to Group 2 (2.7±1.0 and 1.8±0.6, respectively, p<0.001). Patients with positive direct Coombs'test had higher UCB levels than those with negative ones (3.1±0.9 and 1.8±0.6, respectively, p<0.001). When cutoff value for UCB was taken as 2.0mg/dl; sensitivity, specificity, positive predictive value and negative predictive value were found to be 77%, 77%, 96% and 31%, respectively. (**Figure 1**)

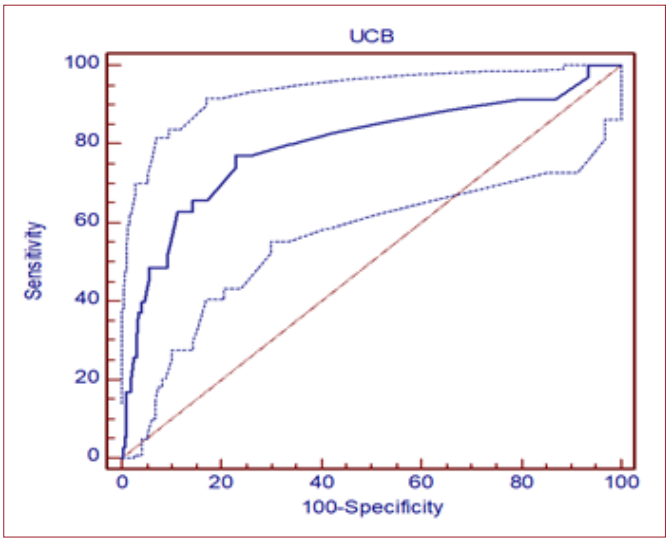

Figure 1. ROC analysis of cord blood bilirubin in determining phototherapy need.

Discussion

The one of the most frequent cause of readmission to neonatal units is hyperbilirubinemia. In the etiology of newborns hospitalized with the diagnosis of indirect hyperbilirubinemia, blood group incompatibility has been reported most frequently.[6] In the study of Yigit et al.[7] it was reported that 21% of the cases had ABO incompatibility and 4.7% of them had Rh incompatibility, while in the study of Bolat et al.[8] 30.2% of the cases had ABO incompatibility and 7.7% of them had Rh incompatibility. In our study, 12% of the cases were hospitalized due to significant hyperbilirubinemia within the first 24 hours after birth, and similar to the literature, mostly ABO incompatibility was found in the etiology of hyperbilirubinemia.

The direct Coombs'test is an important test in the differential diagnosis of indirect hyperbilirubinemia and hemolytic disease of the newborn. It has been reported that the incidence of direct Coombs'test positivity is 1-9% in newborns.[9] In our study, the direct Coombs'test positivity rate was 8.3%. ABO incompatibility was the most common in the etiology of cases with positive direct Coombs'test.

There are many studies in the literature investigating the relationship between direct Coombs' test positivity and phototherapy. In a study conducted by Madan et al.[10] it was reported that babies with a positive direct Coombs'test were not more likely to go back to the hospital for phototherapy than those who were negative. They also emphasized that it is not necessary to routinely perform a direct Combs'test from cord blood in newborns. Procianoy[11] and Schonitzer[12] reported that if the direct Coombs'test is used in combination with UCB, newborns with a high risk of developing hyperbilirubinemia can be detected earlier. On the other hand, there are studies reporting that the bilirubin level in cord blood alone is more determinative and sufficient in determining the risk of developing hyperbilirubinemia.[13] The results in our study show that newborns with positive direct Coombs'test have higher UCB levels than those who are negative, and they need more phototherapy. Our results support the hypothesis that cord blood direct Coombs'test results are useful in early detection of cases with high risk of developing hyperbilirubinemia. It has also been shown that patients who are positive for direct Coombs'test results should be followed up more closely.

Rosenfeld[14] and Knudsen[15] reported that the high UCB level can be used to identify newborns with a risk of development severe hyperbilirubinemia. Rosenfeld et al.[14] reported that the risk of developing hyperbilirubinemia would be high when the UCB level was >2.0 mg/dl. In the study of Knudsen et al.[15] this level was reported as >2.35 mg/dl. Knüpfer et al.[16] it was reported that 70.3% sensitivity and 65.6% negative predictive value for the UCB level of 1.76 mg/dl. In the study of Ipek et al.[17] it was reported that the sensitivity was 50% and the negative predictive value was 97.9% for the UCB of 2.60 mg/dl. In the study of Aktaş et al.[18] it was reported that the sensitivity was 82%, and specificity of 99% for the UCB of 1.67 mg/dl. The fact that different cutoff levels were determined in all these studies may be due to the heterogeneity of the study groups. This situation prevents the standard use of the test. Therefore, we aimed to determine the cutoff value of UCB level in order to predict babies who may be developed significant hyperbilirubinemia. In our study when cutoff value for UCB was taken as 2.0 mg/dl sensitivity, specificity, positive predictive value and negative predictive value were found to be 77%, 77%, 96% and 31%, respectively. The high negative predictive value of the test indicates that the risk of developing severe hyperbilirubinemia is low in cases with UCB <2 mg/dl. In cases with UCB level >2 mg/dl, the possibility of predicting the possibility of significant hyperbilirubinemia and hospitalization will be higher when the evaluation is made together with the direct Coombs'test. This situation is important not only to protect infants against kernicterus, but also to early refer infants from the peripheral centers to tertiary referral hospitals.

Conclusion

To summarize, nowadays, there is no exact method for the prevention of jaundice in newborns with risk factors. Our results suggest that the evaluation of UCB level and direct Coombs'test are a useful indicator for developing significant hyperbilirubinemia in healthy term newborns. It may help us to determine infants at high and low risks. Thus, detection infants of with high risk with a non-invasive method within a few hours after birth will prevent early discharge and provide close follow-up and early treatment.

Acknowledgements: This study was accepted as an oral poster the 6th Anniversary Meeting of the EPA, February 27-29 2020, Kayseri

Conflict of Interest Statement: Author declares that she has not received any financial support or other benefits from commercial sources for the work described in this paper. She also declares that she has no other financial interests that could create a potential conflict of interest or the appearance of a conflict of interest with regard to this work.

Ethics Committee Approval: Local ethics committee was approved this study with the number of 15.05.2016-120.

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

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Peer-review: Externally peer-reviewed.

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Journal of Pediatric Academy

Image Corner

Year: 2020 Volume: 1 Issue: 3
Doi: 10.38092/JPA-2020-212852

Inflammatory Myofibroblastic Tumor of the Bronchus Mimicking Asthma

Author(s)

Melih Hangül[1], Ömer Önal[2] , Alper Özcan[3], Ekrem Ünal[3], Mehmet Köse[1]

Affiliation(s)

[1]Erciyes University, School of Medicine, Department of Pediatrics, Division of Pediatric Pulmonology, Kayseri, Turkey
[2]Erciyes University, School of Medicine, Department of Thoracic Surgery, Kayseri, Turkey
[3]Erciyes University, School of Medicine, Pediatric Hematology and Oncology, Kayseri, Turkey

Article Information

Article Type: Image Corner
Article Group: Pediatric Pulmonology

Received: 22.10.2020
Accepted: 14.11.2020
Available Online: 27.12.2020

Cite this article as: *Hangül M, Önal Ö, Özcan A, Ünal E, Köse M. Inflammatory Myofibroblastic Tumor of the Bronchus Mimicking Asthma. J Pediatr Acad 2020; 1: 103-104.*

An 8-year-old girl was referred to the pediatric chest disease department for pneumonia that did not respond to treatment. It was learned that the patient was diagnosed with non-allergic asthma at the age of 6 because of recurrent wheezing episodes and was on inhaled fluticasone and montelukast for 2 years. It was learned that the patient admitted to another hospital with complaints of cough, fever and respiratory distress 15 days before his last admission. The patient, who was started on vancomycin and meropenem treatment, was sent after the radiological findings and tachypnea continued. The patient had tachypnea on respiratory system examination at the time of admission and respiratory sounds were not heard on the left side. Chest X-ray showed total atelectasis in the left lung, mediastinal shift and compensatoryhyperaeration in the right lung (**Figure 1**). Atelectasis in the lower lobe of the left lung and filling defect in the left main bronchus was observed in the chest radiography taken 1 year ago (**Figure 2**). An intrabronchial mass lesion obliterating the left main bronchus was observed in the thoracic computed tomography (**Figure 3**). In fiberoptic bronchoscopy, a polypoid mass lesion, 2 cm below the carina, completely obliterating the left main bronchus (**Figure 4**), was observed and biopsy was taken. The final diagnosis was Inflammatory myofibroblastic tumor (IMT). According to the pathology report ALK inhibitor crizotinib was given to the patient. The patient is being followed in remission. IMT Primary lung tumors are very rare in childhood (1). IMT is the most common benign tumor of the lung in children. Since the clinical picture of lung tumors is nonspecific and they are rare, it is not considered in the differential diagnosis of lung diseases in children. In the treatment, total excision is performed and the prognosis is excellent (2). Asthma is the most common chronic pediatric disease in the worldwide and most common cause of wheezing in children. Patients with asthma who do not respond to appropriate treatment and have atelectasis on chest X-ray should be investigated in detail for other causes of wheezing (3).

Author Contributions: MK conceived the study. MH, ÖO, AÖ, EÜ, and MK were involved in patient care, including the process of procedure and routine clinical follow-up. MH, AÖ and MK performed the literature review and wrote the manuscript. ÖO, EÜ, and MK also made helpful suggestions to improve the manuscript.

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

Correspondence: Mehmet Köse, Erciyes University, School of Medicine, Department of Pediatrics, Division of Pediatric Pulmonology, Kayseri, Turkey
E-mail: mhmtkose@yahoo.com

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

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

Peer-review: Externally peer-reviewed.

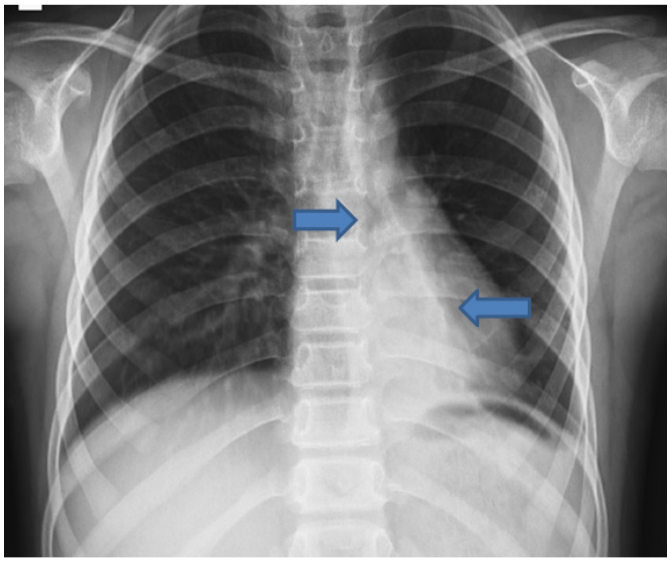

Figure 1. Chest X ray 1 years before admission showing filling defect at the left main bhronchus and and double contour finding in the retrocardiac space

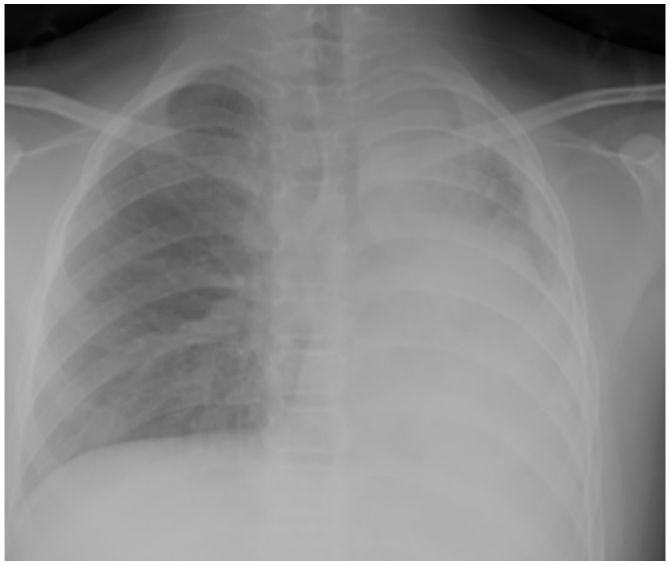

Figure 2. ChestX-ray at the admission showing left lung atelectasis, mediastinal shift and hyperaeration of right lung

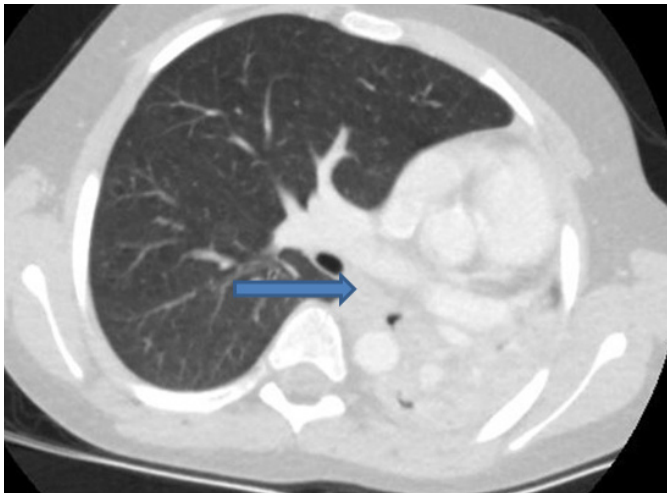

Figure 3. Tomographic appearance of intrabronchial lesion on the left main bhronchus

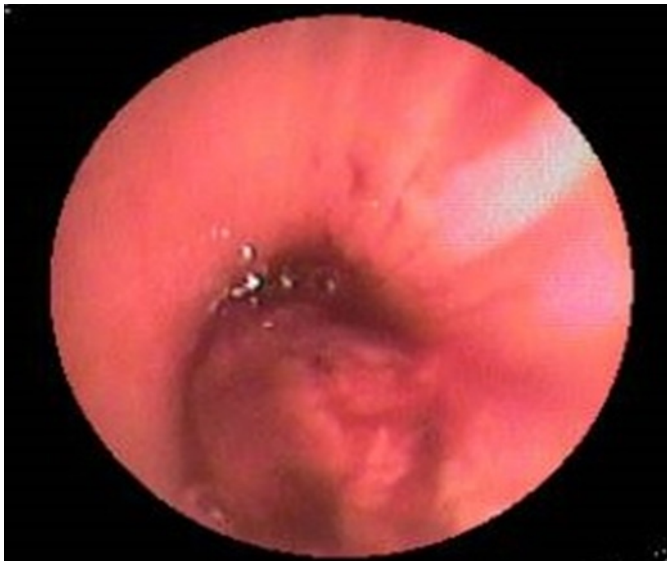

Figure 4. Fiberoptic bronchoscopic image of polipoid mass in the left main bronchus

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Journal of Pediatric Academy

Image Corner

Year: 2020 Volume: 1 Issue: 3
Doi: 10.38092/JPA-2020-236659

Pediatric Takayasu Vasculitis with Extensive Vascular Involvement

Author(s)

Şeyda Doğantan[1], Sema Nur Taşkın[1], Sümeyra Özdemir Çiçek[1], Zehra Filiz Karaman[2], Ayşenur Paç Kısaarslan[1], Muammer Hakan Poyrazoğlu[1]

Affiliation(s)

[1]Division of Pediatric Rheumatology, Department of Pediatrics, Erciyes University Faculty of Medicine, Kayseri, Turkey
[2]Division of Pediatric Radiology, Department of Pediatrics, Erciyes University Faculty of Medicine, Kayseri, Turkey

Article Information

Article Type: Image Corner
Article Group: Pediatric Rheumatology

Received: 22.10.2020
Accepted: 14.11.2020
Available Online: 27.12.2020

Cite this article as: *Doğantan Ş, Taikın SN, Özdemir ÇiçekS, Kahraman ZF, Paç Kısaarslan A, Poyrazoğlu MH. Pediatric Takayasu Vasculitis with Extensive Vascular Involvement. J Pediatr Acad 2020; 1: 105-106.*

An 11-year-old female known to healthy children admitted to the hospital with chest pain for a month. The pain spread from left shoulder to back and increased at night. Her pain did not change with motion and was relieved with non-steroidal anti-inflammatory drugs (NSAIDs). She had no cough, fever, and weight loss. She had no family history of cardiac, cerebrovascular, or rheumatologic disease. Measurements of blood pressure were 100/50 mmHg in the right upper extremity, 90/60 mmHg in the left upper extremity, 90/50 mmHg in the right lower extremity, 90/60 mmHg in the left lower extremity. Other vital signs and physical examination findings were normal. Laboratory values; hemoglobin was 8.6 g/dl, erythrocyte sedimentation rate was 91 mm/hour (normal 0-20 mm/h), C-reactive protein was 37 mg/dl as abnormal findings. The other evaluations for infectious and malignancies were non-significant. Anti-nuclear antibody, Anti-neutrophil cytoplasmic antibodies, anti-ds-DNA, anti-phospholipid antibodies were in the normal range. Echocardiographic findings were normal. Magnetic Rosenans (MR) angiography was performed with a preliminary diagnosis of vasculitis due to unexplained high acute phase reactants and upper and lower extremity blood pressure differences. The vessel wall irregularities were observed in both internal carotid arteries, vertebral arteries, vertebral basilar system, and thoracic aorta (**Figure 1,2,3**). Bilateral renal arteries narrowing were observed at the exit level from the aorta (**Figure 2**). The patient was treated with steroid, cyclophosphamide, and mycophenolate mofetil. Six months later, new artery involvement was detected, and tocilizumab was started.

Takayasu arteritis is diagnosed with angiography (CA, CTA, and MRA) of the aorta, its main branches or pulmonary arteries showing aneurysm/dilatation, narrowing, occlusion, or a thickened arterial wall not due to other causes, plus one of the five following criteria: pulse deficit or claudication, four limb blood pressure inconsistencies, bruits, hypertension, and elevated acute phase reactants.[1] The management of TA is made according to the rare pediatric vasculitides consensus report.[2] Our patient's most important feature was nonspecific chest pain, and elevated levels of acute-phase reactants cannot be explained due to other reasons.

TA should be investigated in a case with unexplained silent clinical findings and high acute phase reactants.

Correspondence: Ayşenur Paç Kısaarslan, Division of Pediatric Rheumatology, Department of Pediatrics, Erciyes University Faculty of Medicine, Kayseri, Turkey
E-mail: aysenurkisaarslan@hotmail.com

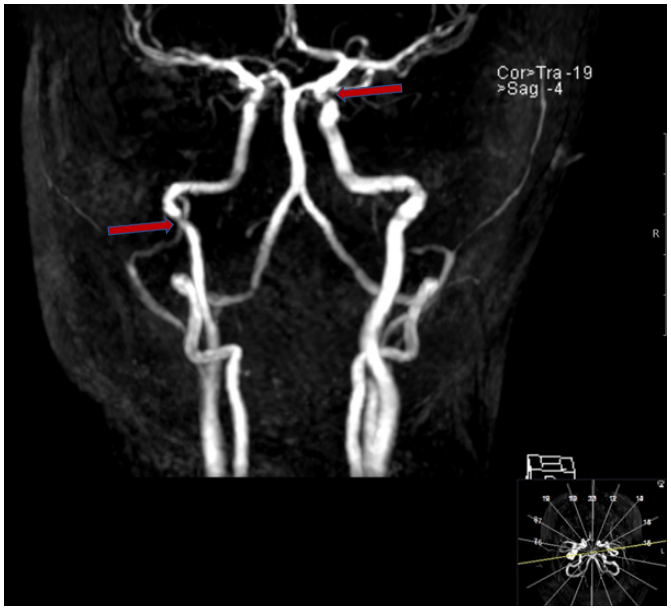

Figure 1. MR Angiography: Wall irregularities are observed in both internal carotid arteries, both vertebral arteries, and the vertebral basilar system

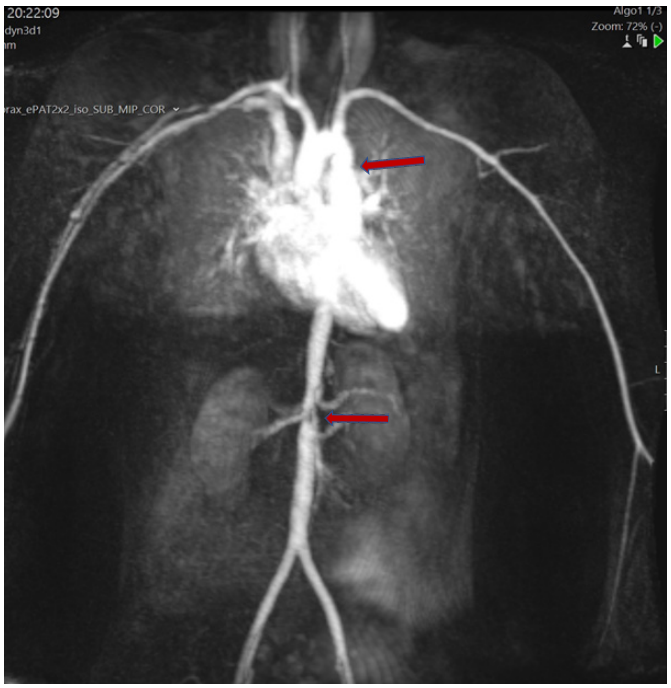

Figure 2. MR Angiography: At the exit of the left common carotid artery arch from the aorta, partly narrowing and wall irregularities are observed in the thoracic aorta. The abdominal aorta was observed with a markedly narrowed

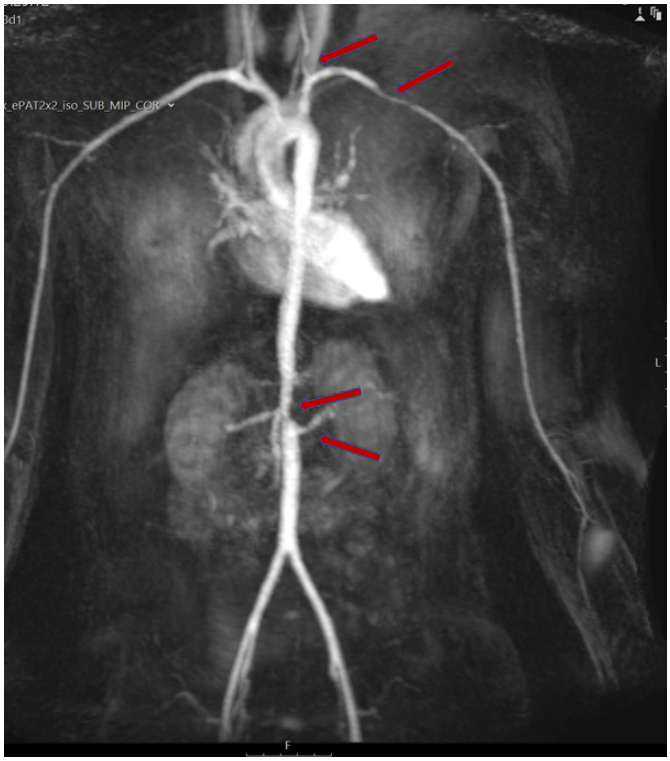

Figure 3. MR Angiography: The left common carotid artery was observed to be markedly narrowed from its exit from the artery. In the middle part of the left subclavian artery, an irregularity that caused significant stenosis in the lumen was observed in a 15 mm segment. There was an irregularity in the abdominal aorta that caused a minimal narrowing of the renal arteries and before the exit level. There is also an irregularity in the proximal left renal artery causing minimal narrowing of the lumen

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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 Statement: The authors have no conflicts of interest to declare.

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

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

Peer-review: Externally peer-reviewed.

Journal of Pediatric Academy

Letter to the Editor

Year: 2020 Volume: 1 Issue: 3
Doi: 10.38092/JPA-2020-181739

Puberty Precocious Due to Chronic Lavender Oil Application

Author(s)

Selim Kurtoğlu[1], Mustafa Armut[2]

Affiliation(s)

[1]Memorial Kayseri Hospital, Department of Pediatric Endocrinology, Kayseri, Turkey
[2]Memorial Kayseri Hospital, Department of Pediatrics, Kayseri, Turkey

Article Information

Article Type: Letter
Article Group: Pediatric Endocrinology

Received: 11.11.2020
Accepted: 14.11.2020
Available Online: 27.12.2020

Cite this article as: *Kurtoğlu S, Armut M. Puberty Precocious Due to Chronic Lavender Oil Application. J Pediatr Acad 2020; 1: 107-108.*

Letter to the Editor

Dear Editor,

Puberty precocious is a problem caused by genetic mutations, organic brain problems, and environmental factors. In this article, we presented a case with puberty precocious thought to be caused or accelerated by the use of lavender for a long time.

An eight-year four-month-old girl presented with signs of acceleration in growth, pubic and axillary hair growth, and breast growth that started approximately 6 months ago. According to her medical history, she was intensely sprayed lavender to her hair every morning to prevent pediculus humanus capitis for the last year.

Physical examination revealed a height of 137 cm (92 p, 1.40 SDS), weight 28.8 kg (56.p, 0.15 SDS), pubic hair Tanner stage 3, axillary hair stage 2, breast Tanner stage 3 (the diameter of breast glandular are right breast 3, left breast 2 cm). Her mid parental length is 157.5 cm SDS -0.95 SDS (maternal height is 163 cm, father's height 165 cm). Her bone development was accelerated and her bone age was evaluated as compatible with 11 years of age. Predictive length is calculated as 151 cm. In pelvic ultrasonography, the uterine length was 45 mm, endometrial line shape, ovarian volumes were 2.3 ml. In hormone analysis, LH and estradiol were measured as 3.69 IU/L and 97.92 pg/ml respectively. These hormonal levels are consistent with puberty. The patient situation was evaluated as accelerated puberty and leuprolide acetate was started for stopping puberty.

The emergence of secondary sex characters in girls before 8 years of age is defined as precocious puberty.[1] While some genetic mutations, head trauma, tumors, arachnoid cysts, hydrocephalus and cranial radiation center can cause puberty, no specific cause can be found in most patients. Chemotherapy, Mc Cune Albright syndrome, and congenital adrenal hyperplasia may cause peripheral puberty precocious.[1]

Correspondence: Selim Kurtoğlu, Memorial Kayseri Hospital, Department of Pediatric Endocrinology, Kayseri, Turkey
E-mail: selimchief@gmail.com

There is an increase in premature thelarche and puberty precocious cases all over the world. In addition to primary etiology, obesity, nutrition, dietary habits, physical activity, and endocrine disruptors may cause or accelerate pubertal progression.[1,2] It has been reported that phthalates, bisphenol-A, tea tree, lavender and fennel can cause premature puberty.[2,3] Endocrine disruptors may act directly, interact with genes regulating puberty, or may affect aromatize activity, sex hormone synthesis, follicle formation, breast tissue development, and estrogen signaling.[2]

Lavender cream is a cosmetic agent used in the form of perfumes. Lavender oil has antibacterial, antifungal, hair lice prevention, smooth muscle relaxant, sedative, and anti-depressant effects, additionally it is useful in burns and insect stings.[4,5] Its hormonal effect has been determined as estrogenic and anti-androgenic.[2,4] Lavender caused prepubertal gynecomastia as it was taken with tea tree oil, which had similar effects.[4,5] Intensive use of lavender products may cause premature thelarche.[5]

In our case, daily lavender was used for 1 year. Thus, it can be argued that precocious puberty or accelerated puberty is associated with long-term use of lavender. This case is peculiar since precocious puberty due to the use of lavender oil has not been reported in the literature before. Also, we would like to emphasize that the exposure of lavender, tea tree (perfume, cream, shampoo, shower gel), and fennel should be questioned in girls who have premature thelarche, and puberty precocious.

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

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

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

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

Peer-review: Externally peer-reviewed.

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