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Research Article

Evaluation of Children with COVİD-19 in the First Month of the Outbreak in Turkey; Initial Pediatric Data from a Tertiary Hospital

Türkiye'de Salgının İlk Ayında COVİD-19'lu Çocukların Değerlendirilmesi: Üçüncü Basamak Bir Hastaneden İlk Pediatrik Veriler

Aybüke Akaslan Kara
Elif Kıymet
Elif Böncüoğlu
Şahika Şahinkaya
Ela Cem
Kamile Arıkan
Nuri Bayram
Yaşar Tamer Alp
Mehmet Burak Öztop
Tanju Çelik
İlker Devrim

ABSTRACT

Objective: *SARS-CoV-2, emerged in December 2019 in the city of Wuhan in the People's Republic of China affects children as well as all age groups. The aim of the study was to evaluate the clinical features and outcomes of pediatric cases with COVID-19 in the first month of the epidemic in Turkey.*
Method: *This single center cross-sectional study was conducted in University of Health Sciences Dr Behçet Uz Child Diseases and Pediatric Surgery Training and Research Hospital during the period of March 11 – April 20, 2020. Demographic, epidemiological and clinical data were collected from medical records. All patients were confirmed by real time reverse transcription- polymerase chain reaction. Chidren were classified as asymptomatic, mild, moderate, severe, and critically ill patients.*
Results: *In this study, we reported the clinical characteristics of a case series involving 30 chilren with COVID-19 aged from 23 days to 16 years. Twenty-nine (96.7%) patients had confirmed contact with family members for COVİD-19. The majority of patients were asymptomatic (50%) or had mild symptoms (26.7%). Fever (46.6%) and cough (33.3%) were the most common symptoms.*
Conclusion: *Our study indicated that COVID 19 in children exhibited less severe symptoms and had better outcomes*

Keywords: *COVID-19, children, Turkey*

ÖZ

Amaç: *SARS-CoV-2, Aralık 2019'da Çin'in Wuhan şehrinde ortaya çıkmıştır ve tüm yaş gruplarını olduğu gibi çocukları da etkilemektedir. Bu çalışmanın amacı, Türkiye'de salgının ilk ayında COVID-19 olan pediyatrik olguların klinik özelliklerini ve sonuçlarını değerlendirmektir.*
Yöntem: *Bu tek merkezli kesitsel çalışma, 11 Mart - 20 Nisan 2020 döneminde Sağlık Bilimleri Üniversitesi Dr. Behçet Uz Çocuk Hastalıkları ve Çocuk Cerrahisi Eğitim ve Araştırma Hastanesinde yapıldı. Hastaların tıbbi kayıtlardan demografik, epidemiyolojik ve klinik veriler toplandı. Tüm hastaların tanısı gerçek zamanlı ters transkriptaz polimeraz zincir reaksiyonu ile doğrulandı. Çocuklar kliniklerine göre asemptomatik, hafif, orta şiddetli, ağır ve kritik olarak sınıflandırıldı.*
Bulgular: *Bu çalışmada, KOVİD-19 tanısı alan 23 gün ile 16 yaş arası 30 çocuk vaka serisinin klinik özelliklerini bildirdik. Yirmi dokuz (%96,7) hastada teyit edilmiş KOVİD 19 tanısı olan erişkin aile bireyleri ile temas mevcuttu. Pediyatrik hastaların çoğunluğu asemptomatik (%50) idi veya hafif semptomlar (%26,7) vardı. Ateş (% 46,6) ve öksürük (%33,3) en sık görülen semptomlardı.*
Sonuç: *Çalışmamız, çocuklarda KOVİD 19'un daha az şiddetli semptomlar sergilediğini ve daha iyi sonuçlara sahip olduğunu gösterdi.*

Anahtar kelimeler: *KOVİD-19, çocuk, Türkiye*

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INTRODUCTION

In December 2019, acute respiratory disease , now known as coronavirus disease 2019 (COVID-19), occurred in a cluster of patients in Wuhan City of People's Republic of China [1]. As a result of rapid spread of COVID-19 worldwide, the outbreak was announced by the World Health Organization (WHO) as a pandemic on March 11, 2020 [2]. In Turkey, the first case was officially confirmed on March 11, 2020 and the total number of confirmed cases increased to 90,980 and the number of deaths due to COVID-19 reached 2,140 on April 20 [3].

COVID-19 is a severe respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Different from the adults, a large proportion of infected children appears to be asymptomatic and may be a source of transmission [4].

The symptoms of COVID-19 in children include flu-like syndrome, fever, cough, and upper respiratory signs as sore throat, stuffy nose, sneezing, and rhinorrhea [4]. Data from China suggest that children with COVID-19 had relatively milder disease and also more favorouble outcomes when compared to adults [5]. In a study from China, among 44,672 symptomatic cases, none of 416 patients aged 0-9 years exited, and only one death (0.2%) was reported among 549 patients aged 10-19 years [6]. On the other hand, severe disease may be seen especially in very young children. In fact, three deaths were reported among the pediatric cases included in the analysis from the United States between February 12-April 2, 2020 [7].

Despite the data on COVID-19 gradually iaccumulate, reports on children are still limited. In this preliminary study, epidemiological and clinical features of pediatric COVID-19 patients were evaluated in the first month of the epidemic in Turkey.

MATERIAL and METHODS

This single center cross-sectional study was conducted in University of Health Sciences Dr Behçet Uz Children's Hospital in İzmir, Turkey, during the period of March 11-April 20, 2020. This hospital is a 400-bed tertiary care center serving approximately 600,000 outpatients and 24,000 in-patients per year.

All children whose diagnosis of SARS-CoV-2 infection was confirmed by quantitative real time reverse transcription-polymerase chain reaction (RT-PCR) analysis of samples taken from upper nasopharyngeal swabs were included in the study. The clinician accountable for collecting respiratory samples was educated by the infection control committee on sampling and the use of personal protective equipment. For SARS-CoV-2 PCR, first an oropharyngeal sample was taken from the patient with fever and cough/shortness of breath, then a nasopharyngeal sample was obtained using the same swab and placed in the transport medium. The samples were sent to the laboratory in accordance with the cold chain logistics rules determined by the Turkish Ministry of Health. Real Time-PCR protocol was compiled with WHO recommendation [8]. Real-time PCR was performed at local government centers for disease control and prevention. Rapid diagnosis with kit, specific SARS-CoV-2 Nucleocapsid (N) gene fragment targeting was performed by one-step reverse transcription (RT) and real-time PCR (qPCR) (RT-qPCR). (Bio-Speedy®, Turkey 2019-nCoV qPCR Detection Kit) [9].

Demographic, epidemiological and clinical data were collected from electronic medical records of the hospital and also checked from the patients written medical files.

All patients with COVID-19 infection were classified as follows: 1) Asymptomatic group included patients with positive RT-PCR test results without any clinical symptoms and signs, and normal chest imaging findings, 2) Mild disease group included patients with symptoms of acute upper respiratory tract infection but without any imaging evidence of pneumonia, 3) Moderate disease group included patients with fever and respiratory tract symptoms with imaging evidence of pneumonia, 4) Severe disease group included patients with acute hypoxia symptoms and respiratory distress, 5) Critical disease group included patients with shock, and respiratory failure [5].

The study protocol was approved by instutional board of Dr Behçet Uz Children's Diseases and Surgery Training and Research Hospital.

RESULTS

During the study period, 30 (14.3%) of 209 children screened due to suspected COVID-19 disease had positive RT-PCR test results. Of these 30 children, 16 cases were female and 14 were male with a median age of 8.5 years (23 days-16 years). A total of 22 (73.3%) patients were hospitalized including one (1/22 case, 3.3%) patient hospitalized in the neonatal intensive care unit and one (1/22 case, 3.3%) in the pediatric intensive care unit (ICU). The patient in the pediatric ICU was a 13-year-old- girl with cerebral palsy and received lopinavir/ritonavir therapy for 14 days, She received treatment in the hospital for 56 days, including 49 days in the intensive care unit. A 23-day-old asymptomatic female patient followed up in the neonatal ICU without any treatment for COVID-19 was discharged with recovery.

Epidemiological characteristics

Among 30 confirmed cases, 29 (96.7%) had a confirmed history of contact with family members with COVID 19. Only one (3.3%) patient had an uncertain history of exposure.

Underlying diseases and comorbidities

Of 30 cases, 28 (93.3%) were previously healthy children without any comorbidity. One patient had bronchial hyperreactivity and the other one was a debilated patient with cerebral palsy hospitalized in the intensive care unit. A 7-year-old child with modarete symptoms and bronchial hyperactivity was treated with hydroxychloroquine and azithromycin in line with the COVID-19 management guide released by Republic of Türkey Ministry of Health [10], and discharged with recovery.

The most common symptoms at the onset of illness were fever (14/30 cases, 46.6%), followed by cough (10/30 cases, 33.3%), sore throat (2/30 cases, 6.6%), and rhinorrhea (2/30 cases, 6.6%). None of the patients were suffering from diarrhea, vomiting, abdominal pain, or conjunctivitis. Fifteen (50%) of 30 children were asymptomatic, 8 (26.7%) had mild, 6 (20%) had moderate symptoms, while one (3.3 %) patient was critically ill. Clinical and demographic characteristics of the cases are shown in Table 1.

Computed tomography (CT) scan of the lung was performed in 15 (50%) patients with obvious infiltrations on chest radiography, and typical patterns of lung CT compatible with COVID-19 disease that were described during pandemic [11,12] were observed in 7 (23.3%) patients. The major CT abnormalities observed were mixed bilateral multifocal ground-glass opacity as detected in all 7 patients.

Treatment

Treatment was not given to the patients who were asymptomatic or with mild symptoms. Among the 30 patients, 7 (23.3%) patients received treatment for COVID-19. Treatment with hydroxychloroquine (6.5 mg/kg/dose PO twice daily in the first day : maximum dose on the first day, 400 mg/dose, and 3.25 mg/kg/dose twice daily for the following 4 days :maximum dose, 200 mg/dose) with or without azithromycine (10 mg/kg/ dose PO once a day; maximum dose on the first day: 500 mg/dose; 2-5. days 5 mg/ kg/dose once a day: maximum dose: 250 mg/dose) were administered in 6 (20%) patients with moderate infection, and CT findings [10]. In additon, one patient in the intensive care unit received lopinavir/ritonavir treatment in combination with hydroxychloroquine [10].

Since arrhythmia was described as the major adverse effect of these drugs and none of the patients had any cardiac rhythm abnormality, all patients receiving hydroxychloroquine and azithromycin treatment were monitorized for cardiac arrhythmia before and during the administration of the drugs. Short-term gastrointestinal and dermatological side effects were not observed in patients.

Currently, all of the patients have been discharged with recovery. Up to date no death has been observed among our patients.

Table 1. Clinical and demographic characteristics of 30 patients enrolled in the study.

Demographic characteristics and underlying medical conditions	n
Number of patients	30
Age (years), median	8.5 (23 day-16 years)
Female, n (%)	16 (53.3)
Exposure to the source of transmission, n (%)	
Close-range contacts with definitely diagnosed cases	29 (96.7)
Data unavailable	1 (3.3)
Clinical course	
Asymptomatic	15 (50)
Mild	8 (26.7)
Moderate	6 (20)
Severe	0
Critical	1 (3.3)
Iniatial symptoms at admission	
Fever	14 (46.6)
Cough	10 (33.3)
Sore throat	2 (6.6)
Rhinorrhea	2 (6.6)
Headache	1 (3.3)
Anosmia	1 (3.3)

DISCUSSION

In this clinical report, the clinical characteristics and our experience concerning the management of our pediatric patients with COVID-19 disease were described. Of 30 patients, only one had a critical course, while half of the patients were asymptomatic and approximately one fourth had mild course of the disease.

COVID-19 infection is currently known as a kind of extremely severe infectious disease that was declared a pandemic. Based on available data, it is possible to emphasize that COVID-19 has been rare among children compared to adults [5]. By February 10, 2020, a total of 10,924 adult cases and 398 pediatric cases with a rate of 3.5% were confirmed in China and death was not observed among patients under 10 years of age [13]. In Italy, on March 15, 2020, a total of 22512 cases had been reported, and 1.2 % of these cases were children aged 0-18 years without any incident of death among them [14]. As for April 2020, in Korea, 2.6 % of the COVID-19 cases were 0-9 years and %3.1 of these cases 10-19 years old [15]. In Turkey, the total number of COVID-19 cases was 198.284 on 2 July 2020, and 2% of all COVID-19 cases were in the ≤15, and 13.7% of them in the 15-24 years age group [16].

The COVID-19 disease seems to be associated with a less severe course among children than adults [17]. However, it is unclear that certain pediatric populations (children with chronic illness or on immunosuppressive therapy) will also have a positive outcome [18]. In the current study most of the children (93.3%) were previously healthy, excluding one patient with bronchial hyperreactivity and one debilated patient with cerebral palsy. In a study of 345 pediatric cases with available information on underlying conditions, 80 (23%) had at least one underlying condition and, chronic lung disease (including asthma), cardiovascular disease, and immunosuppressive disorders were found the most common underlying comorbidities [7].

Children at all ages were sensitive to COVID-19, and there was no significant gender difference as was detected in this study [5]. Here, we report 30 patients with confirmed COVID-19 disease, and the

median age of the patients was 8.5 years (range 23 days- 16 years) with a female /male ratio of 1.14 (16 girls / 14 boys). Children are often diagnosed with COVID-19 after exposure to an infected adult inside or outside the family circle, however in some cases the source of the infection could not be identified. In our study most children (96.7%) had epidemiological contact history from their families, and transmission route of the infection was unknown in only 1 patient. Schools were closed on 16 March 2020, on the 5th day of the outbreak, and then the curfew was imposed on individuals under 20 years of age on 3 April 2020, on the 22nd day of the outbreak. In other words, we think that the majority of the sources of transmission to children in Turkey was mostly their parents or other family members. According to our experience, most important epidemiological linkage for COVID-19 positivity in children is the presence of a family member with COVID-19 infection.

The presenting clinical symptoms of pediatric COVID-19 are often atypical, mainly fever and cough. Some patients experience gastrointestinal symptoms, including abdominal discomfort, nausea, vomiting, abdominal pain and diarrhea [(4)]. The most frequently encountered symptoms at admission were fever and dry cough in 46.6%, and 33.3% of the patients, respectively. In this study, there were no children presenting with gastrointestinal symptoms. In adults, anosmia is reported in conjunction with reported symptoms of coronavirus but it is not among the common symptoms in children. In our experience, only a 13-year-old boy who had a history of family contact had anosmia instead of cough and fever.

According to the available data, 90% of the children with COVID-19 infection were asymptomatic, or had suffered from mild or moderate disease course [(19)]. This study also supported this finding with only one patient requiring intubation and 6 patients having moderate disease. In a study conducted in China, among 339 pediatric cases, 5.60% of the children were asymptomatic, 93.81% had mild and 0.29% had severe disease [(6)].

In the study, diagnosis of COVID19 was made with RT-PCR tests performed with throat and oral swab samples. Chest computed tomography (CT) can identify infected lesions, indicating viral pneumonia, which plays an irreplaceable role in the screening of COVID-19 disease in adults [(11)]. However, limited data are available in children regarding the typical chest CT imaging findings and when to make re-imaging. CT imaging was performed in 15 (50%) patients and CT findings were compatible with COVID 19 disease in 7 (23.3) patients. In this study, mixed bilateral multifocal ground-glass opacity were the major CT abnormalities observed

Currently regarding treatments for COVID-19 infection in children, there is no data with sufficient level of scientific evidence. Most literature relates to adult-onset COVID-19 disease, but these findings are not always applicable to children. Also, in children, possible side effects should also be considered when making a treatment decision. At the moment, treatment recommendations to date are based on only observations. In our clinic, treatment was not started for the asymptomatic child. Hydroxychloroquine with/without azithromycin treatment was received by 6 (20%) children with moderate infection and CT findings compatible with COVID 19, while one patient treated in the intensive care unit received lopinavir/ritonavir treatment. However with increasing knowledge and experience derived from studies performed in adults, we preferred to treat children with moderate infections and relevant CT findings with hydroxychloroquine alone. None of the patients treated with hydroxychloroquine with/without azithromycin had abnormalities in their electrocardiograms (ECG).

This study has several limitations. Firstly, it has a small sample size. A larger, cohort study population will be needed to characterize more fully the clinical characteristics of children with COVID-19 infection . Secondly, the diagnosis of the cases was established based on only the results of the RT-PCR tests. Indeed, CT scans in children are not diagnostic for COVID-19 disease, unlike adults. Thus, many cases with asymptomatic or mild disease might remain undiagnosed in this population.

CONCLUSION

Our preliminary clinical findings concluded that pediatric patients with COVID 19 disease mostly have mild respiratory infections than adult cases and the transmission in children might primarily occur through contact with adult patients, mainly through household exposure. Though, current information about COVID-19 disease in children is still limited, the disease in children seems to have a mild course. However the activity and disease spectrum of the COVID-19 disease should be monitored in children for possible development of COVID-19 spectrum.

Ethics Committee Approval: The study protocol was approved by instutional board of Dr Behçet Uz Children's Diseases and Surgery Training and Research Hospital and Türkey Ministry of Health, written parental informed consent was obtained for all participants.

Conflict of Interest: The authors declare that they have no competing interests.

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Research Article

Evaluation of the Cases who Applied to University Hospital Child and Adolescent Mental Health Committee Because of Sexual Abuse

Bir Üniversite Hastanesi Çocuk ve Ergen Ruh Sağlığı Adli Kuruluna Cinsel İstismar Nedeniyle Başvuran Olguların Değerlendirilmesi

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ABSTRACT

Objective: *The aim of this study was to examine the sociodemographic characteristics, psychiatric diagnoses and factors associated with psychiatric diagnoses of children and adolescents who are victims of sexual abuse.*
Method: *The files of 92 children and adolescents aged between 0-18 who were referred to University Hospital Child and Adolescent Psychiatry Forensic Policlinic between January 2017 and December 2019 due to sexual abuse were evaluated retrospectively. Psychiatric diagnoses of the cases were made according to DSM 5 diagnostic criteria. Intellectual capacity of the cases was evaluated according to the latest verison of Wechsler Intelligence Scale for Children.*
Results: *In our study, 78 (84.8%) cases were female and 14 (15.2%) were male. Mean age of the cases was 14.1±3.88 years. The most common type of sexual abuse was touching (52.2%, n=48). There was a psychiatric diagnose in 50 (54.3%) of them. The most common psychiatric diagnoses were posttraumatic stress disorder (n=29, 31.5%) and major depressive disorder (n=25, 27.2%). The rate of psychiatric diagnosis was significantly higher in cases exposed to coercion and violence (p=0.032). In 32 cases (34.8%), it was determined that the abuser was within the family.*
Conclusion: *Sexual abuse has an effect on child's development throughout life.In our study, the rate of psychiatric diagnosis was high. It is very important to provide the necessary psychiatric support to the victims of sexual abuse. With the studies to be done in this area, awareness can be increased and necessary precautions can be taken.*

Keywords: *Sexual abuse, child and adolescent, mental health*

ÖZ

Amaç: *Bu çalışmanın amacı cinsel istismar mağduru çocuk ve ergenlerin sosyodemografik özelliklerini, psikiyatrik tanılarını ve psikiyatrik tanılarla ilişkili faktörleri incelemektir*
Yöntem: *Ocak 2017-Aralık 2019 tarihleri arasında Üniversite Hastanesi Çocuk ve Ergen Psikiyatrisi Adli Polikliniğine cinsel istismar nedeniyle başvuran 0-18 yaş arası 92 çocuk ve ergenin dosyaları geriye dönük olarak değerlendirildi. Olguların psikiyatrik tanıları DSM 5 tanı ölçütlerine göre konuldu. Olguların zihinsel kapasiteleri, Wechsler Çocuklar İçin Zeka Ölçeği'nin (Wechsler Intelligence Scale for Children) son sürümüne göre değerlendirildi.*
Bulgular: *Çalışmamızda olguların 78'i (%84,8) kız, 14'ü (%15,2) erkekti. Olguların yaş ortalaması 14.1±3.88 yıl idi. En sık görülen cinsel istismar türü dokunma idi (%52,2, n=48). Bunların 50'sinde (%54,3) psikiyatrik tanı vardı. En yaygın psikiyatrik tanılar post travmatik stres bozukluğu (n=29, %31,5) ve majör depresif bozukluk (n=25, %27,2) idi. Zorlama ve şiddete maruz kalan olgularda psikiyatrik tanı oranı anlamlı olarak daha yüksekti (p=0,032). Otuz iki olguda (%34,8) istismarcının aile bireyi olduğu belirlendi.*
Sonuç: *Cinsel istismarın çocuğun gelişimi üzerinde yaşam boyu etkisi vardır. Çalışmamızda psikiyatrik tanı oranı yüksek bulunmuştur. Cinsel istismar mağdurlarına gerekli psikiyatrik desteğin sağlanması çok önemlidir. Bu alanda yapılacak çalışmalar ile farkındalık arttırılabilir ve gerekli önlemler alınabilir.*

Anahtar kelimeler: *Cinsel istismar, çocuk ve ergen, ruh sağlığı*

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INTRODUCTION

Sexual abuse of the child is a wide-ranging problem with physical, emotional, social, moral, cultural and legal dimensions. According to the World Health Organization, child sexual abuse is the involvement of a child in sexual activity that he or she does not fully comprehend, is unable to give informed consent to, or for which the child is not developmentally prepared and cannot give consent, or that violates the laws or social taboos of the society [1].

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) discusses the sexual abuse of the child under the subheading of "Problems related to abuse or neglect", and recommends using this category when sexual abuse of a child is the focus of clinical attention [2].

It is difficult to reach a precise statistical data on the frequency of sexual abuse, because sexual abuse in the society is mostly hidden and not recorded [3]. It is estimated that the average worldwide prevalence of child sexual abuse is approximately 11.8% [4,5]. In studies on child sexual abuse in our country, it was reported that this rate varied between 9.0% and 18.0% [6-8]. Studies reported that sexual abuse was 2-5 times more common in girls than boys [9-12].

Child sexual abuse is considered as an important public health problem and it has negative consequences in the short and long- term. The early reactions can be fear, anxiety, avoidance, anger, inappropriate sexual words and behaviors. Especially, anxiety disorders can occur in a short time in children who are sexually abused [13]. In addition, increased curiosity to sexuality, increased frequency of masturbation or masturbation in inappropriate environments, and sexual games can be seen. In the middle and long- term, anxiety disorder symptoms such as nightmares and fears, dissociative disorders such as amnesia and trance state, major depression, post-traumatic stress disorder and sexual behavior disorders such as excessive sexual behavior may be present [14]. It was stated that individuals with a history of sexual abuse in childhood were especially at risk for post traumatic stress disorder (PTSD) compared to those who were not been abused [15]. Moreover, it was shown that women with a history of sexual abuse were more prone to display panic episodes and depressive symptoms [16]. At the same time, it was found that anxiety disorders were observed with a higher rate in those with a sexual abuse history [17]. In addition, sexual abuse may be a determinant of early substance use [5]. It was shown that the history of abuse was a risk factor, especially in terms of smoking and cannabis use, and it was a strong determinant of early onset of alcohol use [18]. However, in studies conducted, it was stated that 20-50% of the cases exposed to sexual abuse did not have any psychiatric symptoms [19]. Although it was shown in studies that some children might not have a psychiatric symptom, it was found that child abuse and neglect might result in negative consequences in terms of the behavioral, social, cognitive and emotional development of the child [20-23].

It is important to evaluate the sexually abused child in multiple dimensions. In Child Advocacy Center (CAC) established under the Ministry of Health, there are physicians, specially trained forensic interviewers, family interviewers, representatives of the Provincial General Directorate of the Ministry of Family and Social Policies, nurses and secretaries [24]. The public prosecutor starts the forensic evaluation at CACs and law inforcement officers and lawyers manage the process [25]. Although there are studies on sexual abuse in our country, studies in this field maintain their importance in terms of investigating the factors affecting the mental health of children and adolescents subjected to sexual abuse and taking precautions.

The aim of this study was to investigate the sociodemographic characteristics, psychiatric diagnoses and factors associated with psychiatric diagnoses of children and adolescents who were referred to the child and adolescent psychiatry outpatient clinic between January 2017-December 2019 for forensic evaluation because of being sexually abused.

MATERIAL and METHOD

Ege University School of Medicine Child and Adolescent Psychiatry Forensic Committee is a multidisciplinary committee consisting of three Forensic medicine specialists, one Child and Adolescent Psychiatry specialist, and one neurologist. Psychiatric examinations of the cases, who are directed by the judicial authorities, are performed by the Child and Adolescent Psychiatry Specialist, psychiatric diagnoses are made according to DSM 5 diagnostic criteria, and their sociodemographic and clinical features are recorded in their files. After application of psychometric and projective tests by psychologists, the evaluation scales are filled, if it is necessary a family interview and school interview with the social worker is planned. After these evaluations, the case is seen in the forensic research committee on the date of appointment.

In this study, the files of 92 children and adolescents aged between 0-18 who referred to Child and Adolescent Psychiatry Forensic Policlinic between January 2017 and December 2019 for forensic evaluation due to sexual abuse were evaluated retrospectively. Ethics committee approval for this study was obtained from the Medical Research Ethics Committee of our university (Decision No: 20-7T/90, Date: 08.07.2020).

Age, gender, education level, parental information, socioeconomic level of the family, characteristics of sexual abuse and sexual abuser, whether they had a psychiatric diagnosis and the result of the report were evaluated. The socioeconomic level of the family was classified according to the income level based on the minimum wage amount of that day in our country.

The intellectual capacity of all the cases were evaluated with the Wechsler Intelligence Scale for Children-New Version (Wechsler Intelligence Scale for Children-R-WISC-R), which is a widely used intelligence test in our country, and the final diagnosis was made clinically. In addition, the results of the Beck Depression Scale in their files given during the evaluation were also recorded.

Diagnostic Tools

1. Wechsler Intelligence Scale for Children-R (WISC-R)

The Wechsler Intelligence Scale for Children (WISC), developed by David Wechsler in 1949, is an individually administered intelligence test for children between the ages of 6 and 16. In his study in 1974, he made some changes and carried out the standardization study on a sample of 2200 people between the ages of 6-16 [26]. Standardization of the scale on Turkish children was done by Savaşır and Şahin [27]. WISC-R consists of two parts; Verbal and Performance. While Verbal Intellectual Section has the subtests such as Information, Similarities, Arithmetic, Vocabulary, Comprehension and Digit Span; Performance Intellectual Section includes subtests such as Picture Completion, Picture Arrangement, Block Design, Object Assembly and Coding Image Editing, Pattern With Cubes, Merge Parts, Password and Labyrinth subtests. Total Intellectual Section score is obtained from the sum of Verbal Intellectual Section and Performance Intellectual Section points [26].

2. Beck Depression Inventory (BDI)

It is a self-assessment scale with 21 items that measures somatic, emotional, cognitive, and impulsive symptoms seen in depression. The items are evaluated on a scale ranging from 0 to 3 according to the severity of depression. It has a score range of 0-63. The cut-off point is 17 and those who score above this score are considered at risk for clinical depression. The aim of the scale is not to diagnose depression, but to count the degree of symptoms objectively [28]. The scale has two forms. The first of these is the original form developed by Beck in 1961 [29]. The second version was also developed by Beck in 1978 [30]. According to Hisli et al. [31], and separate studies by Hatzenbuehler, Bryson, Golin, Byerly and Glambra on university students, the reliability coefficients of the scale were between .60 and .87, and in the separate studies by Meites, Hatzenbuehler, Glambra, Burkhart, Byerly, the validity coefficients of the scale ranged between .65 and .68. Studies

conducted in our country have reported high values regarding the validity and reliability of the scale [31,32]. The split-half and test-retest reliability coefficients of the 61 forms of the scale were reported as .78 and .65 for university students. The same form's split-half reliability coefficient was found to be .61 for depressive patients. In Hisli's study on university students, the split-half reliability coefficient of the scale was calculated as .74 [31].

Statistical Analysis

The statistical evaluation of the data obtained was made by using SPSS Windows 22.0 package program. Age, gender, education level, parental information, socioeconomic level of the family, characteristics of sexual abuse and sexual abuser, whether they had a psychiatric diagnosis, the result of the report were evaluated by using methods of descriptive statistical analysis, and frequency analysis. Cross tables were created for categorical data and Pearson chi-square analysis was performed. The data are summarized as numbers and percentages. A p value below 0.05 was considered statistically significant for all analyzes.

RESULTS

In our study, 78 (84.8%) cases were female and 14 (15.2%) were male. Mean age of the cases was 14.1±3.88 years. When the educational status of the cases was evaluated, it was found that the patients were receiving preschool education (n=2; 2.2%), and special education (n=2; 2.2%), while 37 (40.2%) of them were primary school students, 39 (42.3%) were high school students, and 2 (2.2%) patients were high school graduates. Still 9 (9.8%) patients dropped out of school, and 1 (1.1%) case was illiterate. Besides, the patients were coming from families with low (n=55; 59.8%), medium (n=32; 34.8%), and high (n= 5:5.4%) socioeconomic status. Sociodemographic characteristics of the cases are summarized in Table 1.

The rate of smoking was 16.4% among the cases with available data in the study group (n=67). Three patients (3/65) were alcohol users. Based on accessible data 6 (9.1%) of 66 patients were substance users.

Sexual abuse was in the form of touching in 89 (96.7%) of 92 cases, while in 40 of them (43.5%) sexual abuse involving penetration was revealed. The most common type of sexual abuse was touching without penetration (n=48; 52.2%), followed by vaginal penetration (n=24; 26.1%). Sexual abuse was commited with anal penetration in 13 (14.1%), oral penetration in 3 (3.3%), exhibitionism in 2 (2.2%), by dragging into prostitution in 1 (1.1%) and video shooting in 1 (1.1%) case.

It was determined that coercion and physical violence were used in 63 (68.5%) cases. While 48 (52.2%) cases were exposed to sexual abuse once,

Table 1. Sociodemographic characteristics of sexual abuse victims.

Sociodemographic characteristics (n, %)					
Gender (n=92)			Family Status (n=92)		
Female	78	84.8	Together	50	54.3
Male	14	15.2	Not Together	42	45.7
Educational Status (n=92)			Who he/she lives with (n=92)		
Illiterate	1	1.1	With mother and father	49	53.3
Dropped out of school	9	9.8	With mother	30	32.6
Special education	2	2.2	With father	3	3.3
Pre-school education	2	2.2	With parent and step parent	3	3.3
Elementary School	37	40.2	With relatives	4	4.3
High School	39	42.3	In the institution	2	2.1
High School Graduate	2	2.2	With spouse	1	1.1
Socioeconomic Staus (n=92)					
Low	55	59.8			
Middle	32	34.8			
High	5	5.4			

Table 2. Characteristics of sexual abuse.

Characteristics of sexual abuse (n, %)					
Contact for sexual purpose (n=92)			Number of the sexual abuser (n=92)		
Yes	89	96.7	One	75	81.5
No	3	3.3	More than one	17	18.5
Penetration (n=92)			Gender of the sexual abuser (n=92)		
Yes	40	43.5	Female	1	1.1
No	52	56.5	Male	91	98.9
Use of force and physical violence (n=92)			Sexual abuse within the family (n=92)		
Yes	63	68.5	Yes	32	34.8
No	29	31.5	No	60	65.2
Number of the sexual abuse (n=92)			Another victim or other victims (n=92)		
Once	48	52.2	Yes	10	10.9
More than once	44	47.8	No	82	89.1

Table 3. Psychiatric diagnoses of the cases.

Psychiatric diagnoses	n	%*
Post Traumatic Stress Disorder	29	31.5
Major Depressive Disorder	25	27.2
Attention Deficit and Hyperactivity Disorder	6	6.5
Enuresis Nocturna	6	6.5
Bipolar Disorder	4	4.3
Substance Use Disorder	3	3.3
Anxiety Disorder	2	2.2

**Numbers and percentages were calculated separately for each diagnosis.*

and 44 (47.8%) cases more than once.

It was observed that there was one abuser in 75 (81.5%), and more than one abuser in 17 (18.5%) cases. It was determined that the abuser was male in 91 (98.9%) cases, and female in only 1 case. In 32 (34.8%) cases, the abuser was within the family, and in 60 (65.2%) cases the abuser was not. There were another victim or other victims in 10 (10.9%) cases. Table 2 shows the characteristics of the sexual abuse.

Table 4. Comparison of the cases with and without a psychiatric diagnosis in terms of the characteristics of sexual abuse.

		With a psychiatric diagnosis		Without a psychiatric diagnosis		
Characteristics of sexual abuse		**n**	**%**	**n**	**%**	**P**
Contact for sexual purpose	Yes	48	53.9	41	46.1	0.663
	No	2	66.7	1	33.3	
Penetration	Yes	25	62.5	15	37.5	0.169
	No	25	48.1	17	51.9	
Number of the sexual abuse	Once	25	52.1	23	47.9	0.649
	More than once	25	56.8	19	43.2	
Number of the sexual abuser	One	39	52.0	36	48.0	0.342
	More than one	11	64.7	6	35.3	
Sexual abuse within the family	Yes	17	53.1	15	46.9	0.863
	No	33	55.0	27	45.0	
Use of force and physical vio-lence	Yes	39	61.9	24	38.1	0.032
	No	11	37.9	18	62.1	
Another victim or other victims	Yes	5	50.0	5	50.0	0.770
	No	45	54.9	37	45.1	

A psychiatric diagnosis was found in 50 (54.3%) participants. The most common psychiatric diagnoses were posttraumatic stress disorder (n=29; 31.5%) and major depressive disorder (n=25; 27.2%). Psychiatric diagnoses are summarized in Table 3. Intellectual disability was found in 16 (17.4%), and borderline intellectual functionality in 7 (7.6%) victims of abuse. Since the diagnoses related to

Table 5. The results of forensic reports of the cases.

The results of forensic reports of the cases	n	%
His/her statements can be relied on	30	32.6
His/her mental health is impaired	14	15.2
His/her statements can be relied on, but he/she does not perceive the legal meaning and consequences of the act	10	10.9
He/she does not perceive the legal meaning and consequences of the act	9	9.8
His/her mental health is not impaired	6	6.5
Post-observation evaluation is appropriate	6	6.5
His/her statements can be relied on and his/her mental health is impaired	4	4.3
His/her statements can not be relied on	3	3.3
He/she perceives the legal meaning and consequences of the act	3	3.3
He/she did not come to committee	3	3.3
His/her statements can be relied on and he/she perceives the legal meaning and consequences of the act	2	2.1
His/her statements can be relied on and his/her mental health is not impaired	1	1.1
His/her statements can not be relied on and he/she does not perceive the legal meaning and consequences of the act	1	1.1
Total	92	100.0

intellectual capacity existed before sexual abuse, they were excluded from the scope of psychiatric diagnosis.

When the sexual abuse characteristics of 92 cases with and without psychiatric diagnosis were compared, the presence of a psychiatric diagnosis was found to be significantly higher in cases exposed to coercion and violence (p=0.032) (Table 4). The mean BDI score was 24.86±13.28. There was no significant difference in terms of BDI scores between the group with psychiatric diagnosis and those without (p=0.069).

Various issues were inquired by the judicial authorities. They investigated whether the victims perceived the legal meaning and consequences of the act (n=11; 12.0%), whether they could rely on the statements of the victims (n=31; 33.7%) and whether victims had mental health impairment (n=22; 23.9%). The other issues inquired by the judicial authorities were about the reliability of the child's statement, possible impairment of mental health due sexual abuse. In one case, they wanted to know whether the victim could defend himself/herself against the sexual assault. Table 5 shows the results of forensic reports of the cases.

DISCUSSION

In our study, a psychiatric diagnosis was detected in 54.3% of the cases. The most common psychiatric diagnoses were posttraumatic stress disorder and major depressive disorder. The presence of a psychiatric diagnosis was found to be significantly higher in cases exposed to coercion and violence.

Mean age of the cases included in our study was 14.1±3.88 years which was comparable to other studies conducted in Turkey [33-36]. In the literature, there were many studies showing that sexual abuse was seen with a higher rate in girls compared to boys [33,34,36-38]. In our study, 84.8% of 92 cases evaluated were female and 15.2% of them were male. The significantly greater number of female patients among sexual abuse victims was also confirmed in previous studies on this topic. It was stated that sexual abuse of boys occured, and reported less frequently than girls [39]. This situation was associated with the fact that sexually abused boys saw seeking help in this regard as an inappropriate behaviour for manhood and might be more reluctant to describe their experiences due to their thoughts of being considered homosexual [39]. Although sexual abuse cases are mostly seen in cases with a low socioeconomic level, it should not be overlooked that they are seen in all economic classes. In studies conducted in Turkey, it was reported that a significant portion of the children who were victims of sexual abuse were the children of families with low socioeconomic status [40,41]. It was observed that 59.8% (n=55) of 92 cases included in our study came from families with a low socioeconomic level. Low socioeconomic level may be an important risk factor in terms of sexual abuse as well as physical abuse

and neglect; it was stated that this risk might be related to the problems in parental functions such as crowded family structure, decreased time allocated to the child, insufficient parental supervision, control and guidance [9,42,43].

Studies have showed that almost all of the abusers were male [33,44]. In a study, it was found that the abuser was a familiar person in 64.4% (n=58) and a family member in 21.1% (n=19) (45) of the cases. In 34.8% (n=32) of the cases in our study, the abuser was within the family. It was thought that the reason for the higher rate of sexual abuse within the family in our study might be the result of the characterictics of forensic cases applied to our committee.

In one study it was found that sexual abuse was committed mostly by touching and handling (46.8%) [38]. In a study in which 157 children and adolescents who were sexually abused were evaluated, it was reported that 56.1% of the sexual abuse was committed by touching-caressing-rubbing followed by vaginal penetration [44]. In our study, the most common form of sexual abuse was touching with 52.2% (n=48), followed by vaginal penetration with 26.1% (n=24).

When the literature was reviewed, it was observed that repetitive attempts at sexual abuse frequently occurred [46]. In a study where 183 children and adolescents as victims of sexual abuse were evaluated, it was stated that 42.1% of the cases were abused more than once [47].

In our study, it was found that 47.8% (n=44) of the cases were exposed to sexual abuse more than once.

It has been demonstrated that a history of sexual abuse could induce development of many psychiatric disorders in childhood and later on [48]. It was known that psychopathologic disorders were more frequently encountered in children who experienced more severe sexual trauma [14]. It was stated that psychopathology of adolescents is more frequently impaired due to their higher knowledge of sexual issues than younger children [49]. In a study conducted with approximately 43 thousand cases in the USA, it was found that suicide attempts were higher in individuals who were victims of abuse [50]. In the literature, it was stated that the family's supportive attitudes towards the child who is the victim of abuse decrease the prevalence of depression among them [51]. In our study, a psychiatric disorder was diagnosed in 50 (54.3%) of them and the most common psychiatric diagnosis was posttraumatic stress disorder (n=29; % 31.5), followed by major depressive disorder (n=25; % 27.2). When the sexual abuse characteristics of 92 cases with and without psychiatric diagnosis were compared, the presence of a psychiatric diagnosis was found to be significantly more frequent in cases exposed to coercion and violence. In the study of Öztürk et al., similar to our study, it was found that the rate of psychiatric diagnosis was higher in cases subjected to physical violence [52]. Children with intellectual disability are at higher risk for sexual abuse [46,53].

In studies performed in Turkey higher rates of intellectual disability was detected in sexually abused cases, [54,55]. When the psychiatric diagnoses of 92 cases in our study were examined, it was observed that 17.4% (n=16) of the cases had intellectual disability and 7.6% (n=7) of them had borderline intellectual functioning.

It was observed that the judicial authorities inquired most frequently namely in 58 (63.0%) cases, whether statements of the victims could be relied on. Deficiencies in mental capacity and deprivation of social support can prevent children from expressing themselves fully and cause an opinion that there is contradiction in expressions. In addition, children can change their expressions during the judicial process due to the fact that they can be easily influenced and exposed to pressure by adults for various economic and socio-cultural reasons. This situation may cause this problem to be brought to the agenda frequently, especially in judicial processes regarding children.

The second most frequently asked question (n=34; 37.0%) by the judicial authorities was whether mental health of the victim was impaired. This concept, which was included in our criminal code between 2005 and 2014, was considered as an aggravating factor in punishment. This concept, which caused great controversy between lawyers

and physicians, associations and non-governmental organizations after entering in the Turkish Criminal Code, was removed from the criminal code in 2014. Although the applications between 2017-2019 were analyzed in our study, the concept of mental health impairment was still an issue to be evaluated in previous cases. The concept of "mental health impairment", which is required to be evaluated, is legally different from the presence of a psychiatric diagnosis. In short, it is defined as a sustained psychologically traumatic condition which fully meets the diagnostic criteria of a psychiatric disease, and impairs functionality of the victim, but does not improve despite regular and adequate psychiatric follow-up and treatment, [56]. Considering these criteria, it was observed that mental health was impaired in 18, and was not in 7 cases. In 6 cases, evaluation after observation was found to be appropriate. It was seen that 3 of the 34 cases did not come to the committee. The decision that there was no impairment in mental health in 7 cases did not eliminate the existence of crime of sexual abuse and did not mean that the child was not affected by this incident. It meant that it did not exert a permanent mental adverse effect on the victim that resulted in impairment of functionality and increase in legal punishment of the abuser.

Judicial authorities also inquired whether the abused child perceived the legal meaning and consequences of the act (n=25; 27.2%), whether the victim could defend himself/herself (n=1; 1.1%) and whether he/she had mental illness (n=1; 1.1%). Although the punishment of sexual crimes committed against children is heavier than adults in our criminal law, these questions reveal the existence of aggravating factors in crimes committed against more risky groups among abused children.

CONCLUSION

It is very important to provide the necessary psychiatric support to the victims of sexual abuse. With the work to be done in this field, awareness can be increased and necessary precautions can be taken.

When conducting forensic-medical evaluations in cases of sexual abuse, it is important to evaluate the issues asked objectively after examining court files, and the results of the necessary psychiatric examinations, tests and family interviews. In addition, from a legal perspective, the purposes of the forensic reports written should be known and action should be taken in accordance with the legal legislation.

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Research Article

Does Mannose-Binding Lectin Gene Polymorphism in Pediatric Patients Undergoing Peritoneal Dialysis Cause Susceptibility to the Development of Peritonitis?

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Periton Diyalizi Yapılan Çocuk Hastalarda Mannoz Bağlayan Lektin Gen Polimorfizmi, Peritonit Gelişimine Yatkınlık Oluşturur mu?

ABSTRACT

Objective: *This study aims to investigate the relationship between peritonitis attacks and mannose-binding lectin (MBL) gene polymorphism in patients undergoing peritoneal dialysis.*
Method: *Codon 54 polymorphism found in exon 1 of the MBL gene was investigated by polymerase chain reaction-restriction fragment length polymorphism method in 45 patients with chronic renal failure undergoing peritoneal dialysis.*
Results: *The frequency of the mutant B allele was not significantly higher in the patient group (4.4%) than the control group (2.1%). The AB genotype was found at a rate of 15.6% and 34% in the patient group and healthy control group, respectively. The AA genotype was found in 80% of children who underwent peritoneal dialysis and 63.8% of the healthy control group.*
Conclusion: *In our study, no relationship was found between peritonitis attacks and MBL gene polymorphism in patients undergoing peritoneal dialysis.*

Keywords: *Peritoneal dialysis, peritonitis, mannose-binding lectin, PCR*

ÖZ

Amaç: *Bu çalışmada, periton diyalizi yapılan hastalarda peritonit ataklarının mannoz bağlayan lektin (MBL) gen polimorfizimi ile arasındaki ilişki incelenmiştir.*
Yöntem: *MBL geni ekson 1'inde bulunan Codon 54 polimorfizmi, periton diyalizi yapılan 45 KBY hastasında ve 45 sağlıklı kontrol grubunda polimeraz zincir reaksiyonu kısıtlama fragman uzunluğu polimorfizm yöntemi ile araştırıldı.*
Bulgular: *Mutant B allel sıklığı hasta grubunda (%4.4) kontrol grubuna (%2.1) göre anlamlı derecede yüksek değildi. AB genotipi, hasta grubunda ve sağlıklı kontrol grubunda sırasıyla %15,6 ve % 34 olarak bulundu. Periton diyalizi yapılan çocukların% 80'inde ve sağlıklı kontrol grubunun %63.8'ünde AA genotipi bulundu.*
Sonuç: *Çalışmamızda periton diyalizi yapılan hastalarda peritonit atakları ile mannoz bağlayan lektin (MBL) gen polimorfizmi arasındaki ilişki bulunamamıştır.*

Anahtar kelimeler: *Periton diyalizi, peritonit, mannoz bağlayan lektin, PCR*

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INTRODUCTION

Peritoneal dialysis is one of the renal replacement treatments used in patients with chronic renal failure (CRF). In patients undergoing peritonitis CRF is a common complication of peritoneal dialysis, which is caused by microorganisms that reach hematogenously or by other means into the peritoneal cavity through the catheter lumen. It is important to detect and treat a predisposition to peritonitis, as inability to use or remove the catheter inserted into the peritoneal cavity may lead to conversion to hemodialysis, temporary loss of ultrafiltration, permanent membrane damage, and morbidity and

mortality [1]. In children undergoing peritoneal dialysis, the factors that predispose them to the development of peritonitis are very important in terms of the prognosis of the patients. In the literature, mannose-binding lectin (MBL) gene polymorphism is emphasized among the variables that predispose patients undergoing peritoneal dialysis to the development of peritonitis [2].

MBL is a calcium-bound C-type lectin that acts as the primary defense mechanism against infections. A wide variety of bacteria, fungi, viruses, and parasitic organisms have connections to MBL.3 MBL plays an important role in host defense, and in cases of deficiency, and it creates a predisposition to infections caused by *Neisseria meningitidis, Haemophilus influenzae,* human immunodeficiency virus (HIV), influenza A, herpes simplex virus, *Candida albicans, Saccharomyces cerevisiae,* and *Aspergillus fumigatus*. The frequency of the MBL variant allele was also evaluated in pediatric patients with infections and suspected immunodeficiency [4.5]. MBL gene polymorphism and MBL deficiency conditions are common and predispose to various infectious diseases. Strong relationships with serious bacterial infections have been demonstrated in patients with neutropenia or meningococcal meningitis [6]. In a study of premature infants, a relationship was found between the MBL2 gene polymorphism and gram-negative late-onset sepsis [7].

There is very little research on the relationship between MBL gene polymorphism and predisposition to the development of peritonitis in pediatric patients undergoing peritoneal dialysis. The few relevant studies present in the literature have stated that mannose-binding lectin (MBL2) and ficolin-2 (FCN2) gene polymorphisms may predispose to peritonitis in patients undergoing peritoneal dialysis [2]. It was also suggested that MBL gene polymorphism may be the primary factor for the development of peritonitis in peritoneal dialysis patients [2]. In this study, our aim was to investigate the relationship between MBL codon 54 polymorphism (Gly/Asp or A/B) (rs1800450) and the development of peritonitis in patients undergoing peritoneal dialysis as suggested by several authors in the literature.

MATERIALS and METHODS

Diagnosis

This study was conducted in Izmir, Turkey, in the Dialysis Units of Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital. A total of 45 patients with CRF undergoing peritoneal dialysis (22 females, 23 males) and 45 healthy controls were enrolled in the study. The diagnosis of peritonitis was based on the presence of diagnostic criteria proposed by the International Society for Peritoneal Dialysis (ISPD) as follows: 1) peritonitis-related clinical features, abdominal pain, and/or turbid dialysate fluid; 2) more than 100 WBC/µL in dialysate fluid or more than 50% polymorphonuclear cells; 3) detection of active microorganisms in dialysate fluid or culture. Patients were diagnosed with peritonitis when at least two of these criteria were present. Age, gender, number of peritonitis episodes, clinical findings, underlying primary disease, peritoneal dialysis method, and MBL mutations were studied in patients included in the study.

Molecular Analysis

In the DNA obtained from the peripheral blood of the patient and control groups, the codon 54 polymorphism of exon 1 of the MBL2 gene was investigated by the restriction fragment length polymorphism (RFLP) method (separation of DNA into fragments of different sizes using restriction enzymes). The first exon of the MBL gene was amplified by PCR (349 bp). Primer sequences were 5'-TAGGACAGAGGGCATGCTC-3' (F) and inverse 5'-CAGGCAGTTTCCTCTGGAAGG-3' (R). The PCR product was obtained at 94°C for 30 seconds after denaturation at 94 °C for 10 minutes, 57°C for 30 seconds, and 72 cycles of 72°C for 45 seconds with final holding at 7°C for 7 minutes. The PCR product thus obtained was kept at 50°C for 60 minutes with 5 IU of BanI restriction enzyme. The normal allele (allele A) of BanI was cut into two parts of 260 bp and 89 bp, while the variant allele (allele B) remained uncut. The products obtained were visualized by electrophoresis on 2% agarose gel.

Statistical Analysis

Statistical analysis was performed using SPSS 15.0 software (SPSS Inc., Chicago, IL, USA). MBL genotype frequencies were compared by chi-square test, where $p < 0.05$ was considered significant. ANOVA testing was used for comparison of numerical parameters between variables with multiple groups, and the Kruskal-Wallis test was used for those variables that did not have multiple groups. Linear and binary logistic regression analyses were used to investigate the frequency and the causative factors of peritonitis.

RESULTS

A total of 45 patients including 23 (51.1%) boys and 22 (48.9%) girls, who underwent peritoneal dialysis with the diagnosis of CRF were included in this study. The mean ages at the time of diagnosis were 11.19±5.56, and 10.50±4.13 years in those who had, and had not peritonitis, respectively. Sixty percent (n=27) of the patients had a history of peritonitis. At least one episode of peritonitis was experienced by 9, and at most 7 episodes by 2 patients. Etiologic factors of CRF were vesicoureteral reflux in 11 (24.4%), nephrotic syndrome in 8 (17.8%), dysplasia/hypoplasia in 7 (15.6%), neurogenic bladder in 6 (13.3%), posterior urethral valve in 5 (11.1%) and Alport syndrome in 2 (4.4%) patients, while no etiological factor was found in 6 (13.3%) patients. Sixty-nine peritoneal fluid cultures obtained from patients with peritonitis revealed the presence of *E. coli* in 7 (10.1%), *Enterobacter* in 3 (4.3 %), *Pseudomonas* in 3 (4.3%), and *S. aureus* in 2 (2.9 %) patients, while in 54 (78.3%) patients bacterial reproduction was not detected in culture (Table 1).

Table 1. Demographic characteristics of patients undergoing peritoneal dialysis with the diagnosis of CRF.

Parameters	CRF cases
Gender (girls/boys)	22/23
Age of onset (years)	
Peritonitis	11.19±5.56(min-max: 1-20)
No peritonitis	10.50±4.13 (mix-max: 0-16)
Fever	11 (24.4%)
Abdominal pain	20 (44.4%)
Nausea-vomiting	12 (26.7%)
Turbid liquid	26 (57.8%)
Origin score	
0	40 (88.9%)
1	5 (11.1%)
Primary disease	
Alport syndrome	2 (4.4%)
Dysplasia/hypoplasia	7 (15.6%)
Nephrotic syndrome	8 (17.8%)
Neurogenic bladder	6 (13.3%)
Posterior urethral valve	5 (11.1%)
Vesicoureteral reflux	11 (24.4%)
Other	6 (13.3%)
Albumin	3.511±0.6624 (min-max: 1.5-5.7)
Dialysis method	
APD	4 (8.9%)
CAPD	33 (73.3%)
CCPD	5 (11.1%)
NIPD	3 (6.7%)

**APD: Automated peritoneal dialysis, CAPD: continuous ambulatory peritoneal dialysis, CCPD: continuous cycling peritoneal dialysis, NIPD: nocturnal intermittent peritoneal dialysis.*

While AA (normal allele), AB (homozygous allele), and BB (variant allele) MBL codon 54 polymorphism were determined in exon 1 at rates of 80%, 15.6%, and 4.4% in children undergoing peritoneal dialysis due to CRF, the corresponding rates were 62.8%, 33%, and 2.1% in the control group. Thus, in terms of codon 54 polymorphism in exon 1, no statistically significant difference was found between the patient and the control groups (p=0.113) (Table 2).

When the association between peritonitis infection and MBL gene mutation was investigated, history of peritonitis was revealed in 19 (70.4%) patients with AA, 7 (25.9%) with AB, and 1 (3.7%) with BB polymorphisms. However any statistically significant relationship was not detected between history of peritonitis and the presence of a MBL mutation (p = 0.630) (Table 3).

Table 2. Distribution of MBL gene polymorphism in patients on dialysis due to CRF and children in the control group.

MBL gene polymorphism	CRF (n=45)	Control (n=45)	p value
AA	80% (36)	62.8% (29)	0.113
AB	15.6% (7)	33% (15)	
BB	4.4% (2)	2.1% (1)	

**APD: Automated peritoneal dialysis, CAPD: continuous ambulatory peritoneal dialysis, CCPD: continuous cycling peritoneal dialysis, NIPD: nocturnal intermittent peritoneal dialysis.*

Table 3. Relationship between peritonitis and MBL mutation.

MBL gene polymorphism	Peritonitis	No peritonitis	p value
AA (n=36)	70.4%(19)	94.4%(17)	0.630
AB (n=7)	25.9%(7)	0	
BB (n=2)	3.7%(1)	5.6%(1)	

**APD: Automated peritoneal dialysis, CAPD: continuous ambulatory peritoneal dialysis, CCPD: continuous cycling peritoneal dialysis, NIPD: nocturnal intermittent peritoneal dialysis.*

DISCUSSION

The MBL defect was first described in cases of primary opsonization disorder in 1989. Ip.W.K et al. revealed the presence of strong association between MBL deficiency , low MBL levels and three missense mutations in codons 52, 54, and 57 of exon 1 in the human MBL gene. These mutations cause disruption in MBL multimerization, decrease ligand binding, and inhibit activation of the complement. Polymorphism was detected in the promoter region of MBL, referred to as H/L, X/Y, and P/Q at positions -550, -221, and +4, respectively. HYP causes medium and high amounts of MBL production, while LXP causes low amounts of MBL production. Five percent of people have MBL deficiency and are homozygous or heterozygous for this three-point mutation. MBL deficiency is not a classic primary immunodeficiency. There are several other mutations with significantly lower clinical penetration [9]. It has been reported in the literature that the third pathway of the complement system, the lectin cascade is initiated by MBL, and MBL gene polymorphism may predispose to infections and autoimmunity [10].

Studies have reported that MBL deficiency increases the tendency to infections, especially when comparing different alleles observed in cases of lower and upper respiratory tract infections. For example, high MBL levels have been reported to be important in preventing sepsis and septic shock. Low levels of MBL have been associated with the development of pneumonia and bacteremia in chemotherapy patients with suppressed cellular immunity, and they were also found to extend the duration of neutropenic fever. It has been reported that MBL plays an important role in the host defense against *N. meningitidis, H. influenzae, HIV, influenza A,* herpes simplex virus, *C. albicans, S. cerevisiae,* and *A. fumigatus,* and its deficiency has been described in infections caused by these agents [11,12]. In a study on the relationship between neonatal gram-negative sepsis and MBL, MBL levels were found to be low in patients who died with septic shock compared to patients with severe sepsis, whereas there was no relationship with MBL levels in terms of early- or late-onset sepsis [13]. In a 9-year observational study conducted by Adrian et al., when dialysis and kidney grafts were compared, no relationship was found between the groups in terms of infection, cardiovascular disease, or development of mortality [14]. When the effects of serum MBL concentrations and MBL codon 54 mutation as risk factors in patients with peritonitis were examined, serum MBL levels of peritoneal dialysis patients with mutation were found to be lower compared to hemodialysis patients with the same gene mutation. It has been suggested that the lower MBL level may be the primary factor for the development of peritonitis in peritoneal dialysis patients [15]. For this reason, we found it appropriate to investigate this subject since we thought that MBL gene polymorphism may cause a predisposition to the development of peritonitis infection in patients undergoing peritoneal dialysis.

In our study, codon 54 (allele B) polymorphism in the first exon of the MBL gene, its distribution, and its effects on clinical laboratory findings, the frequency of peritonitis, and other related factors were evaluated. AA (normal allele), AB, and BB (variant allele) gene frequencies were 80%, 15.6%, and 4.4%, respectively in the group undergoing peritoneal dialysis due to CRF. No significant difference was found in terms of gene polymorphism in patients undergoing peritoneal dialysis when compared with the control group ($p>0.05$). The infectious origin at the onset of the disease was evaluated considering that there may be a predisposition to MBL-defect-related infection in those with MBL gene polymorphisms; however, there was no statistically significant difference in terms of peritonitis between the AB (heterozygous)

and BB (homozygous) groups with polymorphism and the AA (normal allele) group without polymorphism ($p > 0.05$). In patients who underwent peritoneal dialysis, no significant difference was found in terms of susceptibility to peritonitis and MBL gene polymorphism.

Similar to our study, in the study conducted by Erken et al., no significant difference was found between MBL levels between those who had and had not peritonitis among cases with chronic peritoneal dialysis. Though any statistically significant intergroup difference was not reported, greater number of episodes of peritonitis were found in patients with MBL deficiency, when compared with those without [17]. Lam et al., divided their study patients who developed end-stage renal failure into four groups as follows: Group 1: patients who had two or more episodes of peritonitis; Group 2: patients without history of peritonitis; Group 3: patients who underwent hemodialysis, and Group 4: patients who underwent hemodialysis due to the faulty application technique used for peritoneal dialysis. Only 28 of 120 patients who underwent peritoneal dialysis had codon 54 gene mutations, of which only 2 patients had homozygous mutations while the other patients had heterozygous mutations. Although the rate of codon 54 mutations seen in patients undergoing dialysis was similar to the rate among healthy individuals, the MBL level was found to be lower in dialysis patients. Low levels of serum MBL of dialysis patients were found to be independent of MBL gene mutation and dialysis treatment method. Serum MBL levels of peritoneal dialysis patients with codon 54 point mutations were found to be lower compared to those of hemodialysis patients with the same gene mutation. There was no significant difference in terms of MBL codon 54 gene mutation in patients who experienced recurrent episodes of peritonitis, who underwent peritoneal dialysis, and who had not experienced attacks of peritonitis. There was also no difference between the four studied groups in terms of serum MBL levels or codon 54 point mutation [9].

In our study, fluid turbidity, nausea-vomiting, fever, abdominal pain, low albumin levels, peritoneal dialysis method, primary disease, and MBL gene polymorphism were not found to be significant determinants in the patient group ($p > 0.05$). It was observed that MBL gene polymorphism had no effect on the development of peritonitis, and the presence of polymorphism did not lead to the presence of more severe laboratory and clinical findings. In our study, the BB allele mutation was positive in two dialysis patients, while it was positive in one control group patient.

As suggested by several authors the absence of a significant correlation between peritonitis and serum MBL levels does not exclude the importance of MBL in defense immunity in peritoneal dialysis. Host defense and dialysis linkages are important determinants for peritoneal dialysis-associated peritonitis. The role played by other cytokines, complements, and toll-like receptors in such cases of peritonitis requires further investigation. Since the number of patients has increased and the rate of mutation increases as the level of MBL decreases, it would be valuable to perform new studies since the elaboration of polymorphism can give more accurate results during the period of peritonitis.

CONCLUSION

Our study has shown that, based on the results of PCR, MBL codon 54 polymorphism mutation was not associated with the risk of experiencing peritonitis in patients undergoing peritoneal dialysis with the diagnosis of CRF. However, studies with larger patient groups may elucidate the role of MBL mutation in the etiology of peritonitis in patients undergoing peritoneal dialysis.

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Research Article

Examination of Nephrotoxicity in Survivors of Childhood Cancer and Comparison of Methods for Estimating Glomerular Filtration Rate

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Çocukluk Çağı Kanser Yaşayanlarında Nefrotoksisitenin İncelenmesi ve Glomerüler Filtrasyon Hızı Yöntemlerinin Karşılaştırılması

ABSTRACT

Objective: *Increased survival rates in childhood cancers have led the researchers to focus on long-term side effects and possible risk factors for late nephrotoxicity related to the treatment regimens applied. Our aim is to evaluate drug-induced nephrotoxicity in survivors of childhood cancer and to investigate the compatibility of creatinine clearance with the estimated glomerular filtration rate.*
Methods: *The presence of glomerular and tubular dysfunction has been screened among 59 childhood cancer survivors who had completed their treatment regimens with cisplatin, carboplatin, ifosfamide, and /or high dose methotrexate.*
Results: *The mean age of patients was 10.7±5.5 years (2.5-23), and mean follow-up time was 2.6±2.1 years (0.5-8). Renal dysfunction was detected in 65% of the patients. The most prevalent manifestation of renal dysfunction was decreased glomerular filtration rate (n:19, 32.2%), and increased urinary β2-microglobulin excretion (n:12, 20.4%), followed by microalbuminuria (n:6, 10.1%). Survivors treated with combined chemotherapy regimens (cisplatin, carboplatin, ifosfamide) had significantly lower tubular reabsorption of phosphate than those treated with high dose of methotrexate. The glomerular filtration rate analysis was performed using different methods, and a moderate correlation (r=0.563, p=0.00) was found between estimated glomerular filtration rates calculated according to cystatin-C-based equations and Schwartz formula.*
Conclusion: *Childhood cancer survivors demonstrated a high frequency of renal complications in the current study. We have shown that the calculation of the estimated glomerular filtration rate using the Schwartz formula or cystatin-C-based equations is compatible with the creatinine clearance in this specific patient group. In survivors of childhood cancer who cannot perform 24-hour urine collection, determination of estimated glomerular filtration rate is a more practical approach.*

Keywords: *Childhood cancer survivor, glomerular filtration rate, renal function, nephrotoxicity*

ÖZ

Amaç: *Çocukluk çağı kanserlerinde artan sağkalım oranları, uzun süreli tedaviye bağlı yan etkilere ve geç nefrotoksisite için olası risk faktörlerine odaklanmaya yol açmıştır. Amacımız kanser tedavisi alıp iyileşen çocuklarda nefrotoksisiteyi belirlemek ve glomerül filtrasyon hızının hesaplanmasında tahmini glomeruler filtrasyon hızı ile kreatinin klirensinin birbiri ile uyumunu araştırmaktır.*
Yöntem: *Sisplatin, karboplatin, ifosfamid ve/veya yüksek doz metotreksat ile kanser tedavileri tamamlanmış 59 çocuğun glomerüler ve tübüler disfonksiyonları değerlendirildi.*
Bulgular: *Ortalama tanı yaşı 10,7±5,5 yıl (2,5-23), ortalama takip süresi 2,6±2,1 yıl (0,5-8) olan 59 hastanın %65'inde böbrek fonksiyon bozukluğu tespit edildi. Böbrek fonksiyon bozukluğunun en yaygın bulgusu azalmış glomeruler filtrasyon hızı (n:19, %32,2), artmış üriner β2-mikroglobulin atılımı (n:12, %20,4), ardından mikroalbuminuri (n:6, %10,1) idi. Kombine kemoterapi ile tedavi edilenlerde, yüksek doz metotreksat ile tedavi edilenlere göre istatistiksel anlamlı düşük tubüler fosfor reabsorbsiyonu saptandı. Serum sistatin-C ve Schwarz formülü ile hesaplanan tahmini glomeruler filtrasyon hızının birbiri ile tutarlı olduğu (r=0,563, p=0,00) bulundu.*
Sonuç: *Çocukluk çağında kanser tedavisi alıp iyileşenlerde yüksek oranda böbrek komplikasyonlarının geliştiği gösterilmiştir. Çocukluk çağı kanser yaşayanlarında, Schwartz formülü veya sistatin-C ile tahmini glomerüler filtrasyon hızının hesaplanmasının kreatinin klirensiyle uyumlu olduğunu gösterdik. 24 saatlik idrar toplayamayan çocuklarda tahmini glomeruler filtrasyon hızı hesaplaması pratik bir yaklaşımdır.*

Anahtar kelimeler: *Çocukluk çağı kanser, glomeruler filtrasyon hızı, renal fonksiyon, nefrotoksisite*

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INTRODUCTION

The five-year survival rates for childhood cancer have approached to nearly 70-80% due to advances in chemotherapy and supportive care [1,2]. Increased survival rates in childhood cancers have led researchers to focus increasingly on long-term treatment-related side effects. It has been shown that long-term survivors of childhood cancer have a higher risk of morbidity and one-third of the survivors report serious or life-threatening complications 30 years after diagnosis of their primary cancer [3,4]. Intensive chemotherapy may affect endocrine, cardiac, respiratory, nervous, and renal systems [5]. The recent version of Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers recommends screening asymptomatic survivors for the detection of therapy-related late complications and earlier implementation of health-preserving interventions [6-8].

Since many chemotherapeutic and supportive care drugs are cleared by the kidneys, kidneys are particularly exposed to potential toxic injury. Nephrotoxic drugs such as ifosfamide, methotrexate, cisplatin, carboplatin and antibiotics, radiocontrast agents, abdominal irradiation, nephrectomy, and volume depletion may contribute to the development of renal failure. Data on nephrotoxicity in childhood cancer are rare and relatively small studies are available, in part because of the difficulties in obtaining reliable markers of glomerular and tubular function [8-12].

Glomerular filtration rate has commonly been calculated based on 24-hour creatinine clearance (ClCr) rates which also serve to monitor kidney function. Using creatinine clearance rates to estimate GFR has several limitations, especially in children with chronic medical conditions who are at high risk of kidney dysfunction. The clinical practice guidelines recommend calculating estimated glomerular filtration rate (eGFR) in children with the Schwarz formula, which is based on serum creatinine (Cr) concentration and the height of the child [13-16]. For GFR estimation, creatinine and cystatin-C (CysC)-based equations have been also established [17-19]. Low-molecular-weight proteins (LMWPs), such as cystatin C, β2-microglobulin (β-2M) and microalbumin (Malb) are new markers to monitor subclinical kidney damage [20].

Our aim in this cross-sectional study was to examine renal glomerular and tubular function in a cohort of childhood cancer survivors (CCSs), particularly with solid tumors and lymphomas who had completed their chemotherapy regimens and to determine the incidence and possible risk factors for late-term nephrotoxicity. In addition, we compared the usefulness of calculating estimated GFR (eGFR) based on serum CysC (Cys-eGFR) concentrations, and Schwartz (S-eGFR) formula relative to creatinin clearance in pediatric cancer survivors.

MATERIAL and METHODS

This cross-sectional study has been performed among CCSs who were in remission and had received nephrotoxic chemotherapy for at least 6 months prior to this chart review, between the years 2004, and 2016. Patients who had received nephrotoxic chemotherapies such as high dose (>1 g/m^2/day) methotrexate (HD-MTX) cisplatin (CIS), carboplatin (CARBO), and/or ifosfamide (IFO), and those with primary renal tumors were excluded from the study. The ethics committee of the hospital approved the study protocol.

The information about the gender, age, age at diagnosis of the patients, cancer type and stage, duration of disease, chronic renal diseases, nephrotoxic chemotherapeutic agents used, febrile neutropenia episodes, follow-up time, hypertension, and abdominal radiotherapy was exctracted from the medical files of the patients. Detailed information about physical examination findings, weight, height, pathological findings, and blood pressures was recorded. Blood pressure measurements were carried out for more than two times using sphygmomanometers with appropriate cuff size after the patient rested for 5 minutes. Patients were considered hypertensive if the blood pressure measurements were above the 95th percentile for their sex, age and height according to "The Fourth

report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents [21]".

The presence of nephrotoxicity was determined by evaluating serum creatinine concentrations, urine dipstick test results, 24-hour urinary creatinine clearance rates, tubular reabsorption of phosphate (TRP), urinary excretion of low molecular weight urinary proteins (β-2M and Malb), and presence of hypertension.

Estimated GFR was calculated using the Schwartz formula (S-eGFR), and CysC-based equation for estimated glomerular filtration rate (C-eGFR). The precision, and accuracy of the eGFR's were compared with creatinine clearance. Nephrotoxicity was detected in the presence of any of the following findings; hypertension, reduced GFR, and TRP, elevated proteinuria, urinary excretion of β-2M and Malb in the absence of other causes.

The Schwartz equation was used to estimate GFR as follows: GFR= S-eGFR (mL/min/1.73 m^2) =0.413 x height (cm)/PCr (mg/dL) (15). Serum concentration of CysC was measured, and eGFR was estimated according to the Filler and Lepage formula as follows:

Serum Cys-C: C-eGFR (mL/min/1.73 m^2)=logGFR= 1.962+ [1.123log(1/CysC)] [17].

Creatinine clearance (ClCr) was calculated using the standard formula: CrCl = (UCr/PCr) x (U Volume/1440) x (1.73/m^2). (U Cr-urine creatinine, P Cr-serum creatinine, UVolume-urine volume are measured from 24-hour urine collection samples; plasma and urine creatinine values are expressed in mg/dL and body surface area in m^2. The constants 1.73 and 1.440 indicate the standardized adult body surface area and the number of minutes in a day, respectively. GFR <90 ml/min per 1.73m^2 is considered abnormal according to the Kidney Disease Outcomes Quality Initiative guidelines [13].

Fractional tubular reabsorption of phosphate was calculated using the formula: %TRP = 100 x (1-(UPO4. PCr)/(UCr.PPO4)) (UPO4-urine phosphate, and PPO4-serum phosphate). Concentrations of serum and urine parameters were measured on an automatic analyzer (Modular PP) using manufacturer's reagents (Roche Diagnostics, GmbH, Mannheim, Germany). Urine β-2M and Malb were analyzed by the nephelometric method using a BN-ProSpec® device, and serum cystatin (Cys-C) levels were measured by the nephelometric method with SPA Plus analyzer. The presence of proteinuria was defined as urinary protein excretion higher than 4 mg/m^2 per hour. The following cut-off values were adopted for

Cys-C (0.56-0.99 mg/L), and Malb-uria (20-200 mcg/min). Urinary β-2M was defined as "abnormal" in case of an absolute loss of ≥0.20 mg/L or a relative loss of ≥0.04 mg/mmol.creatinine.

Statistics

Statistical analyses were performed using IBM SPSS Statistics V22.0. P value of ≤0.05 was considered as statistically significant. Mean, standard deviation, median, minimum, maximum value frequency, and percentage were used for descriptive statistics. Following verification of biochemical data by Shapiro-Wilk test, Student's t-test was used for normally, and Mann Whitney U-test was used for abnormally distributed data. Chi-Square test and Fisher's exact test were used for the comparison of qualitative data. Comparison of different methods for estimating GFR were determined by Spearman's correlation coefficient or linear regression analyses.

RESULTS

The study group comprised 59 childhood cancer survivors including 40 male (68%) and 19 female (32%) patients. The mean age of the patients was 10.73±5.51 years (range 2.5-23) and the mean follow-up time after cessation of therapy was 2.67±2.19 years (range 0.5-8). Non-Hodgkin lymphomas and brain tumors were the most prevalent group of childhood cancers treated amongst the group. Patient characteristics, and details of chemotherapy are summarized in Table 1. No patient had proteinuria or decreased GFR before chemotherapy at the time of diagnosis. Four patients had recovered from acute kidney injury (AKI) with treatment. Two cases had tumor lysis syndrome at diagnosis, and received dialysis therapy. The other two patients had cisplatin

related AKI, and was treated with prompt hydration and supportive care. The final GFR values of these four patients were 113, 70, 73, and 60 ml/min 1,73 m^2. None had hypertension at follow-up.

Table 1. Demographic and treatment characteristics of childhood cancer survivors.

Demographic and Clinical Characteristics	Mean±SD (range)
Gender	40M/19F
Age (years)	10.73±5.51 (2.5-23)
Age at diagnosis (years)	7.09±4.81 (0.25-16)
Follow-up time (years)	2.67±2.19 (0.5-8)
Weight (kg)	35.6±17.4 (13.0-91.2)
Height (cm)	135.3±25.1 (90.5-183.0)
Diagnosis	**(n=59)**
NHL	15
Brain tumor	13
NBL	10
Germ cell tumor	8
RMS	4
Hodgkin	3
HBL	2
Others	2
Chemotherapy	**Cumulative mean (g/m^2) (range)**
HD-MTX (n=15)	15.48±7.54 (3.0-27.0)
Cisplatin (n=36)	0.51±0.29 (0.1-1.64)
Carboplatin (n=18)	1.69±0.85 (0.45-2.97)
Ifosfamid (n=20)	27.29±18.45 (0.25-54.0)
Clinical Characteristics	**(n)**
AKI	4
HT	2
FN	28
Abd RT	8

NHL: non-Hodgkin Lymphoma, NBL: neuroblastoma, RMS: rhabdomyosarcoma, HBL: hepatoblastoma, ATLS: acute tumor lysis syndrome, AKI: acute kidney injury, HT: hypertension, FN: febrile neutropenia, Abd RT: abdominal radiotherapy, HD-MTX: high dose methotrexate.

Renal dysfunction was detected in 38 out of 59 survivors (64.4%). The most prevalent manifestation of renal dysfunction was decreased GFR estimated with Schwarz equation (n:19, 32.2%), followed by increased urinary β2M excretion (n:12, 20.4%). The other complications in decreasing order of frequency were elevated urine Malb (n:6, 10.1%), decreased TRP (n:5, 8.5%) and hypertension (n:2, 3.4%). None of the survivors had end-stage renal disease (Table 2). Three survivors had chronic kidney disease, including one patient with eGFR of 38 ml/min per 1.73 m^2, metabolic acidosis, and hypophosphatemia, where the other two survivors were asymptomatic. According to the urine dipstick test, two patients had glucosuria.

Table 2. Renal function parameters.

Renal Function Tests (n:59)	Median (range)
eGFR-S (ml/min.1.73 m^2)	103.7 (38.1-266.9)
30-59 (ml/min.1.73 m^2) n:3	54.9 (38.1-57.2)
60-89 (ml/min.1.73 m^2) n:16	84.2 (60.4-89.9)
>90 (ml/min.1.73 m^2) n:40	107.2 (90.61-266.9)
S Cr (mg/dL)	0.55 (0.14-1.24)
TRP (%)	91.24 (42.77-98.98)
Proteinuria (mg/m^2/h)	0.41 (0.14-3.2)
U β-2M (mg/L)	0.21 (0.08-5.47)
U microalbumin (mcg/min)	4.4 (0.72-117.6)

eGFR-S: estimated glomerular filtration rate according to Schwartz formula, S Cr: serum creatinine, TRP: tubular reabsorption of phosphate, U β-2M: urinary beta-2 microglobulin.

The cases were evaluated in two groups as those who received high dose MTX (3 g/m^2) and combined chemotherapy. The high dose MTX group was composed of NHL survivors (15 patients), while the combined chemotherapy group consisted of 44 patients with heterogeneous cancers. While various renal complications were observed in 40% of MTX users (n=6/15), this rate was 72.7% in the non-MTX group (n=32/44) (p:0.05). Survivors treated with combined chemotherapy had lower TRP and higher proteinuria than those treated with HD-MTX.

Cancer survivors were also evaluated for nephrological complications with respect to febrile neutropenia (FN) (n:28, 47.5%) episodes and to abdominal radiotherapy (n=8, 13.5%). Glomerular filtration rate was significantly lower in survivors who had episodes of FN during their treatment (n=28, 47.5%) when compared to those who had not (mean eGFR: 109.5±39.3 ml/min per 1.73 m^2 and 155±84.2 ml/min per 1.73 m^2 respectively, p=0.01). Sixteen out of 28 survivors with FN episodes had used aminoglycosides as antibiotic treatment. All of the survivors treated with local or whole abdominal irradiation were in the group of combined chemotherapy. Urinary Malb and β-2M excretion rates were higher in patients that received abdominal irradiation than those didn't. (mean values for urinary Malb: 35.1±32.6 mcg/min vs 6.1±5.8 mcg/min, p=0.00: mean values for urinary β-2M: 1.11±1.04 mg/L vs 0.56±0.36 mg/L, p=0.02).

The median S-eGFR and C-eGFR values were

Table 3. Demographic, treatment and laboratory characteristics of chemotherapy groups.

Age at Diagnosis	HD-Methotrexate (n:15) Mean±sd	Combined Chemotherapy (n:44) Mean±sd	p
Age (years)	10.67±4.70	10.75±5.80	0.86
Chemotherapy (mg/m^2)	**Mean±sd**	**Mean±sd**	
HD-MTX	15.483±7.540	-	
Cisplatin	-	521.94±292.92	
Carboplatin	-	1.770±818	
Ifosfamide	7.500±1.322	30.785±1.782	0.00
	Patients (n)	**Patients (n)**	
FN	10	18	0.08
AbdRT	-	8	0.02
HT	-	2	
Glucosuria	-	2	
Laboratory results	Mean±sd	Mean±sd	
eGFR-S (mg/min1,73 m^2)	117.2±22.4	104.9±40.1	0.15
S Cr (mg/dL)	0.50±0.15	0.60±0.25	0.09
TRP (%)	92.75±2.85	88.32±9.14	0.01
Proteinuria (mg/m^2/h)	0.36±0.10	0.46±0.41	0.28
U β-2M (mg/L)	0.21±0.01	0.24±0.13	0.56
U microalbumine (mcg/min)	4.54±2.7	4.35±2.95	0.64

AbdRT: abdominal radiotherapy, eGFR-S: estimated glomerular filtration rate according to Schwartz formula, FN: febrile neutropenia, S Cr: serum creatinine, TRP: tubular reabsorption of phosphate, U β-2M: urinary beta-2 microglobulin.

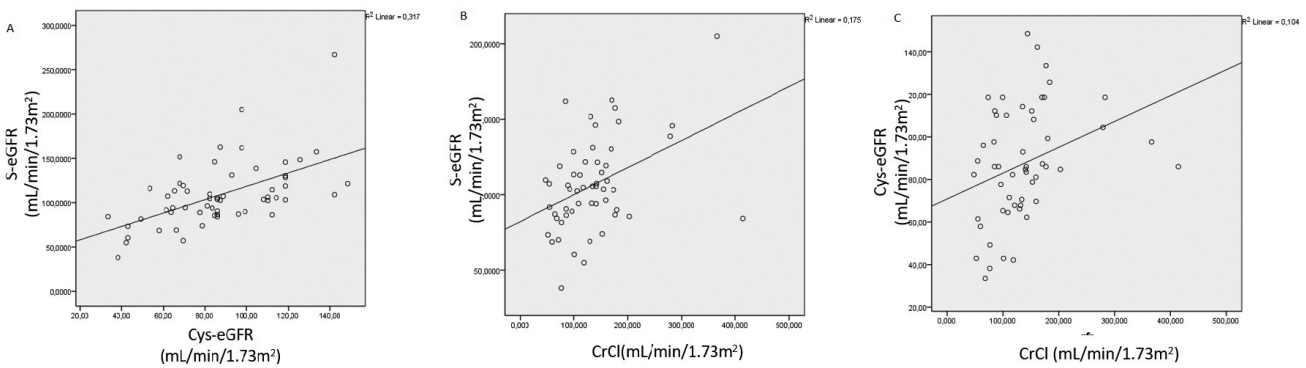

Figure 1. Comparison of creatinine clearance and estimated GFR's revealed positive linear regression lines. A: Correlations between GFR calculated by Cystatin C and estimated GFR with Schwarz formula (r=0.563, p=0.00) B: Correlations between creatinine clearance and GFR calculated with Schwarz formula (r = +0.418, p = 0.02). C: Correlations between creatinine clearance and GFR calculated with cystatin C (r=0.323, p=0.01).

107.20 mL/min/1.73 m^2, and 86,02 mL/min/1.73 m^2, respectively. Median CrCl was 130,64 mL/min/1.73 m^2. When the analysis was made according to the eGFR calculation method used, it was observed that there were moderate correlations between C-eGFR vs S-eGFR (r=0.563, p=0.00); CrCl vs S-eGFR (r=0.418, p=0.02), and CrCl vs C-eGFR (r=+0.323, p=0.01). Comparisons between e GFR calculation methods are shown in Figure 1.

DISCUSSION

In this study, renal glomerular and tubular function were investigated in a cohort of childhood cancer survivors who had completed treatment with nephrotoxic chemotherapy. Our results have shown that 65% of CCSs had at least one marker of renal dysfunction. In the literature, the prevalence of renal complications ranges from 0% to 84% [7-11]. These varying results may be due to different types of malignancies, treatments received, follow-up times,

various surveillance tests offered, and definitions of toxicity in studies performed.

In the current study, the most prevalent manifestation of renal dysfunction was decreased GFR, followed by increased β-2M excretion. In our study, the survivors treated with platinum and ifosfamide-based combined chemotherapy had significantly lower TRP than survivors treated with HD-MTX. It was observed that treatment protocols used in hematologic malignancies had reduced nephrotoxic potential and in these regimens lower cumulative doses of nephrotoxic chemotherapies had been used. In addition, our study showed that, the GFR values in HD-MTX group were preserved, which is compatible with many studies. It has been reported that MTX may cause acute reversible damage but it less frequently leads to renal dysfunction in the long run [5,22-24]. It has been reported that combined chemotherapy for ALL is not associated with severe or long-term impairment of renal function [5]. In contrast, Grönross et al. [25] showed that HD-MTX treatment significantly decreases GFR and may cause albuminuria in pediatric cancer patients several years after treatment. Wiedeman et al. [26] reassessed the current incidence of HD-MTX-induced renal dysfunction in patients with osteosarcoma, a patient population that is usually treated with HD-MTX, and estimated an incidence rate of 1.8% for patients with renal dysfunction following treatment with HD-MTX. Stefanowicz et al. [20] reported that solid tumor groups in CCSs had the lowest GFR and higher low-molecular-weight protein excretion compared with patients with leukemias and/or lymphomas.

We found lower GFRs in 32% of all survivors. Reduced GFR was more prevalent in survivors who had FN episodes during their treatment. Nephrotoxic antibiotics, including aminoglycosides, vancomycin or amphotericin given during FN episodes could lead to nephrotoxicity. However, there was no significant difference in the GFR results between patients treated with potentially more nephrotoxic chemotherapy drugs, such as cisplatin, ifosfamide, and/or HD-MTX. There are studies demonstrating that cisplatin, ifosfamide chemotherapy, and nephrotoxic antibiotics which were used during FN episodes were associated with lower estimated GFR [22,27-28].

All of the survivors treated with both abdominal irradiation and combined chemotherapy had significantly impaired renal function demonstrated by elevated urinary Malb and β-2M excretion. Combined chemotherapy and radiotherapy may have contributed to overt renal toxicity. Dekkers et al. [22] reported in a large CCS series with median follow-up time of 18 years that IFO was associated with increased urinary β-2M excretion. Stefanowicz et al. [20] reported also higher low-molecular-weight protein excretion in solid tumor survivors who were treated with radiotherapy. Other studies have also shown that children receiving higher doses of radiation have a higher risk of renal insufficiency [22,29]. In addition, there is a meta-analysis reporting an increased risk of nephrotoxicity after concomitant treatment with aminoglycosides and vancomycin in CCS receiving radiotherapy, but studies yielded conflicting results [27].

In our study, microalbuminuria was detected in 10.1% of the cases. Other studies have showed similar results; Oberlin et al. [30] detected proteinuria in 24-hour urine samples of 11.3 % of survivors. Kninjenburg et al. [29] reported the presence of albuminuria in 14.5% of survivors treated with chemotherapy. This complication has been reported to be clinically important in this young population. We found that hypertension was present in only 3.4% of CCSs, which is relatively low compared with previously reported findings of 15% and 28% among CCS [29,31]. This discrepancy could be explained by the fact that our survivors were younger children and follow-up time was shorter in the current study.

In our clinical practice, the most frequently available, and easily performed test of renal glomerular function is the estimated GFR calculated with Schwarz formula. Twenty-four-hour urine collection is a challenging procedure in children, therefore CrCl rest may not be reliable. Creatinine is affected by glomerular filtration and by tubular secretion, thus CrCl- based GFR can be overestimated by 10-40% than inulin clearance [32,33]. In the present

study, CrCl measurements were higher than S-eGFR, and equations for eGFR demonstrated various differences between S-eGFR and C-eGFR. Some meta-analyses have reported that CysC is superior to creatinine as a marker of renal function [34,35]. Cystatin C is eliminated mainly by glomerular filtration, correlates with GFR, and it is very sensitive even in mildly impaired kidney function so some studies have suggested it as an ideal GFR marker in pediatric oncology [36]. The validation of the Schwartz formula and the calculations based on serum CysC was done in several studies by comparing them to nuclear scanning methods, which suggest that they are closely correlated to GFR [37-39]. In our study, we found the strongest correlation between the CysC -GFR and the Schwartz- GFR calculations, and comparison of CrCl and eGFRs revealed positive linear regression lines, which may be used as alternatives to creatinine-based estimations in CCS.

The major limitation of the study is the low number of heterogeneous patient groups, and its retrospective design. Therefore definitive conclusions could not be drawn regarding the prevalence of renal dysfunction or its risk factors. Future large prospective cohort studies with adequate control groups are needed to clarify the applicability of estimated equations to children and CCSs for late renal toxicity.

In the current study, childhood cancer survivors (CCSs) demonstrated higher rates of renal complications. The significant impairment in glomerular filtration rate and overt renal tubular protein excretion in childhood cancer survivors treated with combined chemotherapies other than HD-MTX, FN episodes, and abdominal radiotherapy were significant parameters for late nephrotoxicity and subclinical renal dysfunction. Early detection of subclinical damage and early intervention may prevent long-term problems that may progress to chronic kidney disease. In addition, according to our results, we can recommend calculation of eGFR using Schwartz formula or Cys-C-based equations, wherever applicable in CCSs who are not able to collect urine 24 hours a day.

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Research Article

Acute Pancreatitis vs. Acute Recurrent Pancreatitis: Investigation of Clinical and Etiological Factors

Akut Pankreatit ve Akut Tekrarlayan Pankreatit: Klinik ve Etyolojik Faktörlerin Araştırılması

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ABSTRACT

Objective: *It was aimed to evaluate the etiology, clinical, laboratory and imaging findings and treatment methods of patients who have admitted with acute pancreatitis (AP) and progressed to chronic pancreatitis (CP) with ARP (acute recurrent pancreatitis).*
Methods: *The data of children under the age of 18 years who were admitted to our hospital between January 2013-July 2020 and were diagnosed with acute, acute recurrent or chronic pancreatitis according to INSPPIRE diagnostic criteria were evaluated retrospectively.*
Results: *There were 77 patients who were followed-up with the diagnosis of acute pancreatitis. Pancreatitis attack did not recur in 53/77 patients and no underlying cause was found in 35.84% (19/53) of the patients. The most common factor in those whose cause could be determined was gallstones (15.1%) (8/53). The pancreatitis attack recurred in 24 (31%) of the patients. Congenital anomalies (9/24) and hereditary pancreatitis (5/24) were the most common causes of pancreatitis in these patients and these factors were a risk factor for the recurrence of pancreatitis attack. There was no difference between the groups in terms of complications (p=0.423); however, chronicity was more common in the group with ARP (p=0.003).*
Conclusion: *Beside the pancreatitis is a rare disease in childhood, with the increase of awareness and increased accessibility to diagnostic imaging methods, more and more pancreatitis is diagnosed day by day. Idiopathic acute pancreatitis cases still constitute the largest group. If other causes are excluded in these cases, it is important to investigate congenital anomalies, genetic and metabolic etiologies.*

Keywords: *Acute pancreatitis, acute recurrent pancreatitis, etiology, children*

ÖZ

Amaç: *Çalışmamızda akut pankreatit (AP) ile başvuran ve tekrarlayan pakreatit ile kronik pankreatit (KP) ilerleyen hastaların etiyolojilerinin, klinik, laboratuvar ve görüntüleme bulgularının ve tedavi yöntemlerinin değerlendirilmesi amaçlanmıştır.*
Yöntem: *Ocak 2013-Temmuz 2020 yılları arasında başvuran, 18 yaşından küçük olan, INSPPIRE tanı kriterlerine göre akut, akut tekrarlayan ve kronik pankreatit tanısı alan çocukların verileri geriye dönük olarak taranmıştır*
Bulgular: *Akut pankreatit tanısı ile izlenen 77 hasta mevcuttur. Akut pankreatit nedeniyle başvuran ve pankreatit atağı tekrarlamayan hastaların %35,84'ünde (19/53) altta yatan bir neden saptanmamıştır. Nedeni saptanabilenlerde en sık etken safra taşlarıdır (%15,1) (8/53). Hastaların 24'ünde (%31) pankreatit atağı tekrarlamıştır. Bu hastalarda konjenital anomaliler (9/24) ve kalıtsal hastalıklar (5/24) pankreatitin en sık nedenidir ve bu etkenler pankreatit atağının tekrarlaması açısından bir risk faktörüdür. Komplikasyon açısından gruplar arasında fark yoktur (p=0,423), ancak akut tekrarlayan grupta kronikleşme daha fazladır (p=0,003).*
Sonuç: *Çocukluk çağında nadir görülen pankreatitlerin sıklığı; farkındalığın ve ileri görüntüleme yöntemlerinin artması ile her geçen gün artmaktadır. En büyük hasta grubunu hala idiyopatik akut pankreatit olguları oluşturmaktadır. Bu olgularda genetik ve metabolik nedenlerin araştırılması önemlidir. Tekrarlayan pankreatitler kronik pankreatit gelişimi açısından yakından takip edilmelidir.*

Anahtar kelimeler: *Akut pankreatit, akut rekürren pankreatit, etyoloji, çocuklar*

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INTRODUCTION

In children, incidence of acute pancreatitis (AP) has reached up to 13/100,000 in the last twenty years, which approaches the incidence reported in adults. The increase in incidence rates may represent a true increase or enhanced awareness in childhood pancreatitis [1]. Episodes of acute pancreatitis do not recur in most children. Single-center studies have shown that 15-35% of children with AP develop acute recurrent pancreatitis (ARP), and the annual incidence of chronic pancreatitis (CP) is 0.5/100,000 [2]. The factors that predispose to emergence of recurrent episodes of AP and progression from ARP to CP are unknown. While the majority of episodes of pancreatitis in adults are associated with gallstones or alcohol, etiologic factors in children are much more diverse [3]. A multicenter cross-sectional study performed by the International Study Group of Pediatric Pancreatitis (INSPPIRE) has indicated genetic variations as risk factors among patients with ARP and CP, showing that smoking and alcohol abuse is rare in this population [4].

In our study, we evaluated the etiology, clinical, laboratory, and imaging findings and treatment methods of patients who were admitted with acute pancreatitis (AP) which progressed to chronic pancreatitis (CP) with ARP.

MATERIAL and METHOD

A retrospective study was conducted in a pediatric gastroenterology, hepatology and nutrition department at a tertiary-care hospital. The children under the age of 18 years with accessible archive records and presented with the diagnosis of pancreatitis according to INSPPIRE diagnostic criteria, between January 2013 and July 2020 were included in the study. The study protocol has been approved by our hospital ethics committee on human research with the decision number E-20/12-60.

Acute pancreatitis was defined based on the presence of typical abdominal pain, serum amylase and/or lipase levels ≥ 3 times higher than normal, and 2 findings suggestive of acute pancreatitis as revealed by radiological imaging techniques. Acute recurrent pancreatitis was defined based on the presence of 2 or more attacks in which all symptoms resolve completely between attacks. Chronic pancreatitis was defined according to characteristic imaging findings associated with typical abdominal pain or exocrine or endocrine pancreatic insufficiency [5]. The demographic characteristics, clinical and laboratory findings, imaging methods and causes of the pancreatitis of the patients were retrospectively retrieved from electronic records.

Statistical analysis

The data obtained were evaluated using "SPSS version 20.0 program". Descriptive statistics were stated as number, percentage (%), ratio, median, mean, standard deviation. For numerical variables with normal distribution between two groups Student's T-test, for variables that do not conform to the normal distribution Mann-Whitney U-test and for categorical variables chi-square test were used, respectively. Statistical significance was accepted as $p<0.05$.

RESULTS

A total of 77 patients including 44 (44%) male, and 43 (56%) female patients followed up with a diagnosis of acute pancreatitis were included in the study. The mean age of the patients at the first AP attack was 11.12±4.78 (min. 2 months-max. 18 years) years. The most common complaints of the patients were abdominal pain (88%), nausea, and vomiting (32.5%). The median duration of these complaints was 3 (min. 1-max. 30) days. An underlying cause was not found in 29.9% (23/77) of the patients. The most common etiological factors were congenital anomalies (19.5%), gallstones (11.7%), infections (9.1%), trauma (7.8%), and hereditary pancreatitis (7.8%).

Attacks of pancreatitis recurred in 24 (31%) of the patients. The median time to the recurrence of the attack was 137.5 (minimum 13, maximum 840) days. Nine (37.5%) male,and 15 (67.5%) female patients had recurrent attacks of acute pancreatitis. Gender was not a risk factor for the recurrence of pancreatitis attack (p=0.467).

The etiological factor could not be found in 35.84% (19/53) of the patients who were admitted with acute pancreatitis without recurrent bouts, and in (15.1%) (8/53) of these cases, gallstones was determined to be the most common etiology (Table 1). In 6 patients in this group, due to the severe course of the disease and the development of complications, genetic studies were performed including sequencing of CFTR (cystic fibrosis transmembrane conduction modifier), PRSS1 (cationic trypsinogen), and SPINK1 (serine protease inhibitor Kazal type 1).

Congenital anomalies (9/24) and hereditary pancreatitis (5/24) were the most common causes of pancreatitis in patients with recurrent pancreatitis attacks (Table 2). Genetic studies were performed in 11 patients and concomitant hereditary pancreatitis was diagnosed in 4 patients with congenital anomalies.

Table 1. Causes of acute pancreatitis.

Etiology	(n:53) (%)
Idiopathic	19 (35.84)
Congenital anomalies Choledochal cyst (n:3) Pancreaticobiliary junction anomaly, choledochal cyst (n:2) Stenosis in the choledoch (n:1)	6 (11.3)
Hereditary pancreatitis *CFTR* mutation	1 (1.9)
Gallstones	8 (15.1)
Infections EBV infection + Kawasaki disease (n:1) Hepatitis A (n:1) Mumps (n:1) Mycoplasma (n:4)	7 (13.2)
Trauma Direct trauma (n:5) Duodenal hematoma developing after upper GIS endoscopy (n:1)	6 (11.3)
Metabolic causes ApoC2 deficiency	1 (1.9)
Medicines L-asparginase (n:1) Bismuth subcitrate (n:1)	2 (3.8)
Endocrine causes Type 1 DM + dyslipidemia	1 (1.9)
Other Sclerosing cholangitis+autoimmune pancreatitis (n:1) Acute lymphoblastic leukemia (n:1)	2 (3.8)

Table 2. Causes of acute recurrent pancreatitis.

Etiology	(n:24) (%)
Idiopathic	4 (16.6)
Congenital anomalies Pankreas divisum (n:2) Pankreas divisum+CTFR mutation (n:2) Pankreas divisum+SPINK1 mutation (n:1) Annular pankreas +atypical gallbladder (n:1) Pancreaticobiliary junction anomaly, choledochal cyst n: (2) Pancreaticobiliary junction anomaly, choledochal cyst +CTFR mutation (n:1)	9 (37.5)
Hereditary pancreatitis CFTR mutation(n:1) PRSS 1 mutation (n:2) SPINK1 mutation (n:2)	5 (20.8)
Gall stones	1 (4.2)
Metabolic factors Type 1 hyperlipidemia (n:1) Type 4 hyperlipidemia +gallstone (n:1) Izovaleric acidemia (n:1)	3 (12.5)
Endocrine causes Hypercalcemia (CASR gene mutation)	1 (4.2)
Other factors Torsion of the wandering spleen, torsion of the stomach and sigmoid colon	1 (4.2)

While congenital anomalies and hereditary pancreatitis were seen in 37.5% (9/24) and 20.8% (5/24) of the patients in the group with, and 11.3% (6/53) and 1.9% (1/53) of the patients without recurrent bouts of pancreatitis. The differences between the two groups regarding these etiologies ($p=0.012$, $p=0.01$) were statistically significant.

When patients with acute pancreatitis and ARP are compared in terms of clinical and laboratory features, AST, GGT, and direct bilirubin values were found to be higher in the group of patients with AP ($p<0.05$) (Table 3).

Seventeen (22.1%) patients were followed only by abdominal ultrasonography (USG) and other

imaging modalities including computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP) were not performed. Advanced imaging in addition to ultrasonography was performed in 71.7% (38/53), and 87.5% (21/24) of the patients followed up with the diagnosis of AP and ARP, respectively. There was no difference between the groups in terms of diagnostic methods (p=0.156).

All patients received intravenous fluid-electrolyte support and pain control was provided. Cholecystectomy was performed in 5 patients with gallstones (3 patients with AP, and 2 with ARP). Reduction of gastro-sigmoid volvulus, splenic detorsion, gastropexy, and splenopexy were performed on the patient with wandering spleen and secondary gastric-sigmoid volvulus and splenic torsion. ERCP was performed in 16 patients (8 patients from each group) for treatment purposes. A stent was placed in the narrow segment of the pancreatic duct of 10 patients using ERCP, and gallstone was removed in 6 patients. There was no difference between the groups in terms of treatment options (p>0.05) (Table 4).

Complications were observed in 7 (13.2%) patients with AP during the follow-up. These complications included pancreatic necrosis in 2, necrosis, peritonitis and pseudocyst formation in the pancreas in 1, splenic vein thrombosis, infarction and pseudocyst formation in the spleen in 1, necrosis in the pancreas, infarction of spleen and splenic vein thrombosis in 1, acute liver failure in 1, and intra-abdominal abscess in 1 patient. Chronic pancreatitis developed in only 3.7% (2/53) of the patients.

While pancreatic necrosis was observed in 1 (4.16%) patient with acute recurrent pancreatitis, chronic pancreatitis (7/24) developed in 29.16% of the patients. However there was no difference between the groups in terms of complications (p=0.423). Whereas chronicity was statistically more common in the recurrent AP group (p=0.003). None of our patients who were followed up with a diagnosis of pancreatitis exited.

Table 3. Clinical and laboratory features of patients with acute pancreatitis and ARP.

	AP group (n:53) (%)	ARP group (n:24) (%)	P values
Gender			
Boys	25 (47.2)	9 (37.5)	0.295
Girls	28 (52.8)	15 (62.5)	
Age (years)	11.12±5.1	11.28±4.35	0.849
Symptomps			
Abdominal pain	45(84.9)	23 (95.8)	0.259
Nausea, vomitting	18 (34)	7 (29.2)	0.795
Jaundice	2 (3.8)	0	1.0
Discomfort (1), conscio-usness (1), diaerrhea (1)	3 (5.7)	0	0.548
Symptom duration (day)	6.07±7.16	13.52±38.8	0.39
AST (U/L)	76.61±113.13	34.43±35.83	0.018
ALT (U/L)	74.03±119.63	37.33±65.45	0.089
GGT (U/L)	104.77±169.12	57.85±98.26	0.042
Total bilirubin (mg/dL)	1.73±3.70	0.86±0.61	0.253
Direct bilirubin (mg/dL)	0.79±1.79	0.25±0.23	0.036
Amilase (U/L)	1086.98±13	804.50±819.37	0.343
Lipase (U/L)	1623.09±17	1334.62±14	0.482
White blood cell	12.056±4287	10.400±2882	0.096
Sedimentation (mm/hour)	31.35±24.64	32.41±28.26	0.893
CRP (mg/L)	36.62±56.66	35.01±54.43	0.950
HDL (mg/dl)	47.45±38.23	37.26±15.57	0.244
Total cholesterol mg/dl)	157.89±123.48	142.04±39.88	0.569
Triglyceride (mg/dl)t	133.75±216.41	329.52±880.41	0.326

Table 4. Methods used in pancreatitis treatment.

Treatment method	AP group n (%)	ARP group n (%)	P values
İnterventional	8 (15.1)	8 (33.3)	0.078
Surgery	3 (5.7)	2 (8.3)	0.644

DISCUSSION

The most common symptom in children with acute pancreatitis is abdominal pain (80-95%), especially in the epigastric region [6]. The second most common symptom is nausea and vomiting, which has been reported in 40-80% of patients [7-9]. Additionally, the most common symptoms in our patients were also abdominal pain, nausea and vomiting in concordance with the literature.

Despite better diagnostic methods and increased awareness for the etiologies of pancreatitis, surprisingly, the proportion of patients diagnosed with idiopathic pancreatitis did not decrease. Studies have shown that the proportion of patients with idiopathic pancreatitis varies between 13% and 34%.

Examination of the current data shows that other important causes of AP in children are biliary diseases (gallstones and bile duct diseases), drugs, systemic diseases, and trauma, followed by infectious, metabolic and hereditary pancreatitis [3,8,10]. In our study, no definitive cause was found in 29.8% (23/77) of the patients who presented with pancreatitis. But in 70.2% of them identifiable risk factors were found for AP including congenital anomalies, gallstones, infection, trauma, and hereditary pancreatitis as stated in previous studies.

Pancreatitis attacks recurred in 24 (31%) of our patients during follow-up. This rate falls within the range of previously published recurrence rates of 7-34% [3]. Sweeny et al. [10] stated that in 70% of their patients, bouts of recurrent pancreatitis developed within the first 5 months after onset of AP and this finding could be helpful in could be helpful in the parental counseling of pediatric patients presenting with the first AP attack. Similarly, the median time elapsed till the development of a second pancreatitis attack in our study was 4.5 months.

CFTR, PRSS1 and SPINK1 mutations and genetic changes in other genes that cause hereditary pancreatitis, are considered to be the most common risk factors in children with acute recurrent pancreatitis and CP [11]. Another risk factor is obstructive causes primarily involving pancreatic divisum [12]. Pancreatic divisum is found in 7% of the general population. Interestingly, it is found in almost half of the patients with pancreatitis who harbor genetic mutations (mainly CFTR mutations) and pancreatitis. This suggests that the pancreatic divisum synergizes with genetic mutations to cause ARP and CP [2]. The most common causes were congenital anomalies and hereditary pancreatitis in our patients with recurrent pancreatitis attacks. The most common congenital anomaly was pancreatic divisum in 5 patients, and 60% (3/5) of them had accompanying genetic mutations. Our results support the hypothesis that genetic factors are is one of the strongest risk factors strongly contribute to the etiopathogenesis underlying ARP. The limitation of our study is that genetic analysis was not performed on all our patients, because of the higher cost of genetic testing compared to other laboratory studies and consideration of a step-by-step approach for the etiological factors as genetic studies were planned after other causes of pancreatitis have been excluded.

In our study, no difference was found between the children with the diagnoses of AP and ARP in terms of demographic and clinical findings. When laboratory findings were compared, it was seen that AST, GGT and total bilirubin values were higher in patients with AP. It was thought that this situation was caused by the fact that obstructive pathologies as gallstones (n:8), pancreaticobiliary compound anomaly (n:6) and other reasons (1 patient with duodenal hematoma) were more common in patients with AP.

Endoscopic retrograde cholangiopancreatography is a method used for the diagnosis and treatment. Common indications for using ERCP in children are biliary obstructions and pancreatitis [13]. In our study ERCP was performed 16 patients so as to stent the narrow segment and remove stones. Among them 10 patients had congenital pancreaticobiliary anomalies such as pancreatic divisum, common bile duct cyst, pancreaticobiliary composition anomaly, and annular pancreas, and 2 had mutations causing hereditary pancreatitis.

Unlike adults, only a small percentage of pediatric patients have been reported to have serious complications [3]. These complications are sterile and infected collections, fistulas, and vascular complications [14]. Complications developed in 13.2% of our patients whose pancreatitis attack did not recur. While there was no difference between the groups in terms of complications (p=0.423), it was found that chronicity was statistically higher in the acute recurrent group (p=0.003) [15]. Despite the hypotheses stating that recurrent acute pancreatitis attacks may turn into CP, there are no data on the conversion of ARP to CP in children, excepting possibly the cases with hereditary pancreatitis [16]. Poddar et al. [17] reported that 37 (42%) of 88 children with ARP developed CP and therefore, ARP is the precursor of the chronic process and chronicity is associated with idiopathic etiology and genetic

mutations. Our study supports this thought as 29.16% of our patients with ARP developed chronic pancreatitis and recurrent attacks were the precursors of a chronic pancreatitis.

CONCLUSION

Nowadays, greater number of children receive the diagnosis of pancreatitis thanks to the increase in awareness and accessibility to diagnostic imaging methods. However, in a significant portion of the cases, still a specific cause cannot be determined. In our study, in 29.8% of the patients a defined etiologic factor could not be found. Congenital anomalies of the pancreas and biliary tract and genetic causes have been found to be important etiologic factors for pancreatitis. For this reason, further investigations including MRCP, ERCP and genetic examinations are necessary to clarify the etiology of pancreatitis. In our study, it was determined that the most common complication in AP and ARP was pancreatic necrosis. Patients with pancreatitis should be closely followed up with clinical findings and, if necessary, laboratory examinations should be performed to determine the risk of serious complications. Although there was no difference between the groups in terms of the risk of developing complications, it was found that chronicity was more common in ARP cases. Long-term follow-up of recurrent acute pancreatitis cases is extremely important so as to prevent development of the risk of chronic pancreatitis and pancreatic insufficiency.

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Research Article

The Role of the Fetal MRI to Predict the Postnatal Survival in Fetuses with Congenital Diaphragmatic Hernia

Konjenital Diyafragma Hernili Fetüslerde Doğum Sonrası Sağkalımı Tahmin Etmede Fetal MRG'nin Rolü

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ABSTRACT

Objective: *To assess the role of the magnetic resonance imaging (MRI) to predict the postnatal survival in patients with congenital diaphragmatic hernia (CDH).*
Method: *25 patients with CDH who had fetal MRI between 2015 and 2020 were enrolled in this retrospective study. Patients were divided into two groups according to the postnatal survival at 30 days of age: alive and dead. The fetal MRI images were assessed to calculate the lung-to-liver signal intensity ratio (LLSIR), and the total lung volume (TLV). In addition, the site of the defect (right or left), accompanying liver herniation (present or absent), detectable-ipsilateral lung parenchyma at the apex (present or absent) were also recorded. MRI images were evaluated by two pediatric radiologists. A p value lesser than 0.05 was considered statistically significant.*
Results: *Among 25 fetuses, 6 were alive and 19 were dead within 30 days after birth. The detectable lung parenchyma had a relationship with the alive group (p = 0.023). Observed-to-expected TLV (p = 0.001) and LLSIR (p = 0.023) were significantly lower in the dead group. Using the cutoff values for the observed-to-expected TLV as 0.27 (a sensitivity of 84%, a specificity of 84%) and for the LLSIR as 2.02 (a sensitivity of 89%, a specificity of 67%) were found as predictors for death.*
Conclusion: *The postnatal survival in CDH may be predicted using the observed-to-expected TLV and LLSIR on the fetal MRI. The presence of the detectable-ipsilateral lung parenchyma at the apex may also be associated with the postnatal survival.*

Keywords: *congenital diaphragmatic hernia, fetal, magnetic resonance imaging, prognosis, total lung volume*

ÖZ

Amaç: *Çalışmamızın amacı konjenital diyafragma hernisi (KDH) olan hastalarda fetal manyetik rezonans görüntüleme (MRG)'nin doğum sonrası sağ kalımı öngörmedeki rolünü değerlendirmektir.*
Yöntem: *Çalışmaya 2015 ile 2020 yılları arasında KDH ön tanısıyla fetal MRG ile değerlendirilmiş olan 25 KDH hastası dahil edildi. Hastalar postnatal 30 günlük dönemde sağkalıma göre yaşayan ve yaşamayan olmak üzere iki gruba ayrıldı. Fetal MRG görüntüleri, akciğer-karaciğer sinyal yoğunluğu oranını ve total akciğer volümünü (TAV) hesaplamak için geriye dönük olarak değerlendirildi. Ek olarak, herni tarafı (sağ veya sol), eşlik eden karaciğer herniasyonu (var veya yok), herni tarafı ile ipsilateral apekste tespit edilebilir akciğer parankimi (var veya yok) kaydedildi. MRG görüntüleri iki pediatrik radyolog tarafından değerlendirildi. Prognozu tahmin etmek için duyarlılık-özgüllük analizleri kullanıldı. P değerinin <0.05 olması istatistiksel olarak anlamlı kabul edildi.*
Bulgular: *Postnatal 30 günlük dönemde 25 fetüsten 6'sı yaşayan ve 19'u ise yaşamayan gruptaydı. Herni tarafı ile ipsilateral apekste tespit edilebilir akciğer parankimi varlığı ile hastaların sağ kalımı arasında anlamlı ilişki saptandı (p=0.023). Yaşamayan grupta Gözlenen/beklenen TAV (p=0.001) ve akciğer-karaciğer sinyal yoğunluğu oranı (p=0.023) anlamlı olarak daha düşüktü. Gözlenen/beklenen TAV'nin <0.27 olması % 84 duyarlılık, % 84 özgüllük ve AKSO değerinin <2.02 olması % 89 duyarlılık, % 67 özgüllük postnatal ölümü öngörücü olarak bulundu.*
Sonuç: *Sonuçlarımıza göre KDH'de postnatal sağkalım, fetal MRG'de gözlenen/beklenen TAV ve akciğer-karaciğer sinyal yoğunluğu oranı kullanılarak tahmin edilebilir. İpsilateral apekste tespit edilebilir akciğer parankiminin varlığı doğum sonrası hayatta kalma ile ilişkilendirilebilir.*

Anahtar kelimeler: *konjenital diyafragma hernisi, fetal, manyetik rezonans görüntüleme, prognoz, total akciğer hacmi*

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INTRODUCTION

Congenital diaphragmatic hernia (CDH), which has a frequency of almost 1 in 2500 live births, is a severe anomaly that has the potential for mortality and morbidity [1,2]. Abdominal organs displace to the thoracic cavity by a defect in the diaphragm. Many important lung diseases like abnormal lung development, pulmonary hypoplasia, and pulmonary hypertension may occur due to the compression of the lungs [3-5]. The significative factors for the mortality in CDH are noted as the grade of pulmonary hypoplasia and the presence of incurable pulmonary hypertension [6].

Imaging has an essential role to evaluate the lung antenatally to estimate the prognosis and to decide the follow-up strategy. Although ultrasound plays an important role in the diagnosis of the CDH, it may give limited information due to many maternal, fetal, and technical factors. However, magnetic resonance imaging (MRI) provides more accurate and detailed information about fetal anatomy, as it is known. MRI has been considered as a potential method for identifying prognostic factors associated with the degree of pulmonary hypoplasia [2,7]. Many centers have adopted using the fetal total lung volume (TLV) which is calculated on MRI to determine the degree of pulmonary hypoplasia in CDH [9-12]. Besides, the lung-to-liver signal intensity ratio (LLSIR) [13], lung-to-spinal fluid signal intensity ratio [14], and liver position on MRI were also investigated to estimate the fetal prognosis in CDH.

The aim of this study was to assess the role of the fetal MRI to predict the prognosis in patients with CDH. For this purpose, the diagnostic performances of the LLSIR and TLV, as well as the qualitative MRI features were taken into consideration.

MATERIALS and METHODS

Patient selection

This study was approved by our institutional review board. Our radiology and obstetrics and gynecology archives were retrospectively reviewed to determine the fetuses who had been diagnosed with CDH by antenatal ultrasound and evaluated by fetal MRI between January 2015-December 2020. Two patients with motion artifacts on T2-weighted Half Fourier single-shot turbo spin-echo (HASTE) sequences were excluded. After the exclusion, 25 patients with CDH were enrolled in this study. Patients were divided into two groups according to the postnatal survival at 30 days of age: alive and dead. The alive group was defined for patients who lived after postnatal 30 days and the dead group was defined for patients who were not survived. The same management strategy was performed for all neonates after birth. Neonates were transferred to our neonatal intensive care unit after intubated nasally in the delivery room. Treatment strategies were performed according to the respiratory and hemodynamic issues. Surgical repair was performed on patients whose respiratory and hemodynamic conditions were stable.

MRI protocols

All examinations were performed on a 1.5-T MRI scanner (Siemens Aera, Germany). No maternal sedation was administered. Mothers were placed in the supine position. A torso phased array coil was wrapped around the mother's pelvis, centered at the area of the fetus. The MRI protocol included T2-weighted HASTE sequences in three orthogonal planes of the head and the body. For more details, true fast imaging with steady-state free precession, dixon T1-weighted and echoplanar sequences were also added in some of the patients. HASTE sequences of the fetal body were provided with no overlap or gap. HASTE sequence was acquired with the following parameters: HASTE sequence was acquired with the following parameters: time to repetition/time to echo, 1100/122 ms; slice thickness, 4-5 mm; field of view (FOV), 300-400 mm; matrix, 256×256; flip angle, 180; number of excitations, 1.

MRI interpretation

MRI images were evaluated by two pediatric radiologists in consensus. The site of the defect (right or left), accompanying liver herniation (present or absent), detectable-ipsilateral lung parenchyma at the apex (present or absent) were recorded (Figure 1). The LLSIR was calculated on T2-weighted HASTE

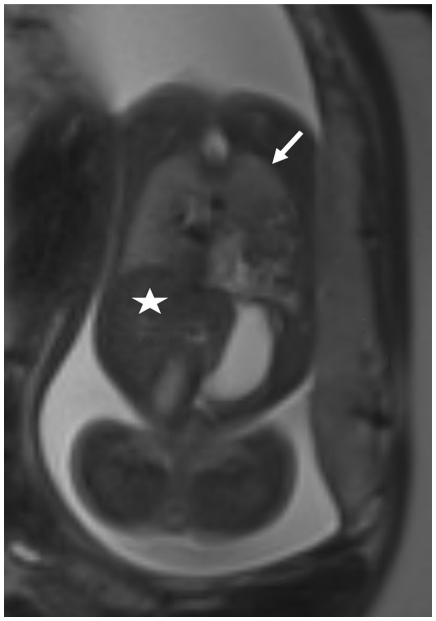

Figure 1. A 26-gestational week- fetus with left side herniation. A detectable-ipsilateral lung parenchyma at the apex was seen (arrow). Liver was in normal position (star).

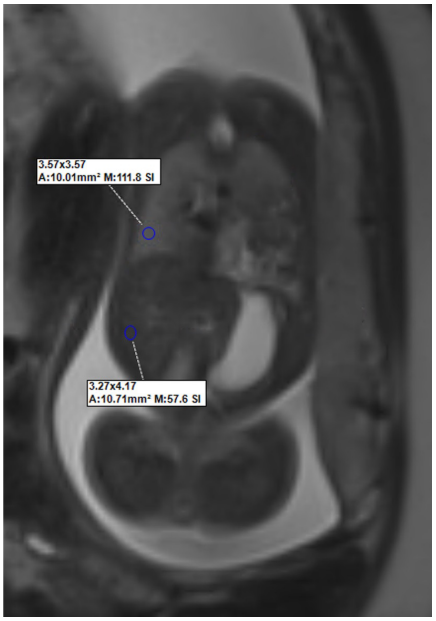

Figure 2. The calculation of the LLSIR. The ROIs are placed at the homogeneous zones of the lung parenchyma and the liver. LLSIR: Lung-to-liver signal intensity ratio, ROI: Region-of-interest.

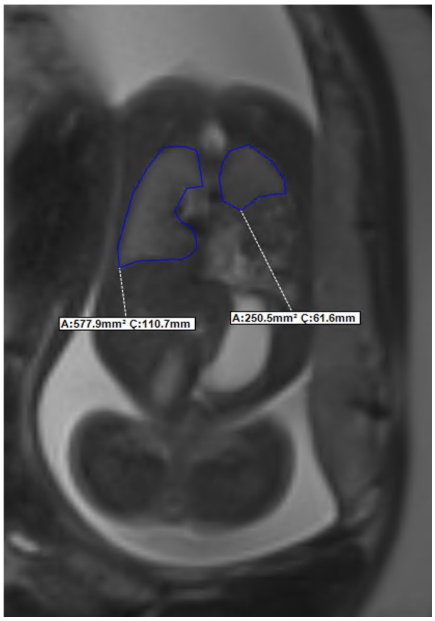

Figure 3. The measurement of the total lung volume. The freehand ROI on each contiguous slice was delineated to provide the lung area.

coronal sequences. The signal intensities of the lung and liver were obtained from the same section to avoid the signal changes on the different slices. The lung parenchyma signal intensity was measured on the homogeneous zone of the contralateral lung parenchyma according to the herniation site by a single region-of-interest (ROI). The portal vein and major branches were not included to the ROI when measuring the liver parenchyma signal intensity (Figure 2). Sizes of the ROIs were manually adjusted as approximately 1 cm^2.

For the calculation of the TLV, axial and coronal planes on HASTE sequences were used separately. First, the lung area was calculated using the freehand ROI on each contiguous slice to provide a sum of cross-sectional areas (in mm^2). Then, the total lung area was multiplied by slice thickness (in mm) to provide a volume (in mm^3) [15]. Subsequently, the TLV measured in axial and coronal planes was averaged to obtain the mean observed TLV (Figure 3). The observed-to-expected TLV was calculated by dividing the observed TLV by the expected TLV of a gestational age-matched healthy fetus. In our study, we considered the expected TLV values provided by Meyers et al. [16] that were provided from a large cohort.

Statistical analysis

Statistical analyses were done using IBM SPSS ver. 22.0 (IBM Corp.). Categorical variables were summarized with frequency counts and percentages and the continuous features were summarized with means and standard deviations. Continuous variables were compared by the Mann-Whitney U test. Chi-square and Fisher's exact tests were performed to analyze the association between the categorical variables and prognosis. Receiver operating characteristic (ROC) curve analyses were performed for each statistically significant parameter to evaluate the ability to predict the prognosis. A p-value lesser than 0.05 was considered as statistically significant.

RESULTS

Twenty-five patients were included in this study. The mean gestational week at the fetal MRI was

Table 1. The patients' characteristics.

	Ssurvived group (n = 6)	Non-survived group (n = 19)	p value
Gestational week at fetal MRI	26.17±7,2	24.74±5.3	0.733
Maternal age	24.33±2.5	28.47±5.8	0.138
Birth weight*	2935.0±538.5	2736±553.5	0.319
Apgar score at 1 minutes*	5.67±2.3	3±1.4	0.010

MRI: Magnetic resonance imaging
** Birth weight and Apgar score were calculated in 23 fetuses because of the terminations of the two pregnancies.*

25.08± 1.1 (18-36). Among 25 fetuses, 6 were alive and 19 were dead within 30 days after birth. The demographic characteristics of the patients were shown in Table 1. Two pregnancies underwent termination in terms of the parents' decision and these fetuses were classified under the dead group. Apgar score at 1 minute was significantly lower in the dead group (p=0.010).

The MRI features were shown in Table 2. The left side herniation (23 of 25 patients) was dominant in both groups (83.3% of the alive group and 94.7% of the dead group). 14 of 25 patients had liver herniation and among them, 12 patients had left liver lobe herniation due to the left-sided diaphragmatic defect. The detectable lung parenchyma was found in 83.3% of the alive group (p=0.023).

The observed-to-expected TLV values were significantly lower in the dead group (0.42±0.12; 0.20±0.09, p=0.001). The LLSIR values were also found lower in the dead group (2.31±0.79; 1.7±0.31, p=0.025). The ROC curve analysis showed that the observed-to-expected TLV had a larger area under the curve (0.930) than LLSIR (0.807) to predict death. Using the cutoff value for the observed-to-expected TLV as 0.27 had a sensitivity of 84% and a specificity of 84% for predicting death in fetuses with CDH. The optimal cutoff value for the LLSIR was 2.02, with a sensitivity of 89% and a specificity of 67% for death within 30 days after birth.

DISCUSSION

We evaluated the role of the fetal MRI to estimate the postnatal survival in CDH. According to our results, the observed-to-expected TLV and LLSIR may help to predict the postnatal survival. An observed-to-expected TLV value lower than 0.27 and an LLSIR value lower than 2.02 were the significant predictors for death within 30 days after birth. In addition, the detectable lung parenchyma on the ipsilateral side was associated with survival.

MRI allows more accurate information about fetal TLV since it is not limited by a fetal lie or maternal body habitus [9,11]. Different methods can be used for the measurement of the fetal TLV on MRI. The lung parenchyma can be outlined on each slice by the freehand ROI and multiplied by the slice thickness [7,16]. Moreover, the sequences can be exported to a 3-D workstation for segmentation and can be measured by manual or automated delineation of ROI [16]. Fetal TLV is also estimated by subtracting the mediastinal volume from the total thoracic volume [12]. The formulas for the prediction of expected fetal TLVs adjusted for gestational age (GA) by MRI measurements have been provided by Rypens

Table 2. Magnetic resonance imaging findings.

	Ssurvived group (n=6)	Non-survived group (n=19)	p value
Herniation site (Right/left)	1/5	1/18	0.430
Presence of the liver herniation	3 (50%)	11 (57.9%)	1.000
Presence of the detectable lung parenchyma	5 (83.3%)	5 (26.3%)	**0.023**
TLV	18961.6±19110.3	7422.68 ±6381.2	0.069
Observed-to-expected TLV	0.42 ± 0.12	0.20 ± 0.09	**0.001**
Lung signal intensity	329.5 ± 113.2	282.7 ± 175.8	0.598
Liver signal intensity	147.6 ± 57.3	166.7 ± 104.0	0.733
LLSIR	2.31 ± 0.79	1.7 ± 0.31	**0.025**

TLV: Total lung volume, LLSIR: lung-to-liver signal intensity ratio

et al. [7] and Meyers et al. [16] as follows:

According to Rypens et al. [7] (2001): $TLV=0.0033x(GA)^{2.86}$, in 2001. Recently, Meyers et al [16] suggested a formula according to a larger cohort of fetuses with gestational ages ranging from 18 to 38 weeks as follows: $TLV=0.000865x(GA)^{3.254}$. In cases of pulmonary hypoplasia, observed-to-expected fetal TLV should be used regardless of the measuring method of the TLV.

Cannie et al. [17] showed that the observed-to-expected TLV was an independent predictor of postnatal survival in CDH patients. They showed that fetuses with CDH who had 25% of expected TLV had a survival rate of 25%. Barnewalt et al. [12] demonstrated that patients with observed-to-expected TLV ratio of less than 15% had a higher risk for mortality in their small study population. Our results were compatible with the literature. We found that patients who could not survive had an observed-to-expected TLV ratios of lower than 0.27. In other words, the TLV less than approximately 25% of expected value was associated with high mortality.

There have been several studies that assessed fetal lung maturity by using LLSIR [18-20]. Brewerton et al. [18] showed that the LLSIR ranged from 1.52 to 4.31 between 21st and 34th gestational weeks. Moshiri et al. [19] manifested a normal mean value of LLSIR as 2.5. Oka et al. [20], found that a cut-off value of ≤2.0 for LLSIR was a good indicator for predicting respiratory outcome after birth. These studies have demonstrated that the fetal LLSIR increases with gestational age. The investigators thought that higher LLSIR values could be related to fluid accumulation in the lungs during fetal lung development with increasing gestational age.

Contralateral lung maturity evaluated with the LLSIR provided important prognostic information. Yamato et al. [21] investigated the LLSIR in the unaffected contralateral lungs of patients with isolated left-sided CDH detected on MRI. They observed that the LLSIR increased in parallel with advanced gestational age in the healthy control group but did not in the CDH group with good or bad prognosis. They suggested cut-off values of 2.16, and 2.22 with the aim to identify the fetuses in the early and late stages of CDH with good or bad prognosis. Our results were compatible with the literature.

We also examined the association between the detectable lung parenchyma in the herniation side and survival. We showed a relationship between the presence of a detectable lung parenchyma on the ipsilateral side and survival. We thought that this finding may help to predict the survival along with other specific parameters. Yokoi et al. [22] proposed a risk stratification using both the detectable lung parenchyma at the apex and the contralateral LLSIR with a cut-off value of 2 on MRI. They reported that all fetuses with detectable lung parenchyma had survived.

Although liver herniation is accepted as a prognostic factor for survival and severity of the pulmonary hypoplasia by many authorities, there have been controversial results in the literature. Ruano et al. [23] could not demonstrate any significant association between either the mortality or the need for ECMO and liver herniation. Nevertheless, they found significant differences in the amount of the liver harniation between the groups with good and bad prognosis. In our study, there was no significant relationship between liver herniation and survival. We considered the liver herniation as a dichotomous variable (either absent or present) and did not use it in the quantification of liver herniation. This may be the reason for this incompatibility.

Our study had several limitations. Firstly, the study had a retrospective design, and the number of our patient population was rather small. Secondly, we did not use three-dimensional MRI sequences for volumetric analysis since they were not performed routinely due to the long acquisition time in fetal MRI. Although we used the same method with the literature, three-dimensional MRI sequences might provide more accurate results. Thirdly, the interpretation of the MRI findings was performed by two pediatric radiologists in consensus which might limit to reproducibility of our results. Fourthly, morbidities were not considered in this study, and we grouped the patients as survived and non-survived cases. We did not evaluate other outcome parameters due to the insufficient information about patients in our archives.

CONCLUSION

In conclusion, fetal MRI is an important tool for evaluating patients with CDH. Based on our results, we established that the postnatal survival in CDH may be predicted using the observed-to-expected TLV and LLSIR on the fetal MRI. The presence of the detectable-ipsilateral lung parenchyma at the apex may also be associated with the postnatal survival. To achieve more definitive results of the prognostic value of the fetal MRI, more studies including larger numbers of patients are needed.

Ethics Committee Approval: SBU. Approval was obtained from the Tepecik Training and Research Hospital Clinical Research Ethics Committee (2021/01-17).
Conflict of Interest: The authors declare that they have no conflict of interests.
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Informed Consent: Written informed consent was waived by the Institutional Review Board.

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Research Article

A Bibliometric Analysis in the Field of Pediatric Anesthesia and Turkey's Contribution to Research

Pınar Ayvat

Pediatrik Anestezi Alanındaki Yayınların Bibliyometrik Analizi ve Türkiye Kaynaklı Yayınların Bu Alana Katkısı

ABSTRACT

Objective: *Bibliometric analysis can be used to assess the contributions of scholars, institutions, countries by examining the materials published in a certain discipline. The objective of this study is to make a bibliometric analysis in the field of pediatric anesthesia and to examine Turkey's contribution to research in this field.*
Methods: *I used the search engine of the Web of Science (WoS), and included all types of contributions (original articles, reviews, letters, editorials, etc.) in the bibliometric analysis. I scanned Science Citation Index Expanded (SCIE) and Emerging Sources Citation Index (ESCI) as they were the most relevant indexes for my study. Statistical analyses were performed by using SPSS 22. I used a binomial test to make a comparison between Turkey and other countries in terms of research output, and academic performance.*
Results: *Pediatric Anesthesia is the only journal that positions itself in WoS categories of both "pediatrics" and "anesthesia". A total of 5,791 citations were found in this particular journal of which 227 were from Turkey. In addition to this journal, 2,096 published materials were found in 433 different sources. Turkish authors have made only 61 contributions to these journals. Hacettepe University, Istanbul University, and Baskent University are the predominant institutions from Turkey accounting for a total of 80 published materials.*
Conclusion: *The findings of this bibliometric analysis not only showed the contribution of Turkish authors to the field of pediatric anesthesia but also revealed the areas of improvement for their future research. The study also showed a list of journals that publish articles in the area of pediatric anesthesia.*

Keywords: *Pediatrics, anesthesia, bibliometric analysis, Turkey*

ÖZ

Amaç: *Bibliyometrik analiz yöntemi, belirli bir disiplinde yayınlanan materyalleri inceleyerek akademisyenlerin, kurumların ve ülkelerin katkılarını değerlendirmek için kullanılabilir. Bu çalışmanın amacı pediatrik anestezi alanında bibliyometrik bir analiz yapmak ve Türkiye kaynaklı yayınların bu alana katkısını incelemektir.*
Yöntem: *Web of Science'ın (WoS) arama motorunu kullanarak, her türlü bilimsel yazı çalışmaya dahil edildi (orijinal makaleler, incelemeler, mektuplar, başyazılar vb.). Araştırma için en alakalı indeksler olan Science Citation Index Expanded (SCIE) ve Emerging Sources Citation Index'i (ESCI) çalışmaya dahil edildi. İstatistiksel analizler SPSS 22 kullanılarak yapıldı. Türkiye ile diğer ülkelerin akademik çıktı performanslarını karşılaştırmak için Binom testi kullanıldı.*
Bulgular: *'Pediatrik Anestezi' dergisi WoS kategorilerinde kendisini hem "pediatri" hem de "anestezi" olarak konumlandıran tek dergiydi. Bu dergide 227'si Türkiye'den olmak üzere 5,791 kayıt bulundu. Bu dergiye ek olarak, 433 farklı dergide 2,096 bilimsel yayın bulundu. Bu dergilerde Türk yazarların katkısı sadece 61 yayın ile sınırlı idi. Hacettepe Üniversitesi, İstanbul Üniversitesi ve Başkent Üniversitesi, bu alanda toplam 80 yayın sayesinde Türkiye'de en önde gelen kurumlardır.*
Sonuç: *Bu bibliyometrik analizin bulguları, Türk yazarların pediatrik anestezi alanına katkılarını göstermesinin yanı sıra, gelecekteki çalışmalar için iyileştirme alanlarını da ortaya koydu. Çalışma ayrıca pediatrik anestezi alanında yayın yapan dergilerin bir listesini de sunmaktadır.*

Anahtar kelimeler: *Pediatri, anestezi, bibliyometrik analiz, Türkiye*

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INTRODUCTION

As has been happening in other branches of medicine, we have been observing new subdisciplines in the field of anesthesia and reanimation in recent years. Pediatric anesthesia, neuroanesthesia, cardiothoracic anesthesia, and obstetric anesthesia are some examples of these subdisciplines. This situation caused the academic journals to position themselves according to the needs of new segments of readers in different subdisciplines. The number of articles published in the field of anesthesia around the world has been increasing. One can evaluate and assess the contributions of scholars, institutions or countries, by examining the articles published in a certain discipline. Bibliometric analysis is a method used for this purpose. Thus, we can make comparisons among countries gain information about the contributions of scholars to scientific publications, compare the contributions of state and private institutions in a particular discipline, and examine co-authorship trends.

Unlike intensive care and algology, pediatric anesthesia is not accepted as a subdiscipline of anesthesia in Turkey. However, pediatric surgery and the care of pediatric patients require a different level of know-how. Because of this accumulated amount of expertise, scholars from all around the world have been producing large amounts of academic output. The number of articles on specific disciplines such as pediatric anesthesia is indicative of publication activity in this respective field [1]. This study aims to make a bibliometric analysis of the scientific literature published in the field of pediatric anesthesia and then to determine Turkey's relevant position. The main research questions (RQ) are as follows:

RQ1: How many journals are there in the Web of Science (WoS) collection that position themselves in the WoS categories of "pediatrics" and "anesthesiology" at the same time?

RQ2: How many published materials deserve global scientific value in "pediatrics" and "anesthesiology" categories, and how many of them are produced in Turkey?

RQ3: Are there other journals that publish articles in the field of pediatric anesthesiology even though those journals do not position themselves in WoS categories of "pediatrics" and "anesthesiology" simultaneously. If the answer is yes, what are those journals, and how many published articles are from Turkey, and other countries?

RQ4: In pediatric anesthesiology, what are the main Turkish institutions that contribute to the literature?

RQ5: What is the average cited reference count of published articles from Turkey compared to globally published articles?

RQ6: How many authors contributed to the published materials from Turkey, compared to published materials worldwide?

MATERIAL and METHODS

I conducted all searches in the "Advanced Search" section of Clarivate Analytics' Web of Science (WoS) Core Collection database on 24th October 2020. I checked the "All years (1975-2020)" option for the timespan and I looked for the records in citation indexes of SCIE (Science Citation Index Expanded) and ESCI (Emerging Sources Citation Index). I excluded citation indexes of SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH from my search as they were not relevant for my study. To find the currently published journals on pediatric anesthesia, I checked WoS categories that simultaneously include "Pediatrics" and "Anesthesiology". Therefore I used the search string: WC=(Pediatrics AND Anesthesiology). I looked for records from Turkey in these categories by using the search string: WC=(Pediatrics AND Anesthesiology) AND CU=Turkey. In the address sections of the citations , if there was at least one author from Turkey, that record was accepted as a publication from Turkey.

In addition to this, I made another search with the string: (TS="P*diatric An*esthesi*" OR TI="P*diatric An*esthesi*" OR AB="P*diatric An*esthesi*" OR AK="P*diatric An*esthesi*") NOT (SO=PEDIATRIC ANESTHESIA OR SO=(PAEDIATRIC ANAESTHESIA)). With this, I looked for records that included variations of the words pediatric, paediatric,

anesthesia, anaesthesia, anesthesiology, anaesthesiology, anesthesiolog, anaesthesiolog, etc. in the titles, abstracts, or keywords of the publications in journals that do not position themselves in WoS categories of "Pediatrics" and "Anesthesiology" together. In order to refine this search for Turkey only, I used the search string:

((TS="P*diatric An*esthesi*" OR TI="P*diatric An*esthesi*" OR AB="P*diatric An*esthesi*" OR AK="P*diatric An*esthesi*") NOT (SO=PEDIATRIC ANESTHESIA OR SO=(PAEDIATRIC ANAESTHESIA))) AND CU=Turkey.

Statistical analyses were performed by using SPSS 22. I used a binomial test to make a comparison between academic output performance of Turkey and other countries. Ethical approval for this study was obtained from Ethics Committee of Izmir Democracy University Buca Seyfi Demirsoy Education and Research Hospital.

RESULTS

When I scanned the journals that position themselves in the WoS categories of "pediatrics" and "anesthesiology" simultaneously, I realized that all records were from two journals: "Pediatric Anesthesia" and "Paediatric Anaesthesia". These two journals are actually the same journal as their ISSN is the same (1155-5645). Apparently, the editors changed the title of the journal from "Paediatric Anaesthesia" to "Pediatric Anesthesia" in March 2004 after they obtained an eISSN, which shows that the journal also started to be published online after that particular time. This periodical is from England and its first issue appeared in 1995. Right before it changed its title and started publishing online in 2004, its impact factor (IF) for 2003 was 0.98.

The journal's IF was 2.04 in the year 2018. The journal's ISSN/eISSN is 1155-5645/1460-9592 and it currently publishes 12 issues per year.

Between 1995-2020, there were 5,791 records in this journal, 3,110 of which were articles and 498 were reviews. The rest were letters, notes, editorials, etc. When I checked the records in this journal that were from Turkey, the result was 227 records. Turkish authors started to publish their articles in this journal as early as 1997 with the 7th volume and 5th issue. Articles made up 119 of these records, one of them was a review article and 107 of them were letters.

Obviously, "Pediatric Anesthesia" is the only journal in WoS collection that positions itself in the "Web of Science Categories" of pediatrics and anesthesiology at the same time. I suspected that it was unlikely that this journal was the only journal that published articles about pediatric anesthesia. There should have been some other journals of anesthesia that could accept and publish articles, reviews, letters about pediatric anesthesia, pediatrics, or in some other disciplines of medicine. When I looked for records that included variations of the words pediatric anesthesia/anesthesiology etc. I got 2.096 results. None of these results included published materials in the journal of "Pediatric Anesthesia" , so I did not include this specific journal in my bibiliometric analysis. These 2.096 records were published in 433 different sources. I analyzed the first 20 sources , namely 54% (n:1.130) of all records (Table I). Research domains of all these journals included "Anesthesiology". In fact, the titles of these 20 journals included the word "anesthesia" or" anesthesiology". There were 6 journals from the USA, 4 from England, and 3 from Italy. Sixteen of them are published in English whereas 3 of them accept multiple languages and one is released in German. Eighteen of them are indexed in SCIE and only 2 are indexed in ESCI. The average IF in 2008 for these journals was 2.72. Eight of them were in Q1 whereas 7, 2, and 3 of them were in Q2, Q3, and Q4 quartiles, respectively.

When I checked the records in the 433 different journals mentioned above, 61 records were from Turkey including 49 articles and 12 letters. The earliest work was from 2007. Turkish authors had their works published in 36 different journals.

I looked for 10 institutions from Turkey that contributed most to the literature both in the journal of "Pediatric Anesthesia" and in other journals (Table II). Except for Baskent University, Yeditepe University, and Bezmialem Vakif University, all of the institutions were state universities. Hacettepe University, Istanbul

Table 1. Top 20 journals according to the number of published materials (except "Pediatric Anesthesia").

Order	Journals	Records (Total)	Records (Turkey)	Country of Publication	ISSN/e-ISSN	First Pub. Year	Issues/ year	2018 IF	Quarter
1	Anesthesia and Analgesia	184	0	USA	0003-2999	1921	12	3.5	Q1
2	British Journal of Anaesthesia	104	0	England	0007-0912/1471-6771	1923	12	6.2	Q1
3	Anaesthesia	100	0	England	0003-2409/1365-2044	1946	12	5.9	Q1
4	Anaesthesist	89	0	Germany	0003-2417/1432-055X	1952	12	0.9	Q3
5	Current Opinion in Anesthesiology	84	0	USA	0952-7907/1473-6500	1988	6	2.1	Q1
6	Anesthesiology	74	0	USA	0003-3022/1528-1175	1940	12	6.4	Q1
7	Acta Anaesthesiologica Scandinavica	63	0	Denmark	0001-5172/1399-6576	1957	10	2.2	Q1
8	Journal of Clinical Anesthesia	62	12	Holland	0952-8180/1873-4529	1989	8	3.5	Q2
9	Annales Francaises d Anesthesie et de Reanimation	61	0	France	0373-8701	2015	6	2.7	Q4
10	Journal of Neurosurgical Anesthesiology	36	0	USA	0898-4921/1537-1921	1989	4	3.0	Q2
11	Anasthesiologie & Intensivmedizin	34	0	Germany	0170-5334/1439-0256	1960	12	0.7	Q3
12	Indian Journal of Anaesthesia	31	0	India	0019-5049/0976-2817	1953	12	1.3	Q2
13	Anasthesiologie Intensivmedizin Notfallmedizin Schmerztherapie	30	0	Germany	0939-2661/1439-1074	1966	12	0.3	Q4
14	Journal of Anesthesia	28	3	Japan	0913-8668/1438-8359	1987	6	1.5	Q2
15	European Journal of Anaesthesiology	28	2	England	0265-0215/1365-2346	1984	12	4.1	Q1
16	Anaesthesia and Intensive Care Medicine	27	0	England	1472-0299/1878-7584	2003	12	0.5	Q4
17	Anaesthesia and Intensive Care	26	0	Australia	0310-057X/1448-0271	1972	6	1.4	Q2
18	Canadian Journal of Anaesthesia	25	0	Canada	0832-610X/1496-8975	1908	12	3.4	Q1
19	Minerva Anestesiologica	22	1	Italy	0375-9393/1827-1596	1953	12	2.8	Q2
20	Journal of Cardiothoracic and Vascular Anesthesia	22	0	USA	1053-0770/1532-8422	1986	10	1.9	Q2
	TOTAL	1.130	18						

Table 2. Ten institutions from Turkey that contributed most to the pediatric anesthesia literature.

Number of published materials in "Pediatric Anesthesia"			Number of published materials in journals other than "Pediatric Anesthesia"		
Order	**Institution**	**Records**	**Order**	**Institution**	**Records**
1	Hacettepe University	29	1	Kocaeli University	9
2	Istanbul University	25	2	Cukurova University	6
3	Baskent University	20	3	Adnan Menderes University	4
4	Selcuk University	14	4	Yeditepe University	4
5	Gazi University	12	5	Baskent University	3
6	Çukurova University	9	6	Istanbul University	3
7	Erciyes University	9	7	Adıyaman University	2
8	Kocaeli University	9	8	Ataturk University	2
9	Ege University	8	9	Bezmialem Vakıf University	2
10	Ondokuz Mayıs University	8	10	Dokuz Eylul University	2

University, and Baskent University dominated the other institutions with a total of 80 published materials. That fact is not surprising as Hacettepe University, and Istanbul University are among the oldest medical faculties in Ankara and Istanbul, respectively; and Baskent University is the oldest private university that has a medical school in Ankara.

When I examined the materials published in "Pediatric Anesthesia" and other materials published in other journals that include all variations of the words "pediatric anesthesia" in their titles, abstracts, or keywords, the total number of records was 7.887 including 288 records from Turkey. The earliest publication was from 1980 and the latest from 2020. The cumulative number of published materials in each decade between the years 1980 and 2020 were 108; 1.078; 3.127 and 3.574, respectively. In Table III,

Table 3. Comparative information between Turkey and other countries regarding the published materials.

	Turkey	%	Other countries (n)	%	P
Number of articles	168	58.3	4.045	53.2	0.68
Number of reviews	1	0.3	717	9.4	0.04*
Number of letters	107	37.2	1.750	23.0	0.01*
Number of other materials	12	4.2	1.087	14.3	0.01*
Total	288	100.0	7.599	100.0	
Number of cited references	4,374		142.864		
Average number of cited references	15.2		20.1		
Average number of pages	4.4		5.3		
Average number of authors	4.5		3.82		
Published materials with 1 or 2 authors	47	16.3	2.686	35.3	0.00*
Published materials with 3 or more authors	241	83.7	4.913	64.7	0.03*
Total	288	100.0	7.599	100.0	
Number of published materials between 2016-2020	52	18.1	1.782	23.5	0.45
Number of published materials between 1980-2015	236	81.9	5.817	76.5	0.74
Total	288	100.0	7.599	100.0	

** Statistically significant (P<0.05).*

you can find comparative information between Turkey and other countries regarding the number of published materials, the number of cited references, authors, pages over a specified period of time. Published materials of Turkish authors were cited 15.2 times on average, whereas materials from other countries were cited 20.1 times. The average number of authors per published material was 4.50 for records from Turkey, but this figure was 3.82 for other countries. The average number of pages of articles only was 5.8 for Turkish authors and 6.4 for the authors from other countries. The number of published materials in the last five years from Turkey was 52 which made up 18.1% of the total records from Turkey, whereas it was 1.782 comprising 23.5% of the records from other countries.

DISCUSSION

This bibliometric analysis has yielded important results for researchers in the field of pediatric anesthesia with an emphasis on Turkish scholars' position in the literature. The major journals that publish articles on pediatric anesthesiology, the number of materials published in those journals, average number of cited references, the number of authors per published material, and Turkish researchers' role in the literature have been demonstrated in this bibliometric analysis. With bibliometric analyses, some researchers looked for answers to various research questions. For example, one study identified the top-cited published materials and the most influential journals in the field of anesthesia; and the researchers also identified the institutions and researchers that produce the highest number of academic output [2]. Xie et al. [3] studied China's contribution to researches in the field of anesthesiology between 2005-2014 by retrieving data from the PubMed and WoS databases. They analyzed the total number of articles, type of published materials, number of citations, and citation rates of 6 different countries in 29 journals of anesthesiology. Tripathi et al. [4] compiled a comprehensive list of the most-cited articles in anesthesia between 1945 and 2008 by using the WoS database which was called "ISI Web of Knowledge" at the time of their research. To find the articles related to anesthesiology, the researchers used a similar search string as in my study, which makes use of the "*" symbol as a wildcard to retrieve all possible variations of the word anesthesia [4]. Bould et al. [5] identified the published materials attributed to each country in the anesthesia literature. They also grouped the articles by the

gross national income of a particular country to look for a relationship between economic productivity and academic output. They concluded that 89.2% of the articles were published by contributors from high-income countries.

In recent years, the number of children undergoing operative procedures has increased and many specialists have been devoting their expertise to provide anesthesia for children [1]. Because of this dedication, the number of published scientific materials on pediatric anesthesia also increased. Indeed, in this study, I found that 45.3% (n=3.574) of all the materials in this subdiscipline were published in the last ten years (2010-2020) and 39.7% (n=3.127) of them between 2000 and 2010. Although this number might seem quite high, actually I could identify only a few bibliometric analyses performed in the field of pediatric anesthesia [1,6-8].

Brambrink et al. [1] thought that there was a lack of compilation of literature on pediatric anesthesia. They identified publications, and respective journals regarding clinical practice in pediatric anesthesia, and assessed the academic output of some selected countries for a six-year period between 1993-1998. In their analysis, the scholars limited their search to articles, case reports, reviews, and editorials. Similar to the results of my study, they found that the highest number of materials was published in the journal of "Pediatric Anesthesia" followed by "Anesthesia & Analgesia", "Canadian Journal of Anesthesia", "British Journal of Anesthesia" and "Anesthesiology". In my study, "Pediatric Anesthesia" was also on top of the list, followed by "Anesthesia and Analgesia", "British Journal of Anesthesia", "Anaesthesia" and "Anaesthesist". Brambrink et al. [1] also calculated the IF values of the journals that published articles on pediatric anesthesia. When I compared the top 5 journals of that study with the results of my research, I found out that 2018 IF values for all these journals were higher. This could reflect that the academic reputability of those journals has increased since 1998. Brambrink et al. [1] found that the top five journals accounted for 46% of all published möaterial whereas in my study, they accounted for 79.5% of all published material. The reason for this increase could be the domination of the journal of "Pediatric Anesthesia" in the field of pediatric anesthesia in recent years.

In another study, Brambrink et al. [8] analyzed the range of topics of published materials, as well as the types of them on pediatric anesthesia between 1993-1998. In my study, I did not investigate the spectrum of hot topics. However, such an analysis based on keywords or abstracts, could be used to identify both current trends and the historical hotspots of a specific discipline, as well [9,10]. It could also act as a guide for further scientific research [11]. Brambrink et al. [8] found that 57.1% and 24.9% of the published materials were original articles and case reports, respectively, whereas, in my study articles, and letters constituted 53.4% and 23.5% of the published material, respectively.

In my study, the proportion of the number of articles to the total number of published materials from Turkey was similar to the global figure (58.3% and 53.2%, respectively). For review articles Turkey's figure was statistically significantly lower than the global rate (0.3% vs 9.4%). In Turkey, scholars do not get any credit from reviews for academic promotion. Therefore, scholars might not be willing to spend much effort to publish review articles.

According to my study, the average number of citations referenced from published materials from Turkey (15.2) was lower when compared with other countries (20.1). In another study which assessed the Turkish academic output in SCI and SCIE indexed journals in the field of anesthesiology, it was found that the mean number of citations from Turkish articles was at the very least among 22 countries [12]. These two results may indicate that published materials from Turkey in both anesthesiology and pediatric anesthesiology are not unique and interesting enough for other scholars. In fact, this result could be related to the intense clinical workload of Turkish physicians. According to the World Bank, the number of physicians per 1.000 people in Turkey was 1.85 whereas it was 2.79, 2.61, and 2.92 for the United Kingdom, the United States of America, and OECD countries, respectively [13]. These figures signify the greater workload placed on Turkish physicians.

Scholars in Turkey in the field of medicine are also sometimes faced with permission issues to conduct academic researches. We note that some researches, for which we could not get permission from the ethics committee, could easily be conducted and published in other countries. This fact may have a negative impact on publishing original and unique articles which reduce the number of citations from Turkish articles.

In my study, the average number of authors for each published material from Turkey and other countries were 4.5 and 3.82 respectively. Publishing articles with multiple authors is a common trend. The rate of published materials from Turkey with 3 or more authors (83.7%) was statistically significantly higher than that of other countries (64.7%). Although the average number of authors per publication from Turkey was higher than the global average, when I looked at the academic productivity in the last 5 years, it appeared that the percentage of Turkish authors publishing articles in this field (18.1%) seemed to be falling behind the global rate (23.5%), though this difference was not statistically significant.

There are limitations in my study. I used Web of Science database to determine the country of origin of published materials. Similar searches in some other reputable databases such as Scopus, PubMed, or World Health Organization's databases could have given different results. Another limitation is the fact that I did the research based on the number of published materials, and did not consider the number of citations of these materials. A citation analysis could have given a different perspective. In my study, if the address line for any of the authors included "Turkey", I considered it to be a publication from Turkey. This is may be another limitation since some studies used the first author's country to determine the origin of published materials [14,15] whereas other scholars assigned the country of publication according to the corresponding author [5,16]. However apparently a consensus has not been reached on determining the country of a published material.

Bibliometric analyses are conducted to determine the quantity and quality of published materials as well as the extent of the contributions of countries in a certain discipline, and are often used in different branches of medicine. The findings of this bibliometric analysis not only showed the level of contributions of Turkish authors to the field of pediatric anesthesia but also revealed potential areas of improvement for their future research. The study also revealed a list of journals that publish articles about pediatric anesthesia. Therefore, my colleagues who want to publish in this particular discipline could use this study as a guide for their future research. As the number of academic output and contributions of Turkish scholars in this field increases, similar periodically performed bibliometric analyses would be helpful to determine whether there has been an improvement in these areas.

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Research Article

The Effect of The Covid-19 Pandemic On The Adaptation Process and Psychiatric Symptoms of Children Aged 7-12: A Telemedicine Study

Covid-19 Pandemisi'nin 7-12 Yaş Arası Çocukların Uyum Sürecine ve Psikiyatrik Belirtilerine Etkisi: Bir Teletıp Çalışması

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ABSTRACT

Objective: *The aim of the presented study is to evaluate the adaptive process and psychiatric symptoms in the 7-12 age group followed-up with telemedicine interviews during the height of the pandemic.*
Method: *Patients between the ages of 7-12 who were followed up in our outpatient clinic were called by telemedicine service at the appointment date. The questionnaire prepared by the researchers in order to investigate the adaptation process to the pandemic was administered, the answers provided by the patients and their families were recorded in the case data form together with Clinical Global Impression (CGI) Scale score appraised by the interviewing psychiatrist. Medical records pertaining to each patient were also reviewed, their psychiatric diagnoses, according to DSM 5 criteria and CGI scores recorded in their last face-to-face interviews during the pandemic period, were included in the case data form.*
Results: *Fifty patients were included in the study. The mean age of the participants was 9.14±1.61 years. Attention deficit hyperactivity disorder (60%) was the most common psychiatric diagnosis detected in the participants before the pandemic, followed closely by anxiety and related disorders (20%) and specific learning difficulty (16%). The CGI scores of the cases before, and during the pandemic were 2.72±0.75, and 2.92±0.94, respectively. The difference between the mean scores was statistically significant (p=0.024).*
Conclusion: *Our study emphasizes the importance of follow-up by telemental health practices in cases where face-to-face psychiatric interviews are not applicable, i.e., due to the risk of transmission of COVID-19 disease during the current pandemic.*

Keywords: *Covid 19-Pandemic, telemedicine, child and adolescent psychiatry, telemental health*

ÖZ

Amaç: *Bu çalışmanın amacı, pandeminin yoğun olduğu dönemde, psikiyatrik takipteki 7-12 yaş olguların, teletıp görüşmesi ile uyum süreci ve psikiyatrik belirtilerinin değerlendirilmesidir.*
Yöntem: *Polikliniğimizde takip edilen 7-12 yaş arası hastalar randevu gün ve saatinde teletıp ile aranmıştır. Pandemiye uyum süreci ile ilgili araştırmacılar tarafından hazırlanan anket uygulanmış, görüşme yapan psikiyatrist tarafından değerlendirilen Klinik Global İzlenim (KGİ) Ölçeği puanı ile birlikte vaka veri formuna kaydedilmiştir. Her hastaya ait tıbbi kayıtlar da gözden geçirilmiş, DSM 5'e göre psikiyatrik tanıları ve pandemi döneminden önceki son yüz yüze görüşmelerinde kaydedilen KGİ puanları vaka veri formuna dahil edilmiştir.*
Bulgular: *Çalışmaya 50 hasta dahil edilmiştir. Katılımcıların yaş ortalaması 9,14±1,61'dir. Katılımcılarda pandemiden önce saptanan psikiyatrik tanılar arasında en yaygın olanı dikkat eksikliği hiperaktivite bozukluğu (%60) iken, onu anksiyete ve ilişkili bozukluklar (%20) ve özgül öğrenme güçlüğü (%16) takip etmiştir. Pandemi öncesi olguların KGİ skoru 2,72±0,75, pandemi dönemindeki KGİ skoru 2,92±0,94'dir. Ortalama puanlar arasındaki fark istatistiksel olarak anlamlıdır (p=0,024).*
Sonuç: *Çalışmamız, pandemideki bulaş riski nedeniyle yüz yüze psikiyatrik görüşmelerin yapılamadığı psikiyatrik takipteki çocuk ve ergenlerde, Teletıp uygulamaları ile takibin devam edebileceğini ve bunun önemini vurgulamaktadır.*

Anahtar kelimeler: *Covid 19-Pandemisi, teletıp, çocuk ve ergen psikiyatrisi, telemental sağlık*

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INTRODUCTION

The members of the large, and diverse Coronaviridae (CoV) family has the capacity to cause a variety of diseases ranging from mild common cold to severe life-threatening infections like Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). The novel SARS-CoV-2 can be classified in the latter group, and like all other members of the family, is mainly transmitted by airborne droplets [1]. Considering the rate of transmission and global status the novel SARS-CoV-2 and the associated Coronavirus Disease-19 (COVID-19) has reached; social distancing, use of personal protective equipment, and personal hygiene have become essential in dealing with the present adverse circumstances.

Studies have advocated that epidemics affecting public health can have an array of psychological effects on the general population, the most common being anxiety, fear, and depressive symptoms [2]. The COVID-19 pandemic laid the groundwork for global panic and psychological stress [3]. Furthermore, the crisis precipitated by the present epidemic environment may have deleterious effects on the mental health of isolated individuals and those with preexisting mental illnesses [4]. The feeling of loneliness that comes with social isolation can adversely affect mental health [5]. While the coronavirus pandemic is unquestionably the focus of worldwide attention, the negative psychological, social, and economic effects of the COVID-19 disease deserve utmost consideration for effective management of this extraordinary period [6].

An online study conducted in China during the COVID-19 epidemic reported that 54% of the 1210 participants had described the mental health impact of the pandemic to be moderate to severe, and the most common disclosed symptoms being depression and anxiety [7]. While most studies conducted during this period have focused on the general population and risk groups such as healthcare workers or the elderly, it cannot be denied that the current crisis also presents multifaceted predicaments for children. The epidemic had profound effects on children, youth, and their families necessitating establishment of a new routines and re-planning of daily life [8]. Affected family members and loss of relatives during the pandemic period may also cause post-traumatic stress disorder and depression in youth [9].

Children also experience fear, anxiety and uncertainty, physical and social isolation during the COVID-19 epidemic.

The closure of schools and ongoing online education is a novel experience for many children, presenting a tremendous adaptive challenge. The needs of school-age children are essentially the same all over the world regardless of the climate, race, geographical region, and economic development. In a preliminary study conducted in China, it was stated that the most common psychological and behavioral problems among children and adolescents with the COVID-19 pandemic were distractibility, irritability, clinging behavior, and separation anxiety [10].

Undoubtedly, this period will have detrimental effects on the mental health of children, even youth with established protective factors and decent support systems is adversely affected However, this condition also underscores the potential impact of the pandemic on children previously diagnosed with mental health disorders. Children with existing psychiatric diseases are likely to experience difficulties in maintaining their treatment (examination, therapeutic interview, the supply of medicine, etc.) owing to the regulations imposed due to COVID-19 pandemic. Nonetheless, the proliferation of internet services and smartphones, and fifth-generation (5G) mobile networks, which enable mental health professionals and health officials to provide online mental health services during the COVID-19 outbreak are promising innovations. The speedy transmission of the virus prevents conventional face-to-face mental interventions, making online mental health services a safe alternative. To date, various online mental health services have been widely implemented for those in need during the epidemic in China [3].

Within the scope of protective measures at our university, it was deemed appropriate to continue the outpatient services within the framework of

telemedicine in accordance with the decision of the Coronavirus (COVID-19) Outbreak Coordination Commission dated 18.03.2020. Face-to-face interviews have resumed as of 01.06.2020, but it was decided to continue telemedicine interventions in select cases.

The aim of the presented study is to evaluate the adaptive process and psychiatric symptoms in the 7-12 age group followed-up with telemedicine interventions during the height of the pandemic.

MATERIAL and METHODS

The present study is designed as a descriptive, cross-sectional research. The children aged 7-12 years who had prior presentations to the child and adolescent psychiatry outpatient clinics and had scheduled for telemedicine follow-ups were included in the study after online written informed consent was provided by the children and their families. According to the telemedicine methodology applied, the patients and their families were interviewed via telephone per decision of the Coronavirus Outbreak Coordination Commission in place of the standard face-to-face interviews. The management department of our hospital has integrated the telemedicine methodology into the hospital information system, and the operations of the patients called by telemedicine are performed over the hospital information system. During the study, 65 patients were called by telemedicine services. Fifteen patients could not be reached by phone. Fifty patients and their parents, who could be reached by phone, agreed to participate in the study.

The standard interview framework namely firstly interviewing with the children then their parents was preserved. Psychiatric symptoms were evaluated, followed by the assessment of the functionality of the patient, the effective use of psychotropic medication (if applicable) and then treatment planning. The child and adolescent psychiatrist conducting the tele-interview also provided psychosocial support and guidance to the patients and their families. The allotted time for the complete psychiatric interview was 30-40 minutes, including the administration of the COVID-19 Adaptation Questionnaire prepared by the authors, and the assessment of the patient's global functioning.

The questionnaire prepared by the researchers in order to investigate the adaptation process to the pandemic period was administered, the answers provided by the patients and their families were recorded in the case data form together with the Clinical Global Impression Severity Scale scores appraised by the interviewing psychiatrist. Medical records of each patient were also reviewed, their psychiatric diagnoses, according to DSM 5 criteria and CGI scores recorded during last face-to-face interviews prior to the tele-interview during the pandemic period, were written down in the case data form.

Daignostic tools

The COVID-19 Adaptation Questionnaire: A structured questionnaire to better record the data disclosed by the patient and their families was prepared by the authors. This brief questionnaire inquired whether there was a health worker at home, whether the patient was affected by the epidemic at home or in his/her immediate environment, the daily routine of the patient and his/her family, exposure to news about the epidemic and changes in sleep patterns and appetite.

Clinical Global Impression Scale (CGI): Clinical Global Impression Scale (CGI) has been utilized as a standardized measurement tool to evaluate the severity of any disease and symptomatic improvement. The evaluation based on this scoring system relies on the clinical judgment of the clinician during the interview. The clinician determines the severity of the disease and the degree of improvement in symptoms on a Likert-type rating scale ranging from 1 to 7 (1-normal, not sick, 2-borderline patient, 3-mildly ill, 4-moderately ill, 5-significantly ill, 6-severely ill, 7-most severely ill) [(11)].

Ethics Approval

The present study was submitted to the Ministry of Health in compliance with the national data regarding any scientific research on COVID-19

disease. The study was subsequently approved and presented to the local medical research ethics committee for ethical approval, and the relevant permission was granted on 10.06.2020 with the decision number: 20-6T/48.

Statistical Analysis:

Statistical analysis of the data was conducted using the SPSS 25 package program. Sociodemographic characteristics of the patients, complaints at presentation, distribution of psychiatric diagnoses, The COVID-19 Adaptation Questionnaire, and CGI scores were evaluated by descriptive statistical analysis methods, and frequency analysis. Paired samples Student's t-test was employed to infer the differences in CGI scores before and after the pandemic. The p-values less than 0.05 were considered statistically significant for all analyses.

RESULTS

Sixteen (32%) female, and 34 (68%) male patients were included in the study. The mean age of the participants was 9.14±1.61 years, and a significant number (n=38; 76%) of the participants were living with a nuclear family. Twenty percent (n=10) of the patients participating in the study indicated that they were living with a healthcare professional at home. Patients with relatives affected by the epidemic in their immediate surroundings constituted 6% (n=3) of the participants in the study. Sociodemographic data of the patients are summarized in Table 1.

During lockdown period, the study participants spent their times reading books (n=10; 20%), playing video games (n=27; 54%), watching television or other streaming services (n=33; 66%), in social media applications (n=33; 66%), studying (n=42; 84%), participating in various leisure activities such as drawing, painting, gardening, playing an instrument etc., (n=8; 16%) and 6% (n=3) exercising (n=3; 6%). Compared to the pre-pandemic period sleep patterns of 50% (n=25) of the participants deviated from the baseline. The remaining 50% (n=25) of the participants, however, reported no change in their sleep patterns. Concerning the nutritional status of the participants during the pandemic period, an increase in appetite was reported in 28% (n=14), and a decrease in 12% (n=6) of the patients. An irregularity in mealtimes and portions was reported by 2% (n=1) of the participants, while 58% (n=29) of the cases

Table 1. Sociodemographic data.

	Completed psychiatric interviews n=50
Age, m, (std)	
Male	9.14 ± 1.61
Female	9.26 ± 1.46
Gender, n (%)	8.87 ± 1.92
Male	
Female	34 (68)
Family Structure, n (%)	16 (32)
Nuclear family	
Broken family	38 (76)
Extended family	5 (10)
Foster family	6 (12)
Healthcare Provider Present in Immediate Environment, n (%)	1 (2)
Yes	10 (20)
No	39 (78)
Relatives Affected by the Outbreak, n (%)	
Affected	3 (6)
Unaffected	47 (94)

Table 2. Preferred pastime activities and changes in sleep and appetite during the pandemic.

	Completed psychiatric interviews n=50
Preferred Pastime Activities, n (%)	
Reading	10 (20)
Video games	27 (54)
Television/streaming services	33 (66)
Social media	33 (66)
Educational activities	42 (84)
Physical activities	3 (6)
Other leisure activities	8 (16)
Sleep	
Disruption	25 (50)
No disruption	25 (50)
Appetite	
Increased	14 (28)
Decreased	6 (12)
Disruption in feeding pattern	1 (2)
No difference	29 (58)

Numbers and percentages are calculated separately for each activity.

reported no change in their dietary habits or appetites. A summary of the changes reported by the patients in relation to the pandemic period is presented in Table 2.

While 60% (n=30) of the study participants disclosed that they stayed up-to-date on pandemic related news, 20 (40%) participants said that they had not read, and listen the news about COVID-19 disease. Thirty percent (n=15) of the patients who regularly listened or read COVID-19-related news stated that exposure to pandemic-related media had a moderate impact on their overall wellbeing. While 2% (n=1) of them reported that they were being severely, and 16% (n=8) mildly affected by the news. about COVID-19 outbreak. Seventy-eight percent of the participants in the study stated that they spent time with their families and took part in various activities during the day.

Attention deficit hyperactivity disorder (60%) was the most frequently encountered disease among the psychiatric diagnoses detected before the pandemic in the participants, followed closely by anxiety and related disorders (20%) and specific learning difficulty (16%). Frequencies of the other diagnostic categories are summarized in Table 3.

Table 3. Psychiatric diagnoses of the participants according to DSM-5.

	Completed psychiatric interviews n=50
Psychiatric Diagnoses, n (%)	
Attention Deficit Hyperactivity Disorder	30 (60)
Anxiety and Related Disorders	10 (20)
Specific Learning Difficulty	27 (54)
Mild Intellectual Disability	33 (66)
Communication Disorders	33 (66)
Tic Disorders	42 (84)
Post Traumatic Stress Disorder	3 (6)
Psychosis	8 (16)

Numbers and percentages are calculated separately for each activity accounting for comorbid diagnoses.

No difference was disclosed in the severity or the frequency of existing psychiatric complaints in 56% (n=28) of the participants. While 11 (22%) study participants reported an increase, and 6 (12%) of them stated a decrease in the severity or the frequency of their existing psychiatric symptoms . However, 10% (n=5) of the participants indicated alterations in their existing symptoms as increased irritability (n=4; 8%), decreased sleep time (n=2; 4%), increased anxiety (n=13; 26%) (n=13) increased anxiety, increased appetite (n=1; 2%) and an increase in activity (n=3; 6%).

Postliminary review of the patients' medical records revealed that selective serotonin reuptake inhibitors (SSRIs) (n=4; 8%), antipsychotics (n=2; 2%), stimulants (n=6; 28%), benzodiazepines (n=1; 2%) antipsychotics and SSRIs (n=2; 4%), antipsychotics and stimulants (n=3; 6%) were used by indicated number of the participants. Forty-four percent (n=22) of the cases disclosed that they were not prescribed any psychotropic medication. The mean CGI scores of the cases before, and during the pandemic were 2.72±0.75, and 2.92±0.94, respectively. The difference between the mean CGI scores was statistically significant (p=0.024).

When the participants were inquired concerning the activities they would prefer to do if they had the opportunity, going outside (n=12; 24%), spending time with friends (n=11; 22%), going to school (n=5; 10%), going to school and seeing friends (n=4; 8%), and "stopping the pandemic," were expressed by respective number of patients, while 4% (n=2) of the participants did not specify any activities.

DISCUSSION

It is clear that pandemic will have negative effects on children, irrespective of the presence of a a psychiatric diagnosis [12]. The closure of schools has disrupted both the social and academic lives of children and youth, contributing to the difficulty in maintaining healthy communication with their peers. Prolonged absence from school, being away from friends and teachers, being insufficiently informed about the pandemic or overexposure to pandemic related news, lack of personal space during the lockdown, and the economic burden of the epidemic adversely affected the mental health of children and young people [13].

Studies have indicated that an increase in fear

and anxiety, restlessness, difficulty focusing, refraining from fulfilling responsibilities, and sleep problems are among the reported emotional and behavioral adverse effects for school-age children [14]. In our study, in accordance with the literature, it was determined that there were changes in sleep patterns in 50% of our participants. Parallel to the established literature during the COVID-19 pandemic, during the lockdown period we noticed increased nervousness in 8% (n=4), increased anxiety in 26% (n=13), and increased levels of activity in 6% (n=3) of our patients. However, 39.2% of the participants (n=20) reported no change in their current psychiatric complaints.

It has been clearly demonstrated that the epidemic affects the mental health of both children and parents, but it has been also stated that the psychiatric dimension of the epidemic is very pronounced in people with psychiatric diseases [15]. When the psychiatric symptoms of the cases before and after the pandemic were compared, it was reported that the number of symptoms increased in 22% (n=11), decreased in 12% (n=6), and did not change in 10% (n=5) of the patients. The mean CGI scores of the cases before, and during the pandemic were 2.72±0.75, and 2.92±0.94, respectively with a statistically significant difference in support of the existing literature.

In a study conducted in Shanghai, China with a group of children and adolescents aged 6-17 years, a significant decrease in physical activity together with an increase in screen exposure during the epidemic was recorded. The role of physical activity in maintaining both the physical and mental health of children is well established [16]. In addition, the feelings of loneliness brought about by social isolation can adversely affect mental health [6]. Both a decrease in physical activity and an increase in perceived loneliness due to limited communication with peers would severely disrupt the daily routines of children and youth. However, these disruptions would affect children with ADHD more profoundly. Considering that the most common diagnosis in our sample was ADHD, an increase in our participants' reported symptoms might have been aggravated by the aforementioned factors.

A study in China reported that media entertainment, reading books, and physical exercise were successfully utilized by families to alleviate their children's distress and to relieve their worries about the unfavourable circumstances they experienced [17]. In our study, it was observed that most of the participants spent time playing games on the computer (54%) or social media (66%), while fewer participants spent time reading books (20%) or exercising (6%).

Our literature review revealed few studies on the psychiatric follow-up of the 7-12 age group during the pandemic period. During the pandemic, the mental health of both families and children, their sleep pattern, nutrition, and daily routines were adversely affected. Patients with mental disorders or disabilities require regular psychotherapy and psychiatric treatment. Therefore, the lack of access to healthcare services can adversely impact children and youth with mental health disorders due to delays in both diagnosis and treatment [18].

CONCLUSION

Our study emphasizes the importance of follow-up by telemental health practices in cases where face-to-face psychiatric interviews are not applicable due to the risk of transmission of COVID-19 disease in the current pandemic. The present study was conducted in the early stages of the pandemic; therefore, it would be appropriate to reevaluate the same group in later stages to assess for comorbid psychiatric diagnoses wrought on by the pandemic and associated social distancing, isolation, and lockdown practices. Since the closure of schools resulted in diminished social activities and less time spent with peer groups for children, while increasing time spent with parents resulting in parental fatigue, establishing multidisciplinary support groups and providing parental guidance would be blessing practices during these trying times. Furthermore, implementing and cultivating telemedicine as an evidence-based practice would also prove beneficial as a viable alternative to in-person psychiatric

interviews to prevent interruptions in the psychiatric care of children and youth.

Limitations

Patients aged between 7-12 years are accepted to our specialized polyclinics in The Child and Adolescent Mental Health Department of our university. However, the fact that preschool and adolescent groups were not included in our study constituted a limitation of our study.

Another limitation of the study is that the CGI scores before the pandemic were calculated retrospectively based on file information.

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Ethics Committee Approval: Ege University Medical Research Ethics Committee approval was obtained (10.06.2020/20-6T/48).

Conflict of Interest: The authors declared that there were no conflict of interest.

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Research Article

Does Prophylaxis Against Respiratory Syncytial Virus Infection Affect the Weight Percentiles of Infants with Hemodynamically Significant Congenital Heart Disease?

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Hazım Alper Gürsu

Respiratuvar Sinsityal Virüs Profilaksisi, Hemodinamik Olarak Önemli Konjenital Kalp Hastalığı Olan Bebeklerin Ağırlık Persentillerini Etkiler mi?

ABSTRACT

Objective: *The risk of severe respiratory syncytial virus (RSV) infection with significant morbidity and mortality is greatest in patients with hemodynamically significant congenital heart disease (hs-CHD). The humanized monoclonal antibody, palivizumab, was used as prophylaxis for RSV infection in children <24 months of age suffering from hs-CHD. We performed this study to evaluate the effects of RSV prophylaxis with palivizumab on the weight percentiles of infants with hs-CHD.*
Methods: *During the RSV seasons between 2013 and 2017, children <24 months of age with hs-CHD who received ≥3 doses of palivizumab prophylaxis were included in this study. All patients were evaluated according to their weight percentiles examined at birth, at the first, and the last dose of palivizumab prophylaxis. The third percentile was accepted as the cut-off value of the lower weight percentile, and values below the 25th percentile were accepted as poorly controlled hs-CHD.*
Results: *Sixty-one infants aged between 10 days and 15 months were included in the study. The infants received the first dose of palivizumab at the age of 5 months, and all infants received 4.56±0.78 injections on an average. The number of patients weighing lower than the 25th percentile at the first, and the last dose of palivizumab were 36 (59 %) and 29 (47.5 %), respectively. A statistically significant difference was found between weight percentiles of infants at the first and the last dose of palivizumab (p<0.05).*
Discussion and conclusion: *RSV prophylaxis with palivizumab affects weight percentiles positively, and it may help to reduce the hospitalization rate due to RSV infections in infants with hs-CHD.*

Keywords: *Congenital heart disease, RSV, palivizumab, weight percentile, infant*

ÖZ

Amaç: *Solunum Sinsityal Virüs (RSV) enfeksiyonu, hemodinamik olarak önemli konjenital kalp hastalığı (hö-KKH) olan bebeklerde önemli morbidite ve mortaliteye neden olabilir. Bir monoklonal antikor olan palivizumab, hö-KKH tanılı, 24 aydan küçük çocuklarda RSV enfeksiyonu profilaksi için kullanılmaktadır. Bu çalışmada, RSV profilaksisinin hö-KKH'li bebeklerin ağırlık yüzdelikleri üzerindeki etkilerini değerlendirmeyi amaçladık.*
Yöntem: *2013-2017 yılları arasındaki RSV mevsiminde ≥3 doz palivizumab profilaksisi alan 24 aydan küçük hö-KKH'lı çocuklar retrospetif olarak değerlendirildi. Prematüre doğan olgular, genetik sendrom tanısı, kronik akciğer hastalığı veya ek hastalığı olan hastalar çalışma dışı bırakıldı. Tüm hastalar doğumda, palivizumabın başlangıç ve son dozunda ölçülen vücut ağırlık persentiline göre değerlendirildi.*
Bulgular: *Çalışmaya 10 gün ile 15 ay arasındaki 61 olgu dahil edildi. Olguların 25'i (%41) erkek ve 36'sı (%59) kızdı. Olguların ilk palivizumab dozu uygulandığındaki ortanca yaşı 5 ay, ortalama uygulanan palivizumab dozu sayısı 4,56±0,78 idi. Vücut ağırlığı 25 percantil altı olan hasta sayısı Palivizumab ilk dozu uygulamasında 36 olgu/61 (59 %) olup son doz uygulamada ise 29/61 (% 47,5) idi. Palivizumabın ilk ve son dozlarında bebeklerin ağırlık yüzdelikleri arasında istatistiksel olarak anlamlı bir fark bulundu (p<0,05). 19 (%31,1) hastanın vücut ağılığı persantillerinde en az bir persentile ilerleme oldugu görülürken, 33 olgunun (%54) vucut ağırlığı persantilini koruduğu görüldü.*
Sonuç: *Bu çalışmada RSV profilaksi alan hastaların yaklaşık 1/3'ünün vucut ağılığı percantillerinde en az bir percentile ilerleme olduğu görülürken, hastaların yaklaşık yarısının vücut ağırlığı persantilini koruduğu gösterildi. RSV profilaksisi hö-KKH'lı bebeklerde RSV enfeksiyonlarına bağlı hastanede yatış oranını azaltmaya ve ağırlık persentillerini olumlu etkilemeye yardımcı olabilir.*

Anahtar kelimeler: *Konjenital kalp hastalığı, RSV, palivizumab, ağırlık persentili, infant*

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INTRODUCTION

Respiratory syncytial virus (RSV) is the common pathogen of lower respiratory tract infections in childhood and causes up to 200.000 infant deaths per year worldwide [1]. It is reported that RSV-related hospitalizations lead to increased morbidity and mortality rates in children with hemodynamically significant congenital heart disease (hs-CHD) compared with healthy children [1,2]. The prevention of RSV infections in infants with hs-CHD has been an important goal in the follow-up of these patients [2,3].

RSV infections in infants with CHD increase the rates of hospitalizations, intensive care unit stays, and the requirement for supportive treatments, as well as causing malnutrition by reducing infant's ability to benefit from sufficient amount of breast milk. These disadvantages may cause weight loss, and growth retardation and developmental delay [4,5]. Corrective cardiac surgery may be delayed because of poor nutritional status of the patient.[4-6]. Although studies conducted in developed countries have reported that growth returns to normal after early corrective surgery, it has been shown that malnutrition problems can persist at a high rate in children even after surgery in developing countries [4,5]. Protecting against RSV infection allows for surgery to be performed at the scheduled time and prevents development of these negative consequences as well [5,6].

Palivizumab (Synagis®, Abbvie, Turkey), a monoclonal antibody against the RSV fusion (F) protein, was approved by the United States Food and Drug Administration in 1998 for immunoprophylaxis against RSV in "high-risk pediatric patients." In 2006, the American Academy of Pediatrics (AAP) released a clinical practice guideline recommending palivizumab prophylaxis against RSV for those children identified as high risk based on available data. Updated guidelines, published in July 2014, has recommended palivizumab immunoprophylaxis for all children with hs-CHD [1,3]. Several randomized controlled trials have reported that palivizumab which is also a cost-effective prophylactic modality, reduced RSV-related hospitalizations in children with hs-CHD [2,7-9]. However, no studies have so far been published on the assessment of the weight status of patients, which would suggest good clinical outcomes. The aim of this study was to evaluate the effects of RSV prophylaxis with palivizumab on weight percentiles of infants with hs-CHD.

MATERIAL and METHOD

Study design and population

We retrospectively evaluated the effects of RSV prophylaxis with palivizumab on the weight percentiles of infants with hs-CHD at our Pediatric Cardiology Department between October 1st, 2013, and March 31st, 2017. The study involved children with hs-CHD aged <24 months who received ≥3 doses of palivizumab prophylaxis during the RSV season.

The diagnosis of hs-CHD was provided based on uncorrected or palliated cyanotic or acyanotic disease associated with documented pulmonary hypertension (more than 50% higher than the age-adjusted systemic pressure) and/or requirement for daily medication to manage congestive heart failure. Patients with a genetic syndrome, prematurity, chronic lung disease, or additional disease were excluded from the study.

The medical records of the patients were evaluated retrospectively in terms of patient demographics (age, sex), baseline clinical characteristics (weight, weight percentile, type of CHD and related medical/surgical treatments, heart failure, comorbidities), the age of the patients at the first dose of palivizumab, the duration, and frequency of hospital stays, intensive care unit (ICU) admissions, length of ICU stay, requirement for mechanical ventilation, and mortality.

Palivizumab prophylaxis

The time interval between October 1st and March 31st was accepted as the RSV season. Palivizumab was administered intramuscularly for RSV prophylaxis at monthly doses of 15 mg/kg between October and March. The patients were divided into two groups

according to age of the patients at the first dose of palivizumab as Group 1 (0-6 months) and Group 2 (>6 months), and the two groups were compared and statistically analyzed.

Evaluation of weight percentiles

The recorded weight measurements of patients on each following visit were evaluated, and weight percentiles were calculated according to weight percentile values for Turkish children [10]. All patients were evaluated according to their weight percentiles at birth and at the time when they received the first and last doses of palivizumab. The third percentile was accepted as the cut-off value of the lower weight percentile [10]. In addition, values below the 25th percentile were accepted as an indication of a poorly controlled disease. Thus, weight percentile changes during the palivizumab administration period were evaluated and grouped as consistent, and increased or decreased weight percentiles.

Ethical considerations

Ethics approval was obtained from the Ethics Committee (No: 2018-102, Date: 06.25.2018). The procedures undertaken by participants were performed after obtaining informed consent from the parents.

Statistical analysis

Statistical analyses were performed using the SPSS version 16.0 software package (SPSS, Inc., Chicago, IL, USA). Qualitative and quantitative (continuous) variables are shown as the number of cases (n), percentages (%), and mean±standard deviations (SD), respectively. Freidman test was used to analyse the consecutive body weights. Wilcoxon's signed-ranks test was used for the comparison of weight percentiles at the first and last doses of palivizumab, and the Kruskal-Wallis test was used for the comparison of weight percentiles according to the number of doses. Pearson's correlation analysis was used to examine the relationship between variables of interest. A p-value of <0.05 was accepted as statistically significant.

RESULTS

This study involved 61 infants aged between 10 days and 15 months. The demographic features of the patients are given in Table I. There was a female predominance [25 males (41%) and 36 females (59%)]. The median gestational age was 38 weeks and ranged between 37 and 41 weeks. All patients were fed orally. No patient was given protein or calorie supplements during follow-up period.

Table 1. Demographic features of the patients.

	Median	Range (min-max)
Gestational age (week)	38	37-41
Age	5 months	10 days-15 months
Birth Weight (gr)	3000	2130-4000
	Number	**(%)**
Age at the first palivizumab dose		
0-6 months	40	65
>6 months	21	35
Number of palivizumab administrations		
3 doses	9	13
4 doses	9	13
5 doses	43	74

The most common cardiovascular diagnosis was ventricular septal defect (VSD) (n=29, 47.5%), followed by atrial septal defect (ASD) (n=21, 34%), tetralogy of Fallot (n=6, 9.8%), patent ductus arteriosus (n=3, 4.9%), and atrioventricular septal defect (AVSD) (n=2, 3.2%).

The median age of the infants at the first dose of palivizumab was 5 months (range, 10 days-15 months). Most of the patients (n=40, 65.6%) were aged under 6 months when they received their first dose of palivizumab. The number of palivizumab doses ranged between 3 and 5 (mean±SD: 4.56±0.78). Most of the patients (n=43, 70.5%) received five doses of palivizumab. A total of 278 doses of palivizumab were injected.

The birth weights of the patients ranged between 3rd and 50-75th percentiles (median: 10-25th percentile). The distributions of the weight percentiles of the patients at birth, and at the first and the last doses of palivizumab are shown in Figure 1. At birth,

9 (14.7%), patients had weight percentiles <3rd, and weight percentiles of 31 (50.8%) patients were lower than the 25th percentile. At the first dose of palivizumab, 5 (8.2%), patients had weight percentiles <3rd, and weight percentiles of 36 (59%) patients were lower than the 25th percentile. At the last dose of palivizumab, 8 (13.1%), patients had weight percentiles <3rd and weight percentiles of 29 (47.5%) patients were lower than the 25th percentile.

The changes of the weight percentiles of the patients at the birth, the first and the last doses of palivizumab are shown in Figure 2. The weight percentiles at the last dose of palivizumab in 19 (31.1%) patients showed at least one level improvement and 33 (33/61:54%) patients maintained their percentile value. There was a decline in the weight percentile at least one level of nine patients. A statistically significant difference was found between the weight percentiles at the first and last doses of palivizumab (p=0.03). There was no statistically significant difference for weight percentile change according to age at the first dose of palivizumab between Group 1 (0-6 months) and Group 2 (>6 months) (p>0.05). There was no statistically significant difference between the group

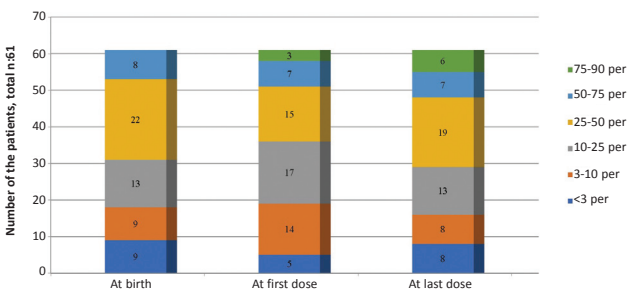

Figure 1. The distributions of the weight percentiles of patients at birth, and the first and the last dose of palivizumab.

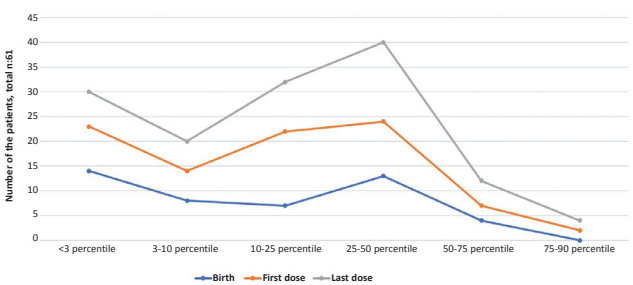

Figure 2. The changes of the patient's weight percentiles of patients at birth, the first and the last dose of palivizumab.

given five (n=43), and three or four doses (n=18) of palivizumab in terms of weight percentiles (p>0.05).

Six (9.8%) patients including 3 cases with VSD, and 3 cases with ASD were hospitalized due to lower respiratory tract infection. Five of the six patients were younger than 6 months (Group 1), the other patient (ASD) was 12 months old. The median hospitalization period was 6 (range, 3-10) days. Only one 2-month-old infant with VSD needed hospitalization in the intensive care unit for 4 days. None of the patients required mechanical ventilation support or exited. Five of the six patients who were five had lower weight percentiles <10th hospitalized, percentile.

DISCUSSION

Children with hs-CHD are at major risk for hospitalization due to respiratory diseases, particularly acute bronchitis and bronchiolitis [1,2]. RSV-related hospitalization has led to increased morbidity and mortality rates in children with hs-CHD [11,12]. RSV is a common pathogen in respiratory tract infections in childhood. Patients with hs-CHD are at risk for RSV-associated lower respiratory tract infections, changes in respiratory mechanisms, pulmonary hypertension, and cyanosis, and ventilation-perfusion mismatch can worsen the effects of respiratory illness with higher morbidity rates than in the general pediatric population [7,12]. Therefore, prevention of RSV in patients with hs-CHD has been an important goal. Although the relevant literature involves several studies that evaluated the cost-effectiveness of RSV prophylaxis, no studies have so far directly evaluated the weight trend of infants with hs-CHD under RSV prophylaxis [2,8,9]. The present study has showed that RSV prophylaxis with palivizumab had positive effects on weight percentiles in infants with hs-CHD.

Children with CHD can experience nutritional deficiencies during follow-up due to many factors such as low energy intake, hypermetabolism, prenatal factors, and infections [4,13]. Chromosomal anomalies or genetic diseases and additional acute-chronic diseases that accompany CHD may contribute to

growth retardation. In the present study, patients with a genetic syndrome, prematurity, chronic lung disease or comorbidities were excluded from the study to avoid bias. In addition, all patients were fed orally and no patients were given caloric support during follow-up. Many studies have emphasized that growth retardation with varying degrees of severity can be seen in different types of congenital heart defects [14,15]. In fact, malnutrition, additional infections, and hospitalization cause infants with hs-CHD to lose weight, which may affect the clinical course and the planned surgery time [14,16]. In the present study, when the weight percentiles were evaluated at the last dose of palivizumab, more than half of the patients maintained their percentile values and one-third of all patients showed at least one level improvement of their weight percentiles. In addition; at the first dose of palivizumab 36 (36/61: 59%), and at its last dose decreased number of patients (n=29: 47.5%) had weight percentiles lower than the 25th percentile A decline in weight percentiles over time was seen only in nine (14.7%) patients. Therefore, RSV prophylaxis with palivizumab may positively affect weight percentiles in children with CHD.

To date palivizumab remains the only approved strategy to protect against RSV. The AAP released a clinical practice guideline recommending palivizumab prophylaxis against RSV for children identified as high risk based on available data and revised their guidelines in 2014, narrowing indications for palivizumab prophylaxis to children aged <12 months with hs-CHD [3]. In Turkey, palivizumab was licensed in 2010, and palivizumab prophylaxis is administered to children with hs-CHD aged <24 months. Studies are showing that RSV prophylaxis administered before 12 months of age is more effective compared with older infants. We administer palivizumab prophylaxis to patients with hs-CHD aged <24 months in our clinic. In the present study, 40 (65.6%) patients were younger than 6 months and only four were older than 12 months when they received their first dose of palivizumab. In the present study, improvements in the weight percentiles of the patients at the first dose of palivizumab were compared according to age and any statistically significant differences were not found between receivers of palivizumab prophylaxis aged 6 months or older in terms of improvements in their weight percentiles.

Palivizumab prophylaxis for RSV has been reported to reduce the risk of hospital admissions related to RSV infection in children with symptomatic cardiac disease [7,17,18]. The incidence rates of RSV-related hospitalizations in hs-CHD were 12% in infants aged <6 months, 7% between 6-12, and 4% between 12-24 months [19]. Although the related literature involves several studies that evaluated the cost-effectiveness of RSV prophylaxis, no studies have directly evaluated the weight trend of infants given RSV prophylaxis [8,9]. The study by Tavsu et al. included infants with gestational age less than 32 weeks, and they reported that palivizumab reduced incidence of RSV infections and hospitalization rates in both the prophylaxis season and the following year, but without any effect on infant development or anthropometric indices [20]. In our study, we found that RSV prophylaxis with palivizumab had positive effects on weight percentiles in infants with hs-CHD. The last dose of palivizumab showed at least one level improvement of weight percentiles in 19 patients, and 33 of 61 patients maintained their weight percentiles. The hospitalization rate in the present study was 9.8% (6/61), similar to those reported in the literature. Only one patient received intensive care treatment without mechanical ventilatory support and there was no exitus. However, five of the six patients who were hospitalized due to respiratory tract infection were aged younger than 6 months and five had weight percentiles <10th percentile. Therefore, it may be thought that improvement of nutritional status in patients with CHD can help to prevent hospitalization.

Study limitations

The present study has some important limitations because of its retrospective design and small sample size. First, there was no control group to compare the improvement in weight percentiles. We did not have a control group because palivizumab has been

given to all infants aged under 24 months with CHD in our clinic since 2010. Secondly, the sample of the present study consisted of patients with different ages and the etiology of CHD was heterogeneous. Although the use of palivizumab cannot be recommended for all patients with CHD, current guidelines about RSV prophylaxis recommend giving palivizumab to patients with hemodynamically significant CHD. The population of the present study was chosen according to this most recent guideline and all of them had hemodynamically significant CHD. Another limitation of the study is that not all patients received five doses of prophylaxis. It can be speculated that if all patients could receive five doses, their weight percentiles might have shown greater improvement. The last and the most important limitation is that the main factors affecting weight gain, such as daily energy intake and nutritional ingredients of infants, were not evaluated. Although other than the vaccine, many factors related to the infant and family can affect growth and weight gain, it was not possible to evaluate them in detail due to the retrospective design of our study. Nevertheless, most of the patients admitted to our hospital have a similar low-moderate socioeconomic status due to the location of our hospital. Therefore, it can be thought that the socioeconomic conditions that affected the growth of the patients were similar in our sample. Larger, multicentered, and well-designed future studies evaluating weight and growth parameters and nutritional condition are required to evaluate the effects of RSV prophylaxis with palivizumab on weight percentiles of children with CHD.

CONCLUSION

Pediatric patients with CHD tend to have malnutrition and growth retardation. Direct evaluation of the weight gain trend in these infants may better reflect clinical outcomes, which may be used as a predictor for the follow-up of these infants. Additionally, weight gain is accepted as an important factor for estimating the optimal timing of surgery. The weight gain trend of patients with CHD should be evaluated at each follow-up visit to the cardiology department. The present study showed that RSV prophylaxis with palivizumab effected weight percentiles positively in infants with CHD. Although our patient sample was too small to claim this absolutely, shorter hospitalization period and good weight gain may be considered to affect patients' general health state favorably with an advantage of faster recovery. Palivizumab prophylaxis for RSV is recommended to decrease morbidity and mortality rates of RSV in children with CHD.

Ethics Committee Approval: Ankara Pediatrics, Hematology Oncology Training and Research Hospital, Ethics approval was obtained from the Ethics Committee (06.25.2018-102).
Conflict of Interest: The authors declare that there is no conflict of interest in this paper.
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Informed Consent: Obtained.

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Research Article

Congenital Neutropenia in Children: Evaluation of Infectious Complications, Treatment Results and Long-Term Outcome

Konjenital Nötropenili Çocuklarda Enfeksiyon Ataklarının, Tedavi ve Uzun Dönem Sonuçlarının Değerlendirilmesi

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ABSTRACT

Objective: *Infections are an important cause of morbidity and mortality for patients with congenital neutropenia. In the present study, we report on the incidence, type, localization of documented infections, as well as the clinical features and long-term outcome in patients with congenital neutropenia in our clinic.*
Method: *We performed a retrospective chart review of children with neutropenia seen at our hospital from 2000-2018. The data of 15 patients with congenital neutropenia were included in this study. Clinical and laboratory data were analyzed retrospectively using patients' files and an electronic data system.*
Results: *The median age at diagnosis was 34 months (range, four months- 150 months) and the median follow-up time was 48 months (range, 13-179 months). The leading causes of hospital admission before the establishment of the diagnosis were upper respiratory tract infection in six, pneumonia in four, gingival stomatitis in three and soft tissue infection in two patients. We reached the documented 74 hospitalization episodes and the most common reasons for hospitalization were pneumonia (35%), fever (21%), stomatitis (16%), cutaneous and deep soft tissue infections (12%).*
Conclusion: *The management of infectious complications in children with congenital neutropenia is crucial. Early diagnosis is essential to prevent infections and permanent organ damage. Congenital neutropenia should be suspected in patients with a history of frequent upper respiratory tract infection, and necessary investigations should be performed accordingly. However, it should be kept in mind that the clinical findings of the patients may vary despite having the same mutation.*

Keywords: *Congenital neutropenia, infection, neutropenia, children*

ÖZ

Amaç: *Enfeksiyonlar konjenital nötropeni hastalarında önemli bir morbidite ve mortalite nedenidir. Bu çalışmada konjenital nötropeni hastalarının geçirdiği enfeksiyon ataklarının sıklığını, tipini ve bölgesini klinik bulgular ve uzun dönem sonuçları ile birlikte değerlendirdik.*
Yöntem: *Hastanemizde 2000-2018 yılları arasında konjenital nötropeni tanısı ile takip edilen 15 hasta çalışmaya alındı. Hastalara ait klinik ve laboratuvar bilgileri hasta dosyaları ve elektronik kayıt sistemi kullanılarak retrospektif olarak incelendi.*
Bulgular: *Çalışmaya dahil edilen 15 hastanın (6 erkek, 9 kız) medyan tanı yaşı 34 ay (aralık, 4 ay - 150 ay), medyan izlem süresi 48 ay (aralık, 13 ay -179 ay) idi. Hastaların tanı öncesi en sık hastaneye başvuru nedeni 6 hastada üst solunum yolu enfeksiyonu, 4'ünde alt solunum yolu enfeksiyonu, 3'ünde stomatit ve 2'sinde cilt bulguları idi. Yetmiş dört hastane yatış episoduna ulasıldı. En sık hospitalizasyon nedeni alt solunum yolu enfeksiyonu (%35), ateş (%21), stomatit (%16), cilt ve derin doku enfeksiyonu (%12) idi.*
Sonuç: *Konjenital nötropenili hastalarda enfeksiyonların yönetimi çok önemlidir. Erken tanı, enfeksiyon ataklarını ve kalıcı organ hasarını önlemek için gereklidir. Sık üst solunum yolu enfeksiyonu geçiren hastalarda konjenital nötropeniden şüphelenilmeli ve gerekli araştırmalar yapılmalıdır. Aynı mutasyonu taşımalarına rağmen klinik bulguların değişken olabileceği akılda tutulmalıdır.*

Anahtar kelimeler: *Konjenital nötropeni, infeksiyon, nötropeni, çocuk*

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INTRODUCTION

Congenital neutropenia (CN) is defined as chronic neutropenia that arises from a constitutional genetic defect. Severe congenital neutropenia (SCN) and cyclic neutropenia (CyN) are two major types of CN encountered in childhood [1]. Because of the rare onset of SCN, its epidemiology, prognosis and clinical manifestations have not yet been fully understood [2]. SCN encompasses a group of disorders that are characterized by peripheral neutrophil counts of $<0.5\times10^9$/L, early-onset recurrent bacterial infection and bone marrow maturation arrest of myelopoiesis at the promyelocyte/myelocyte stage [2]. Different mutations in the neutrophil elastase gene (ELANE) are responsible for the majority of the patients. Other gene mutations associated with SCN are in the genes of HAX-1, G6PC-3, GFI-1, WAS, JAGN and GATA-2. In addition, the glycogen storage disease type Ib (GSD-Ib) is a metabolic disorder that may cause congenital neutropenia [3].

Infections are an important cause of morbidity and mortality in patients with CN. Before the availability of G-CSF treatment, almost all the patients with severe neutropenia died in the first two years of life due to infectious complications. The management of the disease changed with the administration of broad-spectrum antibiotics and G-CSF treatment. Despite these novel treatment strategies, infections are still a significant problem for this group of patients. Patients have frequently been suffering from severe and recurrent bacterial infections that may affect the skin, lungs and deep tissues [1,3].

In the literature, there are few studies investigating the type and frequency of infections in children with CN [1,4], which has remained under-researched. In the present study, we report on the incidence, type, localization of documented infections, the clinical features and long-term outcome in patients with CN.

MATERIAL and METHODS

Collection and Analysis of Clinical Data

We performed a retrospective chart review of children with neutropenia seen at our hospital from 2000-2018, using patients' files and an electronic data system. The data of 15 patients with congenital neutropenia were included in this study. We collected clinical data, including age, sex, absolute neutrophil count (ANC), genetic mutation analysis, treatments received, infectious complications and outcome.

Definitions

Neutropenia: Neutropenia is defined as mild if circulating neutrophils are between 1.0 and $1.5x10^9$/L, as moderate if between 0.5 and $1.0x10^9$/L, and severe if below $0.5x10^9$/L. Neutrophil counts below $0.2x10^9$/L are defined as very severe congenital neutropenia. SCN is an immunodeficiency diagnosed using modified conventional criteria includes; onset at early ages, primary myelopoiesis failure with an absolute neutrophil count (ANC) $<0.5x10^9$/L, severe infections and risk of leukemic transformation [3].

Mutations Analysis: In this study, analysis of genetic mutations causing SCN was performed. DNA was extracted from a 200- µL peripheral blood sample using the QIAamp DNA blood Mini QIcube Kit with a QIcube instrument (QIAGEN, Hilden, Germany) according to the manufacturer's specifications. Analysis of sequencing data were conducted by using the Integrative Genomics Viewer (Thorvaldsd ottir et al., 2013).

Statistical Methods

The data were analyzed using SPSS Statistics 17.0 (International Business Machines Corp, Armonk, NY). The Kolmogorov-Smirnov test was used to investigate whether the distribution of continuous variables was approximately normal, and the Levene test was used to investigate whether the assumption of homogeneity of variance was met. Baseline characteristics were given as medians and interquartile ranges (IQRs) for continuous variables, and numbers of cases and percentages were calculated for categorical variables. To conduct this study, ethical approval was obtained from the local ethics committee of Dr. Behcet Uz Children's Hospital.

Table 2. The Clinical and Laboratory Characteristics of the Patients

Patient	Age at diag. (month)/Sex	ANC at diag.×10^9/L	Genetic Mutation	Infection Leading to the Diag.	Follow-up duration (month)	G-CSF Treat.	Episode of hosp.	Type of Infections	Bacterial culture growth	Episode of hosp. Per month
P1	90/F	0.20	-	URTI	122	-	1	Pneumonia	ND	0.008
P2	11/M	0.30	HAX-1 c.130-131insA (homozygous)	HLH secondary to CMV infection	108	Continue	5	Hlh Pneumonia Anal abscess Stomatitis	ND	0.04
P3	76/M	0.15	HAX-1 c.130-131insA (homozygous)	Pneumonia	141	Continue	8	Pneumonia Fever Cellulitis Tonsillitis	HC (-) UC (-) Wound culture: Staph aureus	0.05
P4	84/M	0.20	HAX-1 c.130-131insA (homozygous)	HLH secondary to EBV infection	141	Continue	10	Fever Stomatitis Viral infection Pneumonia EBV-HLH	HC (-) UC (-)	0.07
P5	33/M	0.38	-	AGE	42	Continue	3	Pneumonia Fever	HC (-) UC (-)	0.07
P6	34/F	0.20	-	Stomatitis	38	-	3	Fever URTI	HC (-) UC (-)	0.07
P7	11/F	0.30	HAX-1 c.130-131insA (homozygous)	Pneumonia	48	-	6	Pneumonia Stomatitis	ND	0.12
P8	75/F	0.47	HAX-1 c.130-131insA (homozygous	Pneumonia	19	-	4	Pneumonia Abscess	UC (-) Wound culture: Staf aureus	0.21
P9	77/F	0.50	HAX-1 c.130-131insA (homozygous)	Stomatitis	43	-	None	-	ND	0
P10	150/F	0.20	HAX-1 c.130-131insA (homozygous)	Cutaneous Abscess	28	Continue	14	Pneumonia Inguinal abscess	HC (-)	0.5
P11	11/M	0.20	ELANE 19p13.3	Preseptal selulitis	16	Continue	9	Fever Cellulitis Stomatitis Abscess Otitis Pneumonia URTI	HC (-) Wound culture: Staf aureus	0.56
P12	8/F	0.48	ELANE c.254 G A (heterozygous)	Cutaneous Abscess	14	-	1	Anal abscess	HC (-)	0.07
P13	5/M	0.07	SLC37A4 Glycogen Storage Type 1	Pneumonia	137	Continue	7	Fever Pneumonia	ND	0.05
P14	4/F	0.20	G6PC3 IVS3-1 GC (g.4234G C) (homozygous)	Pneumonia	179	Continue	13	Fever Acute Gastroenteritis Pneumonia	HC (-) UC (-)	0.07
P15	51/F	0.15	-	Stomatitis	91	Continue	3	Stomatitis Fever	HC (-) UC (-)	0.03

CN; congenital neutropenia, ANC; absolute neutrophil count, G-CSF; granulocyte colony-stimulating factor, MDS; myelodysplastic syndrome, AML; acute myeloid leukemia, URTI; upper respiratory tract infection, HLH; hemophagocytic lymphohistiocytosis, CMV; cytomegalovirus, EBV; Epstein–Barr virus, AGE; acute gastroenteritis, HC; hemoculture, UC; urine culture, (–); negative, (+); positive, ND; not done.

RESULTS

Fifteen patients (six boys, nine girls) with CN were analyzed retrospectively in this study. The median age at diagnosis was 34 months (range, four months-150 months), and the median follow-up time was 48 months (range, 13-179 months). Nine of the 15 patients were from the consanguineous marriage. Skeleton dysplasia was not observed in any of them. The detected mutations were HAX-1 in seven (46%) patients, ELANE in two patients (13%), G6PC3 in one patient (6%) and SLC37A4 in one patient (6%). None of the mutations related to the SCN was detected in four patients (26%). The median ANC at diagnosis was 0.29×10^9/L ($0.07\text{-}0.43\times10^9$/L). The main causes of hospital admission before the establishment of the diagnosis were upper respiratory tract infection (URTI) in six patients, pneumonia in four patients, gingival stomatitis in three patients and soft tissue infection in two patients. The number of patients were diagnosed while being treated for other diseases was as follows: Five patients during pneumonia treatment, three patients during stomatitis treatment, two patients during skin abscess treatment, one patient during acute gastroenteritis treatment and one patient during URTI treatment. The congenital neutropenia (CN) was diagnosed in two patients when they presented with the clinical manifestation of hemophagocytic lymphohistiocytosis (HLH), which was secondary to viral infection (CMV and EBV). The clinical and laboratory characteristics of the patients are presented in Table 1 in summary.

Fourteen (93%) of the patients were hospitalized with infection at least once in a lifetime. No hospitalization was required for one patient (P9) during the follow-up. However, this patient had to use oral antibiotics due to chronic gingivitis, otitis, and recurrent stomatitis attacks. The mutation analysis and neutrophil count of her confirmed the diagnosis of CN. The total hospitalization period of patients contained 662 days and 87 infection episodes. We obtained 74 hospitalization episodes. We were able to access information on seventy-four hospitalization episodes, which were due to infections. The most common reasons were pneumonia (35%), fever (21%), stomatitis (16%), cutaneous and deep soft tissue infections (12%). These episodes accounted for 84% of the total. Blood culture samples were taken from nine patients during their hospitalization periods, and no bacterial growth was detected in any of them (Table 1). Due to early-onset recurrent lung infections before the diagnosis, bronchiectasis developed in one patient (P10) who suffered from severe pneumonia frequently. On the other hand, with the initiation of G-CSF treatment, pneumonia attacks of her were relatively diminished. Sixty percent of all patients (9/15) were treated using G-CSF. An initial dose of G-CSF was 3 mcg/kg/day, and the dose was subsequently modified according to the patient's response. Target ANC level was $1\text{-}5\text{x}10^9$/L. The mean dose of G-CSF was 3.5±0.69 (max: 10) mcg/kg/day; the mean administration duration was 49.8±18.8 (max: 139) months. Despite the administration of high-dose G-CSF treatment (10 mcg/kg/day), P11 did not respond and achieved ANC $>0.5\times10^9$/L. He continued to suffer from severe infections. Therefore, hematopoietic stem cell transplantation (HSCT) from a sibling donor was performed. He was alive after ten months of the HSCT. Yearly bone marrow surveillance was performed for each patient under G-CSF treatment. Morphological evaluation and genetic analysis, including trisomy 8, 5p deletion, 20q deletion, 7q deletion, were taken to determine myelodysplastic syndrome/acute myeloid leukemia (MDS/AML). None of the patients developed MDS/AML during follow-up. No death due to infections or any other cause was encountered in any of the patients during their follow-up.

DISCUSSION

Infections are the major and life-threatening complications of patients with CN. Currently, with the new treatment strategies, the quality and duration of life have improved [3]. Although G-CSF administration is associated with decreased frequency and severity of infections, there are few studies documenting the clinical characteristics of

infections [1,4]. In our study, the median age at diagnosis was 34 months (range, four months- 150 months), and it was older compared with the other studies [1,5-7]. In the literature, most of the patients were diagnosed at an early age because of the encountered infections at unexpected sites [1,4]. According to Fioredda et al. [5], the median age at diagnosis was eight months. On the other hand, the average age at diagnosis was determined as 16.5 months and 25.8 months in studies conducted in our country [8,9]. Given the studies conducted in Turkey, it is seen that the average age at diagnosis is relatively high. Possible underlying reasons for this delay can be explained as follows: Complete blood count (CBC) may not require due to mild symptoms at the patient's admission or the Absolute Neutrophil Count (ANC) in the complete blood count may be high due to the patient's ongoing infection, and the diagnosis may therefore have been overlooked or although the ANC value of the patient is low, this situation may be linked with neutropenia related to infection. Thus, CN has not been considered in the differential diagnosis. Lastly, the diagnosis of CN may be considered and the parents may have been informed accordingly. However, despite this, they might not have been applied to the hematology clinic. We investigated the clinical features of the patients with CN who were followed up in our clinic. The main cause of hospital admission before establishing the diagnosis was URTI, which was consistent with a previous report that described all seven patients who suffered from recurrent URTI during the first six months [1]. In a study in which chronic severe neutropenia cases were examined, URTIs were the most common cause of complaints [2].

Seventy-four hospitalization episodes were observed, and the most common causes of hospitalizations were pneumonia, fever and stomatitis, respectively. In other studies, cutaneous and soft tissue infections, pneumonia and fever were reported as the most common causes [1,4]. However, a small part of our patients (12%) had cutaneous and soft tissue infections. The most common pathogens causing infections in neutropenic patients are S. au¬reus and gram-negative bacteria [10]. No bacterial growth was detected in the blood culture sampling results of any patient during the follow-up. However, S.aureus was isolated from wound culture samples taken from three patients with a diagnosis of soft tissue infection. In a previous study, gram-negative rods were the most common source of infection in patients diagnosed with CN [10]. Interestingly, there is only one case series, which includes our two patients with CN that arise from HAX1 mutation who have presented with HLH [11]. Authors explained this by mutations in the HAX1 gene severely diminish the function of HCLS1, which plays an essential role in G-CSF-mediated granulopoiesis.

CN is a genetically heterogeneous disorder. More than 20 gene mutations, including HAX, ELANE and G6PC3, have been demonstrated. However, 25% of the CN patients' genetic basis remains unknown [12-15]. Similarly, 26% (4/15) of our patients' mutation was not able to be determined. ELANE mutation, an inherited autosomal dominant condition, is responsible for 50-60% of patients [16-20]. However, approximately 50% of our patients had HAX -1 mutation, as compatible with the national data of our country [9]. This finding can be explained by the consanguinity between our patients' parents. Three of seven patients (P7, P8 and P9) with HAX-1 mutation were the same family members. Despite having the same HAX-1 mutation, these three patients had different clinical features concerning infection frequency. This finding suggests that besides mutations, environmental and epigenetic factors may also play a role in clinical features [10]. Patients progressing with varying clinical courses despite carrying the same mutation have also been reported in the literature [8]. Glycogen storage disease type Ib (GSD-Ib) is a metabolic disorder that may cause severe congenital neutropenia. It is characterized by neutropenia and myeloid dysfunctions. Despite the large knowledge about the metabolic component of the disease, the pathophysiology of neutropenia has been unclear. Patients can be treated with G-CSF to prevent severe infections. In the literature, patients with GSD-1b have been reported to develop AML [21]. We have one GSD-1b patient (P13), and he has been

under treatment of G-CSF. With the regular bone marrow examinations, AML/MDS has been excluded.

It was proven that in the management of CN, G-CSF is an effective first-line treatment for preventing life-threatening infection complications at the dose of 3-10 mcg/kg/day. The Severe Chronic Neutropenia International Registry (SCNIR) reported that 95% of the patients with SCN responded to G-CSF treatment [10]. Sixty percent of our patients were under treatment of G-CSF, and most of them (except two patients) responded as clinical and laboratory to the treatment in our study. Despite being under the treatment of G- CSF, one patient (P14) had several episodes of infections. This can be explained by that neutrophil functions are not completely normal despite the increase in neutrophil counts with G-CSF [22,23]. On the other hand, permanent organ damage, such as chronic inflammatory bowel disease, may lead to additional co-morbidities to increase the amount of recurrent infections and hospitalizations. HSCT was not considered in this patient. Because although he had been continued to suffer from infection attacks, none of them was severe and his clinical course was milder. Despite the administration of G-CSF at 10 mcg/kg/day, one patient (P11) continued to have severe infections, and during follow-up, his ANC level was below $0.5x10^9$/L. Therefore, HSCT was performed.

Although the average survival in these patients has reached 80% with the new developments, approximately 10% of them are still dying due to sepsis. During our study, we did not encounter any sepsis-related deaths. In a study, it was reported that six of 101 patients died because of sepsis and severe infections, while in this case series, no patient was treated using G-CSF [6].

SCN is a premalignant disease, and that this risk is increased by G-CSF administration. Leukemic progression in SCN is strongly associated with acquired somatic mutations in the CSF3R (Colony Stimulating Factor 3 Receptor) gene, which encodes the G-CSF receptor [20]. In our study, the mean G-CSF dosage was 3.5±0.69 mcg/kg/day (max: 10 mcg/kg/day); the mean administration duration was 49.8±18.8 months (max: 139 months). None of our patients developed MDS/AML, while we could give 10-year survival rates in the future. SCNIR data demonstrated that the cumulative incidence of MDS/AML in the 15-year follow-up was 22% [24,25]. This rate was reported at 11% and 31% in the French Severe Chronic Neutropenia Registry (SCNFR) and the Swedish Registry, respectively. However, the effects of duration and dose on this development are not clear. In recent studies, patients requiring greater than 8 µg/kg/day of G-CSF had a cumulative incidence of MDS/AML of 40% after 10 years [10].

In conclusion, CN is a rarely encountered clinical picture. The management of infectious complications in CN is vital. Early diagnosis is crucial to preventing infections and permanent organ damage. The history of having frequent URTIs may be the first clue to consider the diagnosis of CN in these patients. However, it should be kept in mind that the clinical findings of the patients may vary despite having the same mutation.

This study has some limitations due to its retrospective design. First of all, cases with CN were reviewed from the medical files and electronic data of the patients. However, we confirmed the infections from the microbiology laboratories, especially for bloodstream infections and the radiology department for pneumonia.

Ethics Committee Approval: S.B.Ü. Izmir Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Ethics Committee approval was obtained (2021/477).

Conflict of Interest: The authors declare that there is no conflict of interest in this paper.

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Research Article

An Investigation of the Quality of Life Regarding Some Demographic Charecteristics of Children with Cancer Aged Between 2 and 7 Years

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İki-Yedi Yaş Arasındaki Kanserli Çocukların Yaşam Kalitelerinin Çocuklara Ait Bazı Özellikler Açısından İncelenmesi

ABSTRACT

Objective: *This is a descriptive study investigating the quality of life among hospitalized children aged 2-7 years with cancer by some of their characteristics.*
Method: *The sample of the present study consisted of the mothers of children aged 2-7 years who were hospitalized in oncology clinics of two university hospitals in Ankara, diagnosed with cancer at least six months ago, and had no major physical and motor development disorders. Accordingly, 35 voluntary mothers were included in the study, and their written consent was obtained. The data were collected with a "Demographic Information Form" and the "Parent-Proxy Report of the Pediatric Quality of Life Inventory (PedsQL) 3.0 Cancer Module," which was developed by Varni et al. (1999) and whose validity and reliability study was conducted by Yıldız Kabak et al. (2016) for children aged 2-7 years.*
Results: *Mean scores of the girls, those aged 49-84 months and those diagnosed with cancer at the age of 49-78 months, children of mothers who did not meet any child development specialists (CDSs), and children of mothers who did not meet and have any idea about CDSs during treatment were high on the subscales of pain and hurt, cognitive problems, worry, and perceived physical appearance, respectively.*
Conclusion: *The findings revealed that age and gender of the child, the age of diagnosis, and meeting any CDSs were factors affecting the quality of life of children with cancer.*

Keywords: *Child with cancer, quality of life, mother, early childhood, child development specialist*

ÖZ

Amaç: *Hastanede yatan iki-yedi yaş arasındaki kanserli çocukların yaşam kalitelerinin çocuklara ait bazı özellikler açısından incelenmesi amacıyla betimsel olarak yapılmıştır.*
Yöntem: *Araştırmanın çalışma grubuna, Ankara'da bulunan iki üniversite hastanesinin onkoloji servisinde yatan, kanser tanısını en az altı ay önce almış, majör fizik ve motor gelişim bozukluğu olmayan, iki-yedi yaşlar arasındaki çocukların anneleri oluşturmuştur. Bu doğrultuda, gönüllü olarak katılan 35 anne araştırmaya dâhil edilmiş ve yazılı onamları alınmıştır. Araştırmanın verileri "Genel Bilgi Formu" ve Varni ve ark. (1999) tarafından geliştirilen ve iki-yedi yaşları arasındaki çocuklarda geçerlik ve güvenirliği Yıldız Kabak ve ark. (2016) tarafından yapılan "Çocuklar İçin Yaşam Kalitesi Ölçeği (ÇİYKÖ) 3.0 Kanser Modülü Ebeveyn Formu" ile toplanmıştır.*
Bulgular: *Elde edilen bulgulara göre, kızların ağrı ve acı; 24-48 aylık olan çocukların bulantı ve endişe; 49-84 aylıkların bilişsel sorunlar yaşama; kanser tanısını 49-78 aylıkken almış olanların bilişsel sorunlar; çocuk gelişimciyi tanımayan annelerin çocuklarının endişe; tedavi sürecinde çocuk gelişimci ile karşılaşmayan ve çocuk gelişimciyi bilmeyen annelerin çocuklarının algılanan fiziksel görünüm alt boyutlarından aldıkları puan ortalamalarının anlamlı düzeyde yüksek olduğu bulunmuştur (p<0,05).*
Sonuç: *Araştırmadan elde edilen bulgulara göre, çocuğun yaşı, çocuğun cinsiyeti, tanı alma yaşı ve çocuk gelişimcilerle karşılaşma durumunun kanserli çocukların yaşam kalitesini etkileyen faktörler olduğu belirlendi.*

Anahtar kelimeler: *Kanserli çocuk, yaşam kalitesi, anne, erken çocukluk, çocuk gelişimci*

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INTRODUCTION

There are many definitions for quality of life, which is an interdisciplinary concept that is investigated in many fields, such as psychology, social work, health, sociology, economics, and political science [1]. According to the World Health Organization (WHO), the quality of life is "how individuals perceive their positions in life in relation to their goals, expectations, standards, and concerns in the context of their culture and value system" [2]. The quality of life, which can be interpreted as "satisfaction" perception of sick people in proportion to their existing functional levels, is a multidimensional concept that includes interpretations about the symptoms and psychological and social aspects associated with the person's disease status or treatment [3].

It is known that chronic diseases, such as cancer, affect the quality of life in many aspects. Children with acute and chronic illnesses, who are hospitalized for a short or long time, have problems in their behaviors and performing daily life activities. These negativities vary by many factors, such as sociodemographic characteristics of the family and child and the types, severity, diagnosis, and treatment methods of the disease [4]. Research on the quality of life among children emerged in the 1980s, and since then, many studies conducted to scrutinize the concept for sick children and their families [5,6] following the preliminary studies of Ditesheim and Templeton [7] and Henning et al. [8].

The previous research has suggested that the quality of life among sick children is affected by age [7], gender or disease status [6,9], the duration of diagnosis [10], the educational attainment of parents [11], maternal age, the number of siblings, the number of households, physical activity, the frequency of symptoms, the ability to take drugs, symptoms [9]. In some studies, however, it has been found that the gender of the child and the educational attainment of the parents do not influence the quality of life among the children [6,12].

It has previously been reported that symptoms of the disease and side effects of chemotherapy and radiotherapy, such as pain, changes in taste, anorexia, alopecia, nausea, vomiting, feeling of fatigue, tachypnea, depression, and anxiety, adversely affect the quality of life [13]. It has been revealed in some studies that children with cancer experience more impulsivity, mistrust, and anger than their healthy [14]; fatigue has a critical determinant role in the quality of life [15]; children with cancer have a high level of anxiety and depression [16]; and stress, exhaustion, weakness, and demoralization are the most common problems, which adversely affects the quality of life [17].

Studies examining the quality of life of children with cancer appear to concentrate mostly on school-age (8-12) and adolescence (13-18) [18-22]. Whereas studies examining the quality of life of children aged 2-7 years with cancer were found to be limited [17,23]. As in other age groups, children with cancer in this age group are affected by the disease in many aspects. The disease, diagnosis, and treatment process may adversely affect the cognitive, language, social and emotional, physical, and fine and gross motor development of such children [24,25]. It was reported that that the psychology and social development of children aged 2-5 may be adversely affected due to chronic diseases [26] and found that they had problems regarding procedural and treatment anxiety and communication. Prolonged and repeated hospitalization lead children to exhibit behaviors, such as finger sucking, enuresis (bedwetting), encopresis, sleep and eating disorders, and increased dependency, to experience depression, anxiety, introversion, decreased communication, aggressive behaviors, and anger attacks, and to face restricted physical movements, which, consequently, may cause adverse effects on their quality of life [24,27]. Previous studies have shown that depressive symptoms, anger, inadequacy, insecurity, impulsivity, hopelessness and anxiety, and depression are experienced much more in children with cancer [14,28].

It is deemed to be quite essential and necessary to investigate the quality of life among children with cancer and to identify the influencing variables. It will be helpful for both children and their families to receive support services from health professionals, especially CDSs, to increase the quality of life of children. Accordingly, it was aimed to examine the

quality of life among children with cancer by some variables, and ultimate objective of the present study was to shed light on the quality of life among children, to deliver programs and services for them, and to assert some recommendations to families and experts to boost their quality of life.

MATERIAL and METHOD

This is a descriptive study investigating whether the quality of life among hospitalized children aged 2-7 years with cancer differs by some of their characteristics.

While the mean scores of the mothers of children with cancer on the PedsQL constituted the dependent variable, independent variables of the study were age, gender, diagnosis, age of diagnosis, presence of alopecia, and meeting a CDS.

Sample of the Study

The sample of the present study was composed of the mothers of children hospitalized in pediatric oncology clinics of two university hospitals in Ankara, which provided relevant permits to conduct the study.

It was found that 34.3% of children were aged 73-84 months, 68.6% were aged 49-84 months. It was also determined that 51.4% of the children were girls, 54.3% were the last child of the family, 88.5% had 1-3 siblings, 85.7% did not attend any school, and 82.9% did not have any physical disabilities. The mean age of the children was 57.51±20.31 months. While 45.7% of the children were diagnosed with cancer at the age of 49-78 months, 57.1% were diagnosed with cancer other than leukemia and lymphoma (rhabdomyosarcoma, neuroblastoma, Wilms tumor, medulloblastoma, retinoblastoma, osteosarcoma, and Ewing Sarcoma), and 80% had alopecia. The mean age of the diagnosis was found to be 42.51±20.17 months.

It was determined that 42.9% of the mothers had no idea about CDSs, and 68.6% of them did not meet a CDS during their child's treatment. Mothers who met a CDS stated that they witnessed a CDS who came to the hospital to care with the children voluntarily, but there were no permanent CDS in the clinics where the children were hospitalized. Among 11 mothers who met a CDS during treatment, 9 were found to be received bedside care from the CDS for their child, and 3 of them received information and recommendations from the CDS about the development of their child.

Data Collection Tools

This research data were collected with a "Demographic Information Form" and the "Parent-Proxy Report of the Pediatric Quality of Life Inventory (PedsQL) 3.0 Cancer Module," which was developed by Varni et al. [29] and whose validity and reliability study was conducted by Yıldız Kabak et al. [23] for children aged 2-7 years. The scale aims at revealing the quality of life among children with cancer through parental evaluation of such children's experiences based on relevant items clustered under eight dimensions. The Demographic Information Form included a number of inquiries about age, gender, birth order, school attendance, number of siblings, diagnosis, age of the diagnosis, physical disabilities, presence of alopecia, and meeting any CDSs during the treatment. This module consists of 27 items within eight subscales: pain and hurt (two items), nausea (five items), procedural anxiety (three items), treatment anxiety (three items), worry (three items), cognitive problems (five items), perceived physical appearance (three items), and communication (three items). The parent filling out the form is asked to respond to the items by considering the last month of their child. The module is a 5-point Likert-type scale scored as never (100 points), rarely (75 points), sometimes (50 points), often (25 points), and almost always (0 points). A form is considered invalid if more than 50% of the items are left non-responded. The high scores on the scale indicate a high quality of life. It was determined that Cronbach's Alpha coefficients of the PedsQL 3.0 Cancer Module ranged from 0.803 to 0.873, just as the test-retest intra-class correlation coefficients ranged from 0.877 to 0.949 [23].

In this study, Cronbach's Alpha internal consistency coefficients were calculated as 0,818 for the Pain and Hurt subscale; 0,693 for the Nausea subscale; 0.720 for the Procedural Anxiety subscale; 0.849 for the Treatment Anxiety subscale; 0.824 for the Worry

subscale; 0.341 for the Cognitive Problems subscale; 0.457 for the Perceived Physical Appearance subscale; and 0.763 for the Communication subscale. This value was found to be 0.806 for the total scale.

Data Collection Method

First off, six hospitals with child hematology-oncology clinics were identified in Ankara, and then the purpose and method of the research were explained to administrative staff through interviews. The relevant bodies of two university hospitals among these hospitals accepted the present study. Accordingly, the official permissions and approval required to conduct the present study were obtained from the two hospitals and the Ethics Committee (25.06.2018/151). The prospective mothers and children were met and explained the purpose and method of the research. The mothers who voluntarily accepted to participate in this research were asked to sign the Informed Consent Form. Then, the scale was administered to the participants by a single investigator (L.C.G), which lasted about 10-15 minutes. The data were collected between July 2018 and March 2019.

Ethical Considerations

A conditional use permit was obtained for the PedsQL 3.0 Cancer Module from V. Yıldız Kabak, who conducted the validity and reliability study of the Turkish version of the scale for children aged 2-7 years. Moreover, official permissions were obtained from the two university hospitals, where the research would be conducted, along with the ethical approval of the Ankara University Ethics Committee (25.06.2018/151). Finally, Informed consent was obtained from all the participating mothers.

Data Analysis

In the data analysis, continuous data were given as mean, standard deviation, median, and minimum-maximum, while categorical data were presented as percent values. The Shapiro-Wilk test was used to check the distribution of the data, and results revealed that the scores on the total scale showed a normal distribution ($p>0.05$). However, the scores on the subscales were found to show a non-normal distribution ($p<0.05$). The T-Test was used to compare normally distributed data with independent variables, while the Mann-Whitney U test and the Kruskal-Wallis H test were used to compare non-normally distributed data with independent variables. The significance level was taken as $p<0.05$ in all statistical analyses.

RESULTS

This section presents the descriptive results pertaining to the scores of the mothers on the PedsQL 3.0 Cancer Module and the findings inferred from the PedsQL 3.0 Cancer Module, where the mothers evaluated their child's quality of life.

Descriptive statistics regarding the quality of life by age are presented in Table 1. The mean scores of the children aged 24-48 months on the subscales of nausea and worry were significantly higher than those of children aged 49-84 months. Moreover, the level of cognitive problems was found to be significantly higher in children aged 49-84 months with cancer than those aged 24-48 months ($p<0.05$).

Considering the children's quality of life by gender, the mean scores of girls on the pain and hurt subscales were significantly higher than those of boys (Table 2) ($p<0.05$).

Descriptive statistics regarding the quality of life by the age of diagnosis are presented in Table 3. The mean scores of children diagnosed at the age of 49-78 months on the cognitive problems subscale were found to be significantly higher than those of cihldren diagnosed at the age of 0-24 ($p<0.05$).

In this study, the mean scores of the children on the subscales of pain and hurt [U=139,500], nausea [U=121,000], procedural anxiety [U=94,000], treatment anxiety [U=134,500], worry [U=142,500], cognitive problems [U=117,500], perceived physical appearance [U=142,000], and communication [U=117,000] and the total scale [t(33)=1.366] did not differ by their diagnosis ($p>0.05$).

The results revealed that the mean scores of the children on the subscales of pain and hurt [U=80.000], nausea [U=97.500], procedural anxiety [U=88.500], treatment anxiety [U=81.500], worry [U=85.000],

Table 1. Analysis results of life quality of children by age groups of children.

Subscales	Child's Age Group	n	Mean Rank	Total Rank	U	p
Pain and hurt	24-48 Months	11	17.91	197.00	131.000	0.986
	49-84 Months	24	18.04	433.00		
Nausea	24-48 Months	11	23.36	257.00	73.000	0.036
	49-84 Months	24	15.54	373.00		
Procedural anxiety	24-48 Months	11	17.86	196.50	130.500	0.958
	49-84 Months	24	18.06	433.50		
Treatment anxiety	24-48 Months	11	16.82	185.00	119.000	0.662
	49-84 Months	24	18.54	445.00		
Worry	24-48 Months	11	24.5	269.50	60.500	0.009
	49-84 Months	24	15.02	360.50		
Cognitive problems	24-48 Months	11	10.05	110.50	44.500	0.001
	49-84 Months	24	21.65	519.50		
Perceived physical appearance	24-48 Months	11	18.27	201.00	129.000	0.930
	49-84 Months	24	17.88	429.00		
Communication	24-48 Months	11	16.45	181.00	115.000	0.563
	49-84 Months	24	18.71	449.00		
		n	**$\bar{X}$**	**S**	**sd t**	**p**
Total scale	24-48 Months	11	1731.81	233.48	33	
	49–84 Months	24	1626.04	496.59	0.669	0.508

Table 2. Analysis results of children's life quality according to gender of children.

Subscales	Gender of Child	n	Mean Rank	Total Rank	U	p
Pain and hurt	Girl	18	21.72	391.00	86.000	0.027
	Boy	17	14.06	239.00		
Nausea	Girl	18	19.72	355.00	122.000	0.318
	Boy	17	16.18	275.00		
Procedural anxiety	Girl	18	18.58	334.50	142.500	0.732
	Boy	17	17.38	295.50		
Treatment anxiety	Girl	18	18.86	339.50	137.500	0.613
	Boy	17	17.09	290.50		
Worry	Girl	18	17.81	320.50	149.500	0.909
	Boy	17	18.21	309.50		
Cognitive problems	Girl	18	18.44	332.00	145.000	0.807
	Boy	17	17.53	298.00		
Perceived physical appearance	Girl	18	17.36	312.50	141.500	0.708
	Boy	17	18.68	317.50		
Communication	Girl	18	18.53	333.50	143.500	0.757
	Boy	17	17.44	296.50		
		n	**$\bar{X}$**	**S**	**sd t**	**p**
Total scale	Girl	18	1713.94	394.34	33	0.311
	Boy	17	1582.35	465.18	1.028	

cognitive problems [U=60.000], perceived physical problems [U=58.000], and communication [U=89.500] and the total scale [U=83.500] did not differ by the presence of alopecia (p>0.05).

Considering the children's quality of life by meeting a CDS (Table 4), The mean scores on the subscales of worry and perceived physical appearance differed significantly by meeting a CDS. Moreover,

Table 3. Kruskal Wallis H Test results according to age of diagnosis of children's life quality.

Subscales	Child's Age Group	n	Mean Rank	sd	χ^2	p
	0-24 Months	11	15.59			
Pain and hurt	25-48 Months	8	23.88	2	3.811	0.149
	49-78 Months	16	16.72			
	0-24 Months	11	21.05			
Nausea	25-48 Months	8	16.19	2	1.452	0.484
	49-78 Months	16	16.81			
	0-24 Months	11	16.86			
Procedural anxiety	25-48 Months	8	15.75	2	1.102	0.576
	49-78 Months	16	19.91			
	0-24 Months	11	15.82			
Treatment anxiety	25-48 Months	8	16.44	2	1.584	0.453
	49-78 Months	16	20.28			
	0-24 Months	11	22.50			
Worry	25-48 Months	8	16.69	2	4.226	0.121
	49-78 Months	16	15.56			
	0-24 Months[1]	11	12.36			
Cognitive problems	25-48 Months[2]	8	16.69	2	6.916	0.031
	49-78 Months[3]	16	22.53			3>1
	0-24 Months	11	19.23			
Perceived physical appearance	25-48 Months	8	15.50	2	0.674	0.714
	49-78 Months	16	18.41			
	0-24 Months	11	18.27			
Communication	25-48 Months	8	21.56	2	1.938	0.380
	49-78 Months	16	16.03			
	0-24 Months	11	18.00			
Total scale	25-48 Months	8	17.56	2	0.022	0.989
	49-78 Months	16	18.22			

Table 4. Kruskal Wallis H Test results according to the children's quality of life by meeting a CDS.

Subscales	Child's Age Group	n	Mean Rank	sd	χ^2	p
	Yes	11	19.14			
	No	9	14.61			
Pain and hurt	No Idea	15	19.20	2	1.448	0.485
	Yes	11	17.64			
	No	9	19.94			
Nausea	No Idea	15	17.10	2	0.458	0.795
	Yes	11	19.32			
	No	9	19.22			
Procedural anxiety	No Idea	15	16.30	2	0.741	0.690
	Yes	11	16.59			
	No	9	23.78			
Treatment anxiety	No Idea	15	15.57	2	4.196	0.123
	Yes[1]	11	16.50			
	No[2]	9	24.50			
Worry	No Idea[3]	15	15.20	2	6.661	0.036
	Yes	11	18.23			2>3
	No	9	13.61			
Cognitive problems	No Idea	15	20.47	2	2.652	0.266
	Yes[1]	11	10.59			
	No[2]	9	22.11			
Perceived physical appearance	No Idea[3]	15	20.97	2	8.651	0.013
	Yes	11	15.73			2>1
	No	9	17.94			3>1
Communication	No Idea	15	19.70	2	1.181	0.554
	Yes	11	15.45			
	No	9	22.00			
Total scale	No Idea	15	17.47	2	2.096	0.351

children of the mothers who did not met a CDS were found to experience more worry than those of mothers did not have any idea about CDSs ($p<0.05$). Finally, on the perceived physical appearance subscale, children of the mothers who did not meet ($p=0.034$) and have any idea about CDSs ($p=0.03$) had higher mean scores than those of mothers who met a CDS, respectively.

DISCUSSION

Disease and treatment can affect the central nervous system of the child, which causes biological stress and adversely affects the childs development. The disease process may also intensify the child's emotions, such as anxiety (especially for bodily harm and loss of limbs), shame, and fear of loneliness, which can also cause worry and regression. The child may have difficulties in showing patience to the repeated, prolonged intervention and hospitalization process since the concept of time is not fully acquired in this period. Children in this age group experience anxiety and worry about bodily harm [24,27,30]. The present results revealed that children aged 24-48 months experienced more problems with nausea and worry than children aged 49-84 months. Eiser et al. [31] found in their study that children having treatment for acute lymphoblastic leukemia had problems in and became worried about perceiving their physical appearance as they got older, but that younger children were less worried about perceiving their physical appearance. Previous studies indicate that younger children experience problems caused by diagnosis and treatment processes (pain and hurt, nausea, exhaustion, procedural anxiety, treatment anxiety, and communication) more than their older counterparts [17,18,32].

In this research, it was determined that children aged 49-84 months experienced more cognitive problems than children aged 24-48 months. Piaget's preoperational stage and Bruner's iconic stage include children aged 3-6 years; therefore, children in these stages convey the knowledge they acquire through words and concepts into their minds by formulating them into images. Children in this age period may not be able to clearly express their symptoms and develop the idea of "contamination" due to the disease. At the same time, the child may have difficulties in showing patience to the repeated, prolonged intervention and hospitalization process since the concept of time is not fully acquired in this period [24,27,30].

The nature of cancer, the diagnosis, and treatment procedures may increase pain over time, create biological and psychosocial stress, and adversely affect the development of hospitalized children. Pain control is an essential component in supporting the development of the hospitalized child [33]. The present results suggested that girls had more problems with pain and hurt than boys. In some studies, it has been reported that girls' quality of life is significantly lower compared to boys, and they experience the disease more severely [34]. Abu-Saad Huijer et al. [18] stated that the procedural anxiety of boys was significantly higher than that of girls, and gender did not make any difference in other subdimensions. In the studies of Jankowska Polanska et al. [17] and Kızmazoğlu et al. [12], the gender of children with cancer was concluded not to make any difference in their quality of life. At the same time, Jankowska Polanska et al. [17] mention that the issue of whether children's quality of life is affected by their gender is a topic of debate in the literature, and there are studies showing that the quality of life of older girls is lower than that of boys.

The present findings, there was a significant difference between the age of diagnosis and cognitive problems. The central nervous system of preschool (3-6 years) children with chronic disease may be affected due to the disease and treatment process, which causes biological stress and adversely affects the child's development. In general, the concept of the disease cannot be understood fully until about four years. Even if they cannot understand the process and mechanism of the disease, children up to 9 or 10 years may think that microbes need to enter the body to cause the disease. The child may have difficulties in showing patience to the repeated, prolonged intervention and hospitalization process since the concept of time is not fully acquired in this period [24,27,30]. Children who are diagnosed at the age of 0-24 months may not be able to express adverse diagnosis and treatment experiences, and their

mothers may not notice these problems. Whereas, children who are diagnosed at the age of 49-78 months can express their experiences related to the disease, hospitalization, and treatment better, which lead their mothers to recognize these problems more quickly. Children diagnosed in this period may have more difficulty in determining what to do in troubled situations, focusing their attention, and remembering what they read.

'Being diagnosed with cancer causes not only side effects, such as pain, fatigue, alopecia, nausea/vomiting, but also the appearance of symptoms, such as anxiety, depression, change in the concept of self, negative body image, pain, and fatigue [35]. Alopecia is one of the undesired effects of chemotherapy and radiotherapy, and it is a condition that causes problems, such as anxiety, depression, negative body image, and low self-esteem in patients [36]. Although the hair does not have a vital biological function in the human body, it plays an essential role in body image and self-definition in both men and women. Medical procedures applied during cancer treatment adversely affect the well-being of the patient, that is, the quality of life, and the symptoms cause threats to the psychological and physical integrity of the person [35,37]. Adolescents regard their physical appearance much more than those in other age groups [24,27]. Since the present study involved children aged 2-7 years, it was observed that hair and eyebrow loss due to alopecia did not affect their quality of life. Physical appearance may not cause anxiety and worry for preschool children.

CDS is a health professional who evaluates children throughout all developmental stages from birth to the end of adolescence, takes part in child health monitoring, and provides services to the child, its family, healthcare professionals, and society through development-related programs. In addition, although CDSs, who work to improve children's quality of life, are categorized among "other" professionals by the Ministry of Health, they have a very critical place in the health-related system [38]. It was found that the mean scores of the children on the subscales of worry and perceived physical appearance differed significantly by meeting a CDS. These results suggest that CDSs bear important roles and responsibilities for hospitalized children and their families. Akar Gençer and Yüksel [39] stated that the presence of a CDS in the hospital meant so much to families. The families in our country have previously stated that they need counseling-guidance services for their children's development, education, nutrition, and behavioral and psychological problems and that the number of Child Development Polyclinics, where they can receive services both free of charge and easily, should be increased. They highlighted that the anxiety of children would decrease upon the informative and sensitive actions of healthcare professionals.

CDSs play an active role in eliminating the negative conditions in case children with cancer need developmental, psychological, and physical support due to their prolonged hospitalization and treatment processes. During the present study, the mothers reported that the presence of a healthcare professional, who would care about their children, play with them, follow their development, and offer the mothers, and support both them and their children, would be much appreciated, which suggest how essential role CDSs play in inpatient services. In addition, considering the daily life-restricting effects of inpatient treatment, CDSs need to take an active role, especially in pediatric hematology-oncology services, to minimize such impacts on sick children and their families. It is believed that CDSs bear a critical mission in order to ensure children with cancer and their families, who have many psychological, developmental, and physical disadvantages, to overcome disease and treatment processes.

Study Limitations

This present study is limited to the mothers of children between the ages of 2 and 7 years of age who were hospitalized at the children's oncology clinic of two university hospitals, who were diagnosed with cancer at least six months ago, receiving active chemotherapy treatment and who did not have major physical and motor development disorders and July 2018 and March 2019. Since the scale used in this study was a cancer module, comparing children receiving cancer treatment with their healthy peers was not applicable.

Clinical Implications

It is well established that chronic illness places quality of life at risk and is usually detrimental to it. Chronic illnesses often trigger invasive or uncomfortable treatment protocols. Cancer disease, which is a chronic disease, also appears as a disease that negatively affects the quality of life. It is known that quality of life is affected by the disease status especially in young children. In the light of all this information, the research was carried out to determine the factors affecting the quality of life of children with cancer, and to make suggestions to improve the quality of life of children.

CONCLUSIONS

As a result of the present study, in which the quality of life of children with cancer was examined according to the opinions of their mothers, it was concluded that children aged 24-48 months experienced nausea and worry more while those aged 49-84 months experienced cognitive problems more; girls had a higher perception of pain and hurt; children diagnosed at the age of 49-78 months experienced cognitive problems more; and children of the mothers who did not have any idea about CDSs had more problems with worry while children of the mothers who did not meet and have any idea about CDSs had more problems with perceived physical appearance ($p<0.05$).

In light of these findings, the following recommendations can be offered to families, specialists, and researchers:

- Since cancer children may experience changes and problems with pain-hurt, nausea, procedural anxiety, treatment anxiety, worry, physical appearance, communication, and cognition in the diagnosis-treatment process, further actions need to focus on increasing the quality of life by identifying their problems and relevant solutions to them based on their ages, developmental characteristics, and ages of the diagnosis.
- Considering the importance of the role and functions of child development specialists in hospitals, children with cancer and their parents, who are required to engage in long-term treatment processes and repeated hospitalizations, can be provided more active support from child developers.
- The number of child developers working in hospitals can be increased, and support services for children and families can be improved.
- In this study, the quality of life of children with cancer aged 2-7 years was evaluated by their mothers' opinions. The subject can be investigated according to paternal opinions, and opinions from mothers and fathers can be compared in terms of their children's quality of life.
- Studies may be conducted to compare the quality of life of children with cancer and their healthy peers.

Ethics Committee Approval: Official permissions were obtained from the two university hospitals, where the research would be conducted, along with the ethical approval of the Ankara University Ethics Committee (25.06.2018/151).

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Case Report

A Mortal Complication in a Case with Mucopolysaccharidosis Type I Following Hematopoietic Stem Cell Transplantation: Pulmonary Haemorrhage

MPS Tip 1 Olgusunda Hematopoetik Kök Hücre Nakli Sonrası Mortal Komplikasyon: Pulmoner Hemoraji

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ABSTRACT

Mucopolysaccharidosis type I (MPS I) is a lysosomal storage disease due to mutations within the gene IDUA encoding the "α-L-iduronidase". The clinical manifestations concern multisystemic involvement. There are two disease modifying therapies, enzyme replacement therapy and haematopoietic stem cell transplantation (HSCT). Pulmonary haemorrhage (PH) is a rare complication of HSCT and the case was presented with the reason that the related reports were few in MPS I.

Keywords: *MPS I, HSCT, pulmonary haemorrhage*

ÖZ

Mukopolisakkaridozis tip 1 (MPS 1) "α-L-iduronidase" enzimini kodlayan IDUA geninde mutasyonlardan kaynaklanan bir lizozomal depo hastalığıdır. Multisistemik tutulumla karakterizedir. Enzim replasman tedavisi ve hematopoetik kök hücre nakli olmak üzere iki güncel tedavi yöntemi mevcuttur. Pulmoner hemoraji HSCT' nin nadir bir komplikasyaonu olup, MPS 1 hastalarında nadir olgu sunumları bildirilmiştir.

Anahtar kelimeler: *MPS 1, HSCT, pulmoner hemoraji*

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INTRODUCTION

The mucopolysaccharidoses are a group of congenital metabolic diseases involving the intracellular deposition of various glycosaminoglycans (GAGs). MPS I is caused by a deficiency of α-L-iduronidase that leads to progressive accumulation of dermatan and heparan sulfate. Furthermore, these undegraded GAGs induce apoptosis in cells. Macrocephaly, coarse facies, hepatosplenomegaly, hernia, stiff joints, recurrent upper airway infections, otitis media, hearing loss, cardiac valve disease and/or cardiomyopathy, and neurologic impairment are the clinical features of MPS I. MPS I has three clinical subtypes based on clinical severity, respectively: a severe form – Hurler syndrome (MPS IH); an intermediate form – Hurler/Scheie syndrome (MPS IH/IS); and the mild form – Schie syndrome (MPS IS). p. Q70X and p.W402X variants severely disrupt protein/gene function; as such, their association with the severe phenotype has been demonstrated [1].

MPS I brings about premature morbidity and mortality if left untreated, mainly due to cardiorespiratory issues.

Intravenous enzyme replacement therapy (ERT) and HSCT are the two major therapies available for the different clinical subtypes of MPS I. ERT (Laronidase – recombinant α-L-iduronidase) has been available since 2003. ERT has been shown to improve somatic symptoms, but the results regarding cognitive function have been poor due to an inability to cross the blood-brain barrier [2]. HSCT was first reported in 1981 [3], although current HSCT treatments have been an option for those diagnosed with MPS IH before reaching two-and-a-half years of age. To the best of our knowledge, more than 500 transplants have been performed in sufferers of MPS I. Following transplantation, engrafted donor leukocytes act as a source of α-L-iduronidase enzyme in the blood and central nervous system [1,4]. If initiated early, HSCT has been shown to preserve neurocognition and to achieve improved developmental outcomes, and is accordingly considered the gold standard of treatment for patients with MPS IH [1]. HSCT has enhanced neurocognitive and survival results with revisions in conditioning regimens, improvement in donor-recipient histocompatibility matching, and an expansion of donor sources. Mortality following HSCT can be divided into two categories: the first is transplant-related mortality, which develops within the first year after HSCT; the second involves mortality occurring after the first year. PH is a rare complication of HSCT, and represents one of the transplant-related causes of mortality [5].

CASE REPORT

The infant was born to healthy consanguineous parents. Family history was non-contributory. A female new-born with a gestational age of 39 weeks and 4 days, and a birth weight of 2800 g, was born following a cesarean section to a 22-year-old primigravida mother whose pregnancy was followed. The patient had a large anterior fontanelle, coarse facies, macrocephaly, organomegaly, and a large Mongolian spot on her initial examination.

Laboratory investigations were notable for high urine GAGs (515 mg/g creatinine, N: <140) and low α-L-iduronidase enzyme activity in dried blood (0.42 nmol/mL/h, N: 2.3-10). She was diagnosed on the basis of enzymatic testing with MPS IH. Later, IDUA gene analysis showed a homozygous nonsense mutation of p.Q70X (c.208C>T).

At the 12th month of life, the patient was diagnosed with MPS I, and was started on a treatment with 0.58 mg/kg/dose intravenous ERT with Laronidase once a week, with continued treatment following HSCT. BMT was performed at the age of 19 months with a 5/6 HLA match, unrelated cord-blood donor. She received a preparatory treatment with fludarabine, busulfan, and melphalan containing myeloablative chemotherapy. She received graft-versus-host-disease (GVHD) prophylaxis with cyclosporine, anti-thymocyte globulin, and prednisolone. Enzyme activity returned to near normal (1.9 nmol/mL/h, N: 2.3-10) on day +31. She showed engrafting of white cells and platelets on day +12; and chimerism studies on day +44 confirmed 100% donor engraftment. The patient had grade-II GVHD on day +41. On day +53, the patient had been afe-

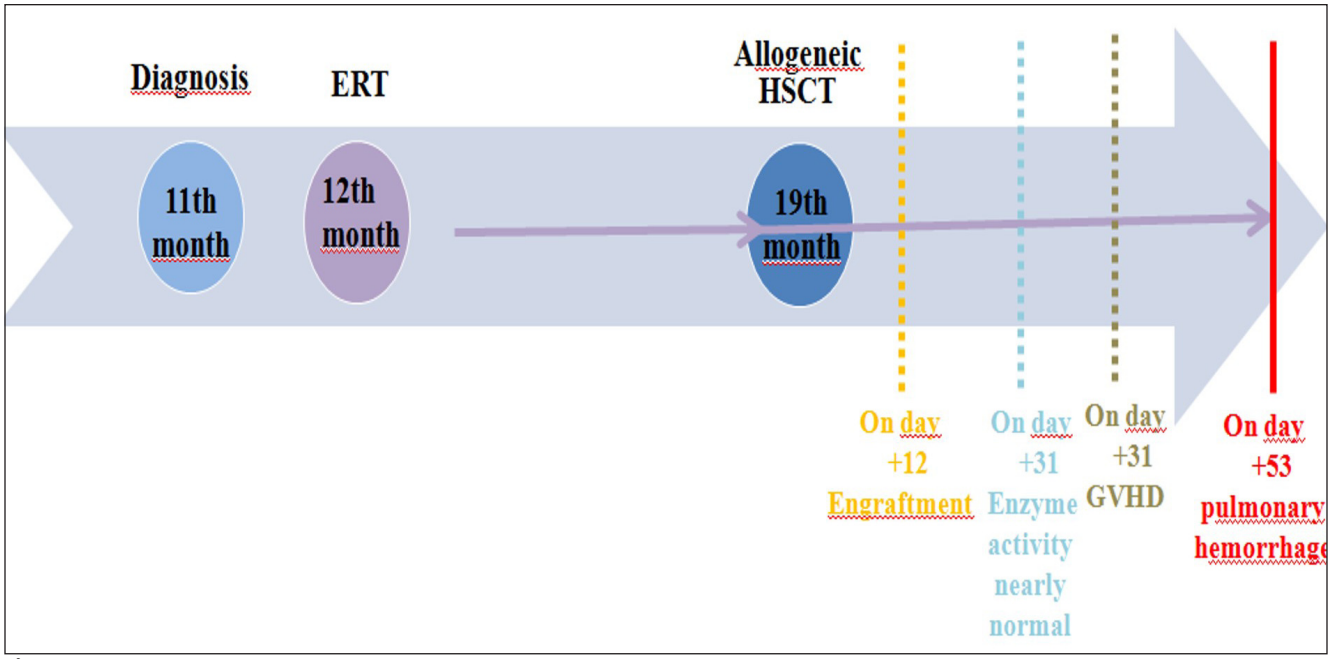

Figure 1.

brile for the previous seven days, and presented with sudden-onset tachypnoea, dyspnea, haematemesis, and unexplained severe oxygen desaturation rapidly followed by cardiorespiratory arrest and death. On day +52, her hemoglobin, white blood cells, and platelets were 8.5 g/dl 18.1x103/µL and 30x103/µL respectively. The family did not allow a post-mortem histopathological examination to be carried out.

DISCUSSION

Untreated Hurler patients would likely die in the first decade of life, but HSCT and ERT are two treatments that slow progression and provide benefit. HSCT has been shown to increase survival, and the best results have been achieved when HSCT is performed before 2.5 years of age and within six months of diagnosis. Hematopoietic stem cell transplantation has been used since 1981 in the treatment of MPS I. In the case we have presented, HSCT was performed at 19 months and seven months after diagnosis. IDUA gene analysis revealed a homozygous mutation for p.Q70X. This nonsense mutation is notably common, and is known to be related to the Hurler phenotype due to a complete lack of residual enzymatic activity. Enzyme replacement therapy with Laronidase has been available since 2003. ERT should be initiated at the first opportunity and a decision is usually made to start ERT on diagnosis. However, the age of diagnosis and initiation of treatment varies depending on whether the new-born-screening program of any given country includes MPS type-I or not. The new-born-screening program in Turkey does not include MPS type-I. Pre-HSCT and peri-HSCT administration of ERT should be considered as a supportive/adjuvant treatment in addition to HSCT for patients with MPS IH, and we also continued pre-HSCT and peri-HSCT [1,6]. In the literature, the age at onset of ERT in MPS type-I cases who underwent HSCT in whom PH had previously been reported was not specified [4,7,8].

We have described PH as a lethal complication in the patient with MPS IH following unrelated donor cord-blood transplantation. The incidence of death from PH was revealed to be highest within the first year following HSCT in patients with MPS I. Patients with inherited metabolic storage diseases are at a higher risk of developing pulmonary complications following HSCT. The pathogenesis of pulmonary complications in patients undergoing HSCT is unclear. Several studies have shown that the local proinflammatory cytokine cascade produced by alveolar mac-

rophages and donor-derived cytokines plays a crucial role in these complications developing following HSCT [7,8].

CONCLUSIONS

PH is rare following autologous and allogeneic BMT. The etiology of PH post-BMT is unclear, but is believed to be multifactorial. There is limited experience described in the literature in relation to PH in patients with MPS I treated with bone marrow transplantation. Therefore, we would like to highlight this case of PH in MPS I following HSCT.

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Case Report

A Case of Spontaneous Pneumothorax with Persistent Air Leakage During the Course of COVID-19

COVID-19 Seyri Sırasında Persistan Hava Kaçağı Olan Spontan Pnömotoraks Olgusu

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ABSTRACT

Development of pneumothorax during the course of COVID-19 is very rare, and may occur secondary to severe pulmonary involvement causing alveolar damage in the parenchyma, or is seen as a complication of respiratory support. Until now, quite a few cases have been reported. Herein, we shared a case of spontaneous pneumothorax with persistent air leakage without any parenchymal or pleural involvement.

Keywords: *Pneumothorax, COVID-19, thoracotomy, air leakage*

ÖZ

COVID-19 seyri sırasında pnömotoraks çok nadirdir, parankimde alveolar hasara neden olan ciddi pulmoner tutuluma ikincil olarak ortaya çıkabilir veya solunum desteğinin bir komplikasyonu olarak görülür. Şimdiye kadar çok az sayıda vaka bildirilmiştir. Burada herhangi bir parankimal veya plevral tutulum olmaksızın persistan hava kaçağı olan spontan pnömotoraks olgusunu paylaştık.

Anahtar kelimeler: *Pnömotoraks, COVID-19, torakotomi, hava kaçağı*

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INTRODUCTION

An emerging infectious disease that causes pneumonia associated with SARS-CoV2 was initially reported in December 2019 in Wuhan City of People's Republic of China, and was named as coronavirus disease 2019 (COVID-19) [1]. Although the situation was declared as a pandemic, many unknowns about this disease were on the agenda [2]. Although it is known that the infection primarily affects the lung, the involvement patterns were being defined as time progressed [2,3]. Individual or combined images of ground glass opacification(s), interlobular septal thickening, bronchiectasis, pleural thickening, subpleural involvement, and consolidative opacities on computed tomography (CT) were identified as the characteristic features for COVID 19 pneumonia [3]. Pleural effusion, cavitation, halo sign, and spontaneous pneumothorax were less common radiological manifestations in large case series [3,4]. Herein, we would like to share our experience with an extremely rare pediatric case of spontaneous pneumothorax

with persistent air leakage seen during the course of COVID-19 disease.

CASE REPORT

A previously healthy 17-year-old male patient was admitted with the complaints of fever and weakness. A naso-oropharyngeal swab sample was obtained, and examined for COVID-19 by Real-Time Reverse Transcription Polymerase Chain Reaction (RT-PCR) method (Bioeksen, Istanbul, Turkey) which yielded a positive result. Since physical examination findings, routine blood test results and thorax CT scans were not remarkable, outpatient monitoring without treatment was planned for the patient. However, the patient was re-admitted nine days after the positive RT-PCR test result was obtained due to newly developed chest pain and shortness of breath. Respiratory distress, low oxygen saturation and decreased respiratory sounds were detected on

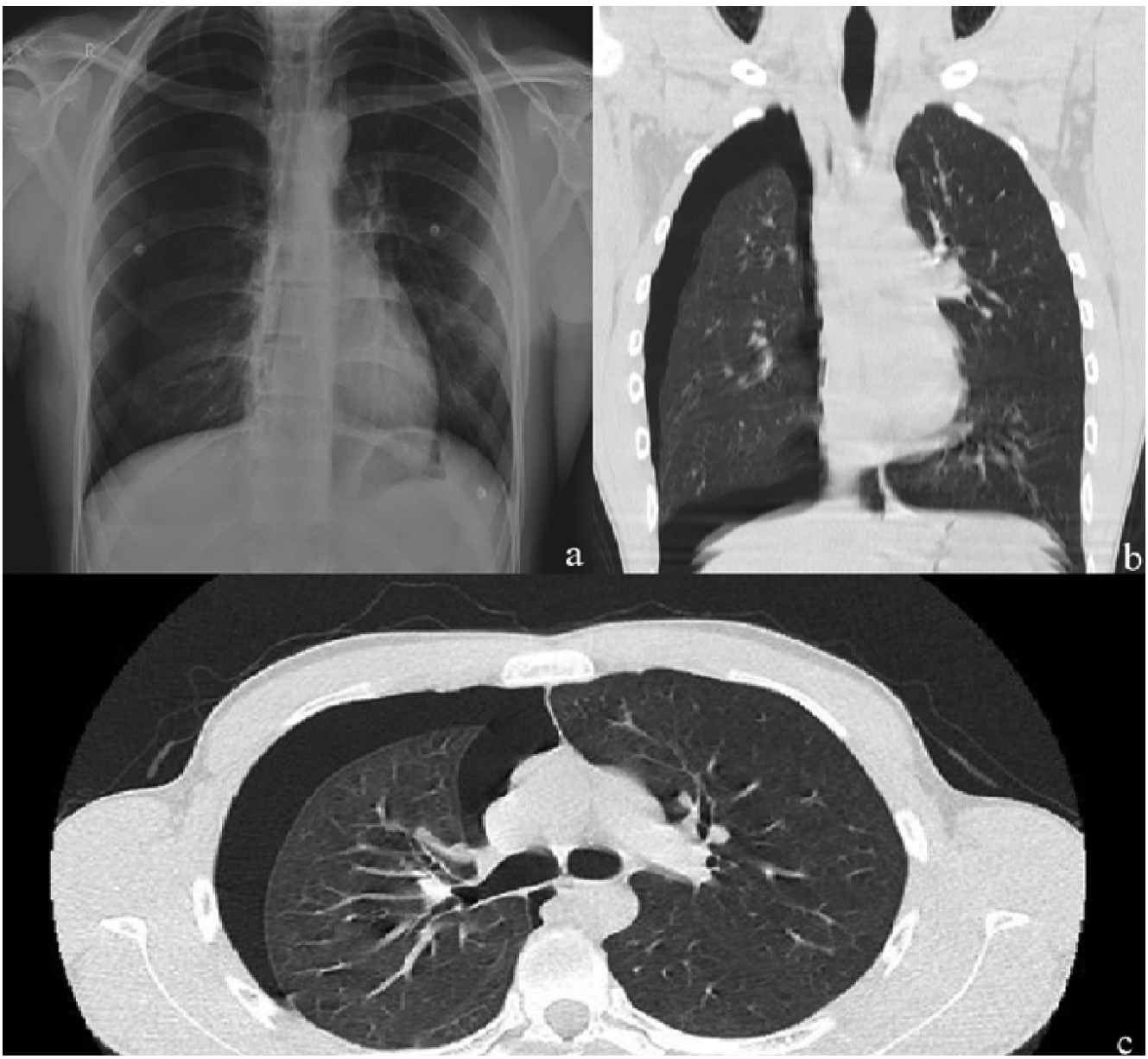

Figure 1. Pneumothorax sign in the right hemithorax of the patient, on chest X-ray (a) and in coronal (b) and horizontal (c) sections of thorax computed tomography.

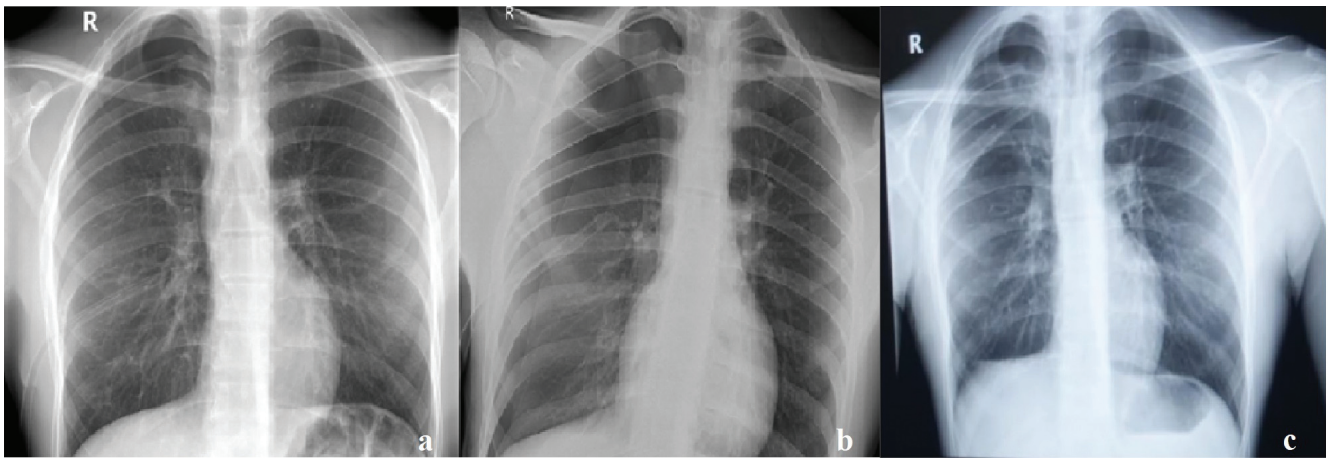

Figure 2. Completely ventilated right hemithorax of the patient after chest tube insertion (a), new sign of pneumothorax on the control radiograph after clamping of the chest tube (b), and postoperative X-ray of the patient during monitorization with thoracic drainage suction pump (c).

the examination. Hemogram, blood biochemistry, cardiac enzymes and acute phase reactants were all within normal limits. Creatinine kinase level was elevated and analysis of arterial blood gas revealed the presence of hypoxemia. A pneumothorax sign in the right hemithorax on chest X-ray (Figure-1a), and thorax CT without any pathological findings in the lung parenchyma confirmed the diagnosis (Figure-1b/1c). A chest tube was inserted into the pleural space by the pediatric surgery clinic. After the procedure, the patient's respiratory distress quickly resolved, the right hemithorax was re-expanded and the pneumothorax sign disappeared on the control radiograph (Figure 2a).

Prophylactic treatment with sulbactam-ampicillin was initiated, and a specific treatment for COVID-19 was not given. The patient was monitored asymptomatically in the first week of hospitalization and the chest tube was clamped on the seventh day. However, patient described a chest pain after clamping of the tube, and a new pneumothorax sign appeared on chest X-ray (Figure 2b). Despite several attempts at removal of the chest tube on different days, the patient could not tolerate the procedure, and the tube was revised. After three weeks of follow-up, a bullectomy, partial pleurectomy and pleurodesis were applied with linear stapings to the right upper lobe apex by performing right thoracoscopy. However, thoracoscopy was switched to thoracotomy as the air leak continued during the operation. Any prominent fistula line was not detected , and patient was connected to the thoracic drainage suction pump (Figure 2c). After monitoring with the thoracic drainage suction pump, the patient was discharged asymptomaticly on the postoperative 23rd day. Any other risk factors for spontaneous pneumothorax such as chronic or previous respiratory tract disease, smoking, tall and thin body structure, or regular risky sportive activities were not identified.

DISCUSSION

Pneumothorax in the course of COVID-19 has been rarely reported as a possible finding that can be seen with disease progression [3]. In the cases previously reported, it has been expressed that pneumothorax occurs secondary to severe involvement causing alveolar damage or bullous lesions in the parenchyma, or is seen as a complication after noninvasive ventilation or positive pressure respiratory support [5]. In the case series reported by Eperjesiova et al, it was stated that all seven patients, who did not receive ventilation support before, developed COVID-19-related spontaneous pneumothorax, had typical images of COVID-19 parenchymal damages on their CT scans that could predispose to pneumothorax [6]. Pneumothorax in the course of COVID 19 is very rare also in children. Until now, a few pediatric cases have been reported including two newborns with parenchymal lesions of the infec-

tion and a 14-year-old patient who underwent a bullectomy operation [7,8]. It is notable that pneumothorax developed in our patient who had not any predisposing factors that may facilitate development of pneumothorax.

To our knowledge, COVID 19-related spontaneous pneumothorax without any parenchymal or pleural involvement has not been reported so far. It is also noteworthy that although there is no facilitating factor, the pneumothorax was serious enough to require surgery and did not benefit from the interventions for a while.

Conflict of Interest: None.

Informed Consent: Obtained from the patient's relatives.

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Case Report

A Cause of Asthma Misdiagnosis: Foreign Body Aspiration That Allows Air Passage Through

Yanlış Astım Tanısının Bir Nedeni: Hava Geçişine İzin Veren Yabancı Cisim Aspirasyonu

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ABSTRACT

Foreign body aspiration is a life-threatening condition in childhood. Clinical and radiological diagnosis may be delayed in cases in which foreign body has a lumen and allows the air passage through and is also misdiagnosed as asthma or chronic cough. The delay in the diagnosis can cause morbidity and mortality. We have reported the case of an 11-year-old boy with foreign body aspiration who has been treated as asthma. His dry cough could not be controlled with the asthma treatment. He had swallowed a piece of pipette before the coughing started. Fiber optic bronchoscopy was applied. The piece of pipette was seen in the left main bronchus which allowed the air passage through its lumen. After the removal, his complaints disappeared. In conclusion, the patients with a history of aspiration and without signs of lateralization in physical or radiological examinations should be evaluated by fiber optic bronchoscopy in terms of foreign body aspiration.

Keywords: *Asthma, children, foreign body aspiration*

ÖZ

Yabancı cisim aspirasyonları çocukluk çağında yaşamı tehdit edebilen bir durumdur. Aspire edilen yabancı cismin lümenli olması ve hava geçişine izin vermesi durumunda, astım veya kronik öksürük gibi yanlış tanıların konulmasına ve klinik ve radyolojik tanının gecikmesine neden olabilir. Tanıdaki gecikme mortalite ve morbiditeye neden olabilir. Yazımızda yanlış astım tanısı ile takip edilen ve yabancı cisim aspirasyonu saptanan 11 yaşında erkek olgumuzu sunduk. Hastanın kuru öksürük şikayeti astım tedavisi ile kontrol altına alınamamıştı. Şikayetinin başlangıcından bir hafta önce hastanın ayran içerken pipet parçasını aspire ettiği öğrenildi. Hastaya fiberoptik bronkoskopi uygulandı. Sol ana bronş içinde lümeninden hava geçişine izin veren pipet parçası görüldü. Yabancı cisim çıkarıldıktan sonra hastanın şikayetleri sona erdi. Sonuç olarak, aspirasyon öyküsü olan ve fizik muayene ve radyolojik incelemelerinde lateralizasyon bulguları saptanmayan hastalar yabancı cisim aspirasyonu açısından fiberoptik bronkoskopi ile değerlendirilmelidir.

Anahtar kelimeler: *Astım, çocuk, yabancı cisim aspirasyonu*

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INTRODUCTION

Foreign body aspiration (FBA) is defined as asphyxia caused by suffocation or inhalation of items of food and nonfood into the respiratory tract and as a cause of morbidity and mortality during childhood. It is frequent in children under 2 years old and is known to be the fourth significant cause of accidental death in children younger than 3 years old and slightly more common in males [1,2].

In most cases, the aspirated foreign bodies tend to lodge in the bronchi, less commonly in trachea and larynx. It causes inflammation and irritation in respiratory tract by impacted object's obstruction of

the respiratory tract. Clinical patients with FBA may present acute respiratory failure or recent onset of symptoms such as cough and wheezing [3]. History and radiological findings may enable the clinician to detect the FBA soon enough in many cases. But delayed diagnosis which is defined as diagnosis time exceeding 24 hours is also common and occurs in approximately 40% of the patients with FBA [4].

Herein, we have reported the case of an 11-year-old boy with asthma misdiagnosis and an unusual type of FBA, a piece of pipette which allowed air passage through. In the presented case, the patient was diagnosed 8 months later with fiber optic bronchoscopy (FOB) and the delay is thought to be caused by the type of the foreign body.

CASE PRESENTATION

An 11-year-old boy, previously healthy, was admitted to our clinic with chronic cough he had been suffering for the last eight months. He had been being followed-up with a diagnosis of asthma for the last 6 months in another center. The patient's cough was dry, increased with effort, and continued both day and night with wheezing. He had a history of secondhand smoke exposure and was keeping a hamster at home. In the patient's history, one week before the onset of the complaint, a piece of pipette had been swallowed while drinking juice, but there was no bruising, choking, or coughing after the aspiration. The chest computed tomography taken with the suspicion of FBA at the time was normal.

Inhaled corticosteroid was started considering asthma in the patient. However, he had no clinical improvement despite regular use of inhaled corticosteroids for six months. Consequently, he was referred to our clinic for further examination due to his unresponsiveness to treatment and FBA suspicion. There was no history of additional complications other than chronic cough in the 6-month- follow-up of the patient.

In his physical examination, wheezing was heard bilaterally. He had no sign of respiratory failure. On the chest x-ray, air trapping was seen in left lung (Figure 1). FOB was planned because foreign body

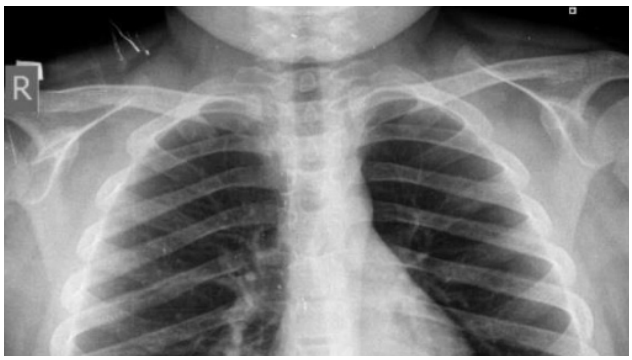

Figure 1. Air trapping in the left lung in the chest x-ray image.

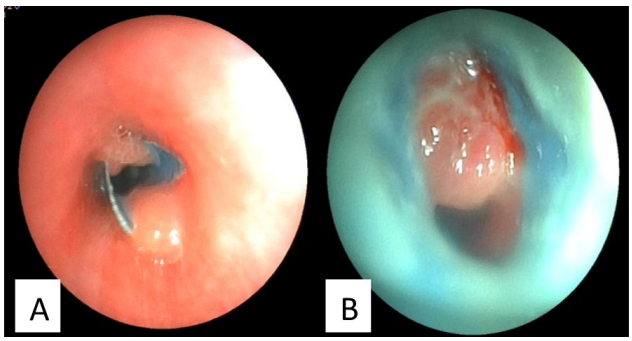

Figure 2. (A) Foreign body (a pipette) appearence in the left main brochus during flexible bronchoscopy operation and (B) the view through the lumen of the foreign body.

aspiration was suspected. During the FOB, a piece of pipette with granulation tissue around it was seen in the left main bronchus, 2 cm distal of the carina. It was possible to pass through the lumen of the pipette piece to the distal with a bronchoscope (Figure 2A,B). The foreign body which had a lumen, approximately 1.5 cm in length, and granulation tissue in it was removed by rigid bronchoscopy (Figure 3). The patient's symptoms improved in the follow-up after the procedure and his medical treatment of asthma was terminated. There was no need for use of medication again in the follow-up.

A written consent was obtained from both the patient and the parents for publishing the case.

DISCUSSION

Foreign body aspiration is a common cause of life-threatening respiratory distress in children, and usually seen under 3 years of age. Generally, acute onset of symptoms such as choking, cough, tachyp-

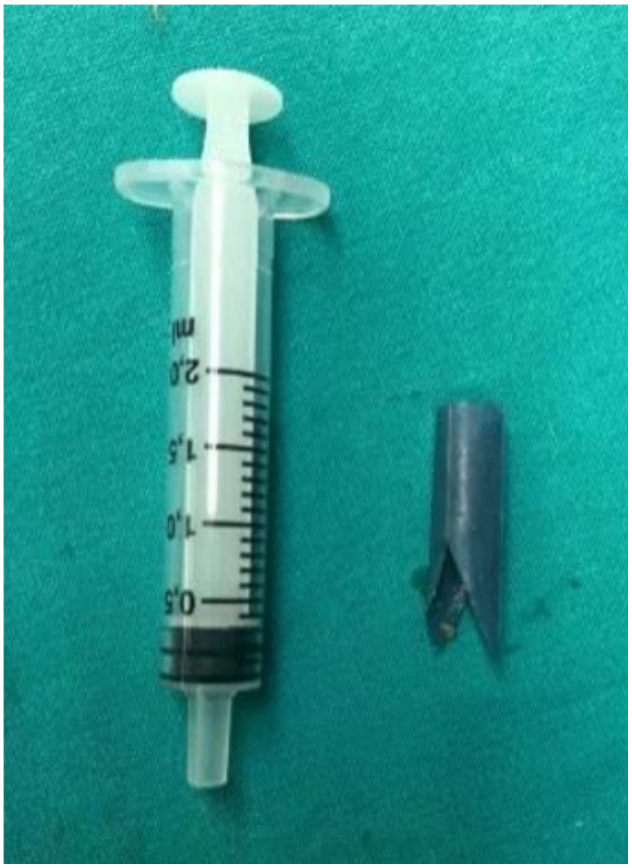

Figure 3. The lenght of the foreign body (approximetely 1,5 cm tall).

nea, stridor and focal monophonic wheezing, or decreased air entry could be presented [5]. Clinical and abnormal chest x-ray findings such as aeration difference are major diagnostic factors for FBA. Besides, it should be kept in mind that physical examination and radiological findings in patients with suspected FBA may be normal or may reveal nonspecific findings [6].

History and clinical findings provide the early diagnosis. Yet, a delay in diagnosis and its complications are not rare either [7]. Respiratory complications such as chronic cough or wheezing, recurrent pneumonias, atelectasis, life-threatening airway obstruction, or lung abscess may be detected in patients with delayed diagnosis [4,5].

Coughing is also the most frequent symptom of asthma and well-being is seen in the interim periods [7]. Detailed history, age of the patient, the time when coughing started, character of the cough, factors that trigger coughing, previous treatments and illnesses, family history, and environmental conditions must be questioned in children with chronic cough [8]. In cases where there is no response to standard asthma treatment, lack of compliance, poor inhalation technique, severe course of asthma, treatment resistant asthma, comorbid conditions, exposure to sensitizing allergens, pollution, or tobacco smoke should be investigated [6]. When all these factors are excluded, asthma diagnosis should be reviewed and different diagnoses such as FBA should be considered and FOB should be evaluated in the diagnosis.

The differences in symptoms and findings in patients with FBA may be related to the type, size and location of the foreign body. Types of foreign bodies may vary from country to country, depending on the diet and traditions of the population in question [5]. Food is mostly detected as aspirated foreign body. In the study of Tan et al. [5] the most common nonfood foreign bodies were plastic objects. The delay is especially evident when the foreign body does not cause airway obstruction and disrupt respiratory physiology. When a foreign body is aspirated, acute inflammation occurs as early as three days after the event and progression to chronic inflammation is observed as early as ten days. It is important that detection of a foreign body aspirated into respiratory tract should be followed by removal as soon as possible to avoid inflammatory reaction and development of granulation tissue [7].

The history taken from parents is very important in the diagnosis of FBA. Especially in patients with or without FBA history, reliance on a negative chest x-ray or computed tomography report may feint the clinician. More than half of the patients with wrong or misdiagnoses were treated as asthma or upper respiratory tract infection in the study of Tan et al [5]. FBA should be kept in mind in patients whose symptom control cannot be achieved. In the diagnosis and treatment of FBA, in addition to the use of rigid bronchoscopy to remove the foreign body from respiratory tract with its wide working channel, FOB plays an important role in diagnosis.

CONCLUSION

In the presented case, the patient was an 11-year-old and he aspirated a piece of plastic pipette and had a lumen that allowed air passage through the lumen. The presence of mild symptoms and vague aeration difference in chest x-ray may have caused the patient to be diagnosed 8 months later. It should be kept in mind that FOB should be performed in patients with suspected FBA.

Conflict of Interest: None.
Informed Consent: Consent was obtained from the patient.

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Case Report

Unexpected Cat Allergy in Infants with Persistent Atopic Dermatitis

Persistan Atopik Dermatitli İnfantlarda Beklenmeyen Kedi Alerjisi

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Suna Asilsoy
Özden Anal
Dilek Tezcan
Seda Şirin Köse
Gizem Atakul
Özge Atay
Özge Kangallı
Nevin Uzuner
Özkan Karaman

ABSTRACT

Atopic dermatitis is a chronic, recurrent inflammatory skin disease usually caused by genetic predisposition, immune dysregulation, epidermal barrier dysfunction and interaction of environmental factors. Atopic dermatitis is part of atopic march and is often accompanied by food allergy. Aeroallergenic sensitization at early age is not an expected finding. Here, we present five cases with moderate-severe atopic dermatitis during infancy, in whom food allergy was detected and the symptoms improved only partially despite elimination and treatment.
Sensitization was investigated in patients with a history of intense exposure to cats by specific IgE and skin prick test in infants with atopic dermatitis who had food allergy and persistant findings.
Egg allergy was detected in four of the cases, wheat allergy in one. Cat allergy was present in all. Elimination diet was started in all cases. When exposure to cats was reduced, a marked improvement in the findings of atopic dermatitis was observed in all cases.
Allergic diseases are increasing day by day. Unexpected aeroallergenic sensitization is now more common in the early stages of life. Allergic patients, regardless of age, should be questioned in detail for aeroallergen exposure. If it is detected; necessary preventive measures should be taken.

Keywords: *Atopic dermatitis, infant, cat allergy, skin prick test*

ÖZ

Atopik dermatit, genellikle genetik yatkınlık, immun disregülasyon, epidermal bariyer işlev bozukluğu ve çevresel faktörler etkileşiminden kaynaklanan kronik, tekrarlayıcı bir enflamatuar deri hastalığıdır. Atopik dermatit atopik yürüyüşün bir parçasıdır ve sıklıkla gıda alerjisi eşlik eder. Erken yaşta aeroerojenik duyarlılaşma beklenen bir bulgu değildir. Burada, bebeklik döneminde orta derecede şiddetli atopik dermatiti olan, gıda alerjisinin tespit edildiği ve semptomların eliminasyon ve tedaviye rağmen sadece kısmen düzeldiği beş olguyu sunuyoruz.
Gıda alerjisi ve kalıcı atopik dermatit bulguları olan bebeklerde, kedilere yoğun maruzuyet öyküsü olan hastalarda spesifik IgE ve cilt prik testi ile duyarlılık araştırıldı.
Olguların dördünde yumurta alerjisi, birinde buğday alerjisi saptandı. Tümünde kedi duyarlılığı mevcuttu. Tüm vakalarda eliminasyon diyetine başlandı. Tüm vakalarda kedi maruziyeti azaltıldığında, atopik dermatit bulgularında belirgin bir düzelme gözlendi.
Alerjik hastalıklar her geçen gün artmaktadır. Beklenmedik aeroalerjenik duyarlılaşma artık yaşamın erken evrelerinde daha yaygındır. Alerjik hastalar, yaşa bakılmaksızın, aeroalerjene maruz kalma açısından ayrıntılı olarak sorgulanmalıdır. Duyarlaşma saptanırsa gerekli önlemler alınmalıdır.

Anahtar kelimeler: *Atopik dermatit, infant, kedi alerjisi, deri prik testi*

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INTRODUCTION

Atopic dermatitis (AD) is a chronic, recurrent inflammatory skin disease usually caused by genetic predisposition, immune dysregulation, epidermal barrier dysfunction and interaction of environmental factors. Allergic rhinitis and asthma may occur in children with AD during infancy and this condition is called 'atopic march [(1)]. AD usually develops in early childhood and is the first step of atopic march before

respiratory allergies. The incidence of other allergic diseases increases in patients with AD and many of their family members have atopy [2]. In these patients, food allergy, which is more common in infancy and early childhood, gradually decreases with age, but sensitivity to aeroallergens increases after the age of three while sensitization to aeroallergens early in life (first two years) is not an expected finding3. The most common aeroallergens are mites, animal dander, pollen, mold and cockroaches [2].

Pet owning and sensitivities to pet allergens are increasing all over the world. Among pets, the cat is important due to its allergic properties. There are controversial data on early cat exposure. While some studies suggest that exposure reduces risk of asthma, others defend the opposite [4,5]. Here, we present five cases with moderate-severe atopic dermatitis during infancy, in whom food allergy was detected and the symptoms improved only partially, despite elimination and treatment. History of exposure to cats during and after pregnancy was revealed, and cat allergies were detected with skin prick test during infancy.

Case 1:

Four month-old girl was admitted with symptoms of atopic dermatitis that started when she was 2 months old. Pre and postnatal history was unremarkable. She was only fed with breast milk. There was no cat exposure at home. She often had a visit to an aunt who owned cats at home. On examination, she had eczematous rash on the cheeks. SCORAD ("SCORing Atopic Dermatitis") score was 38. Laboratory findings were as follows, peripheral blood eosinophil ocunts: 5.3% (500/mm^3), total IgE: 12.2 IU/mL, specific IgE egg white: 14.5 kU/l, specific IgE egg yolk: 1.3 kU/l, specific IgE FX5 (food mixture): 6.15 kU/l. The skin prick test was performed at 4 months of age that revealed formation of wheal and flare of 4 mm with egg white, and 2 mm with egg yolk. Egg elimination diet and local treatment achieved partial improvement, but atopic findings occasionally increased. The results of skin prick test performed at the age of 9 months to evaluate aeroallergenic sensitivity to house dust and cat were as follows: cat: 4 mm; egg whites: 11 mm, and egg yolk: 2 mm. In addition to treatment, avoidance of cat exposure was recommended.

Case 2:

A 7-month-old male patient was admitted with complaints of AD that started 2 weeks before. In the prenatal period, the mother owned a cat at home until the last trimester of pregnancy, and she sent the cat to the grandmother's house during her last trimester but paid frequent visits to her. SCORAD score was 53. Laboratory findings revealed peripheral blood eosinophil count: 2.1% (200/mm^3), total IgE: 17.3 IU/mL, specific IgE egg white: 1.37 kU/l, specific IgE FX5 (food mix): 0.515 kU/l. In skin prick test, cat: 4 mm, egg whites: 5 mm were detected. The patient's complaints were partially relieved by the elimination of the egg from his diet, but improved significantly following eliminating cat exposure.

Case 3:

A 3-month-old male patient presented with the complaint of AD, that started at 2 weeks of age. His family had two cats and one dog at home during and after pregnancy. SCORAD score was 46. Laboratory findings were as follows: peripheral blood eosinophil 2.2% (100/mm^3), total IgE: 9.74 IU/mL, specific IgE wheat: 0.29 kU/l, specific IgE FX5 (food mix): <0.10 kU/l. The patient was recommended to be at follow up in that period. Tests performed when he was 9 months old revealed total IgE: 149 IU/mL, specific IgE wheat: 2.79 kU/l, specific IgE FX5 (food mixture): 18.2 kU/l, specific IgE cat: 34.2 kU/l. Skin prick test results were: cat: 5 mm wheat flour: 5 mm. Wheat was eliminated from the diet of the infant. However, his symptoms improved partially despite treatment, as cat exposure continued at home.

Case 4:

A-3-month-old girl was admitted with symptoms of atopic dermatitis, restlessness and mucus in stool that started when she was 2 months old. They had a cat at home during and after pregnancy. Pre and postnatal history was unremarkable except cat exposure. SCORAD score was 48. Laboratory findings

were as follows: peripheral blood eosinophil 7.3% (600/mm^3), total IgE: 68.9 IU/mL, spesific IgE wheat: <0.35 kU/l, spesific IgE egg white: <0.35 kU/l, spesific IgE egg yolk: <0.35 kU/l, spesific IgE cow milk: <0.35 kU/l, spesific IgE cat: 1.66 kU/l. In skin prick test cat:4 mm egg white:3 mm, egg yolk:3 mm was detected. Egg was eliminated from the diet of the infant. Avoidance of cat exposure was recommended and then symptoms decreased.

Case 5:

A-4-month- old male patient was admitted with complaints of AD that started when he was 1 month old. His father had allergic rhinitis and metal allergy. SCORAD score was 38. Family had a cat at home during and after pregnancy. Laboratory findings were as follows: peripheral blood eosinophil 2.1% (100/mm^3), total IgE: 8.93 IU/mL, spesific IgE FX5 (food mix): 3.20 kU/l, spesific IgE egg white: 5.68 kU/l, spesific IgE cow milk: 2.29 kU/l. In skin prick test cat:3 mm egg white:12 mm, egg yolk:2 mm, cow's milk:8 mm was detected. Egg and milk were eliminated from the diet of the infant. Eliminating cat exposure was recommended and then symptoms decreased.

DISCUSSION

Atopic dermatitis affects approximately 20% of children and 10% of adults in developed countries6 with a still increasing frequency [7]. Industrialization and western life style are thought to facilitate the onset of AD in predisposed individuals [8]. Other allergic diseases are more common in these patients than in the general population. It is considered as a risk factor for asthma and allergic rhinitis especially in childhood and recommended that patients with moderate-severe and treatment-resistant AD should be evaluated for allergy. In these patients, susceptibility to both food and aeroallergens can be triggered. Although the most common triggering factor is food allergy in childhood, aeroallergen sensitivity may also be important. Our patients with a history of cat exposure in the early period presented with AD findings during the infancy and food sensitivity was determined during evaluation of allergy. Allergen food was eliminated from the diet. The patients whose symptoms partially regressed despite treatment were evaluated for cat sensitivity, although there was no expected finding under one year due to history of cat exposure. Exposure should be avoided

Table 1. Characteristics of the patients.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age (month)	4	7.5	3.5	3.5	4
Gender (F,M)	F	M	M	F	M
Cat exposure	often	often	continuous	continuous	continuous
SCORAD	38	53	46	48	38
Blood eosinophil (%, n/mm^3)	5.3% (500)	2.1% (200)	2.2% (200)	2.1% (100)	7.3% (600)
Total IgE (IU/ml)	12.2	17.3	179	8.93	68.9
Specific IgE (kU/L)					
Egg white	14.5	1.37	-	<0.35	5.68
Egg yolk	1.3	-	-	<0.35	-
Cow milk	-	-	-	<0.35	2.29
FX5 (food mix)	6.15	0.515	18.2	<0.35	3.2
Wheat	-	-	2.79	<0.35	-
Cat	-	-	34.2	1.66	-
Skin prick test (mm)					
Egg white	11	5	-	3	12
Egg yolk	2	-	-	3	2
Cow milk	-	-	-	-	8
Cat	4	4	5	4	3
Wheat	-	-	5	-	-
Ongoing cat exposure	no	no	yes	no	no
Food elimination	yes	yes	yes	yes	yes
Clinical improvement	yes	yes	partially	yes	yes

in cases with cat sensitivity detected in their skin prick tests and SpIgE measurements. A significant regression was found in the AD findings of our cases by eliminating the exposure.

The diagnosis of food allergy is made by food-specific IgE measurement, positive skin prick test, elimination of suspected food from diet and food challenge or double-blind placebo-controlled food challenge (DBPCFC), which is considered the most reliable method. The prevalence rates of food allergy confirmed by the food loading test (DBPCFC) in infants with AD ranges from 33% to 63% [8,9]. As aeroallergen susceptibility, association between AD and mite allergy was emphasized. However, pet allergies have been increasing in recent years. As the level of social development increases, pet owning rates increase. Cat ownership has increased by up to 57% in some countries. In our country, the cat ownership rate is determined as 15% [10]. In developed countries, 10-15% of the population has a pet allergy. Cat allergy is one of the most common pet allergies. Recently, eight cat allergens namely, Fel d1-d8 have been identified. The most common sensitization was determined against Fel d1. Sensitization was determined using saliva, danders and urine-dispersed allergens. Cat allergens were associated with eczema, allergic rhinitis, and asthma. The presence of cat exposure at an early age (first year of life) was found to be a risk factor for asthma, rhinoconjunctivitis and eczema symptoms in children aged 6-7 years [5]. A Swedish study found that cat exposure at an early age increases the risk of cat sensitization in skin prick testing [11]. Another study found a high risk of eczema in children with cat exposure at home under one year of age [12]. Cat sensitivity may begin at an early age and accompany food allergy. A significant relationship was found between disease severity and sensitivity to pet dander in children with AD under 2 years of age [13]. Current guidelines recommend avoidance of exposure to these allergens for patients with animal dander allergy [14,15].

Food allergy was determined in our cases, but although the food the patients were sensitive to was eliminated from the diet, symptoms of atopic dermatitis improved only partially. The symptoms were found to be significantly improved when cat exposure was prevented.

CONCLUSION

As the level of social development increases, the rate of pet owning is increased in different cultures. Increased pet exposure may cause allergies at a younger age. Allergic patients, regardless of age, should be questioned in detail for household pet exposure. If there is any, allergy should be detected as early as possible and protective measures should be taken in case of need.

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

Informed Consent: Written informed consent was obtained from the parent of the patient who participated in this study.

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Case Report

Extensive Plexiform Neurofibroma Presenting as Clitoromegaly in Neurofibromatosis Type 1

Tip 1 Nörofibromatoziste Kliteromegali Olarak Gözlenen Ekstensif Plexiform Nörofibrom

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Behzat Özkan

ABSTRACT

Neurofibromatosis type 1 (NF1) is an autosomal-dominant disorder with multisystem involvement. Genitourinary involvement of neurofibromatosis type 1 is a rare condition and involvement of plexiform neurofibroma can cause painful clitoromegaly. A 9-year-old girl with neurofibromatosis type-1 was referred with clitoromegaly to our endocrinology clinic. Pelvic magnetic resonance imaging (T2W images) showed that there was an 8x7x13 cm plexiform neurofibroma in the pelvic floor and peripubic region extending to the external genitalia and progressing to the subcutaneous soft tissue. Cranial and lumbosacral magnetic resonance imaging revealed two neurofibromas in the cerebellar region and the basal ganglia. It should be taken into consideration that suspicious genitalia may develop due to infiltration of space occupying formations such as neurofibromas.

Keywords: *Plexiform neurofibroma, clitoromegaly, neurofibromatosis, NF1*

ÖZ

Nörofibromatozis tip 1 birçok sistemi tutan otozomal dominat bir hastalıktır. Nörofibromatozis tip 1'de genito-üriner sistem tutulumu oldukça nadirdir ve fleksiform nörofibrom ağrılı kliteromegaliye yol açabilir. Nörofibromatozis tip-1 tanısıyla izlenmekte olan 9 yaşında kız çocuğu, endokrinoloji kliniğimize kliteromegali şikayeti ile başvurdu. Pelvik magnetik rezonans görüntülemede (T2W görüntüleri) pelvik taban ve peripubik bölgede 8x7x13 cm boyutlarında, dış genital bölgeye uzanan ve deri altı yumuşak dokuya doğru ilerleyen pleksiform nörofibrom saptandı. Kraniyal ve lumbosakral magnetik rezonans görüntülemede serebellar bölgede ve bazal gangliyonlarda iki nörofibrom saptandı. Nörofibromlar gibi yer kaplayan oluşumların infiltrasyonuna bağlı olarak şüpheli genital yapıların gelişebileceği akılda tutulmalıdır.

Anahtar kelimeler: *Pleksiform nörofibrom, kliteromegali, nörofibromatozis, NF1*

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INTRODUCTION

Clitoromegaly, which is the abnormal growth of the clitoris imitating the penile structure, is a rare condition often associated with androgen excess in sexual differentiation disorders [1-3]. Although hormonal causes of clitoromegaly especially due to congenital adrenal hyperplasia (CAH) are seen more frequently, nonhormonal conditions as pseudo-clitoromegaly and idiopathic clitoromegaly are other rarely seen entities [4]. Nonhormonal disorders of clitoromegaly include neurocutaneous syndromes (neurofibromatosis, and tuberous sclerosis etc.), epidermoid cyst, hemangiomas, nevus and superficial cutaneous lipoma [5].

Neurofibromatosis, a neurocutaneous syndrome, is a progressive autosomal dominant disease which has an incidence of approximately 1 in 3000 live births [5]. The NF1 gene which encodes tumor suppressor protein named neurofibromin, is located on

chromosome 17q11.2. A mutation in the gene leads to uncontrolled cell proliferation in neurofibromas. Plexiform neurofibroma (PN) which is pathognomonic of NF1 can involve any organ in the body [6]. Neurofibromatosis divides as type1 and 2. Two of the following diagnostic criteria must be detected to establish the diagnosis of neurofibromatosis type 1 (NF1): relevant family history, presence of six or more café-au-lait macules, multiple neurofibromas, Lisch nodules, tumor on the optic nerve and skeletal abnormalities [7]. Neurocutaneous nodules which are caused by the infiltration of neurofibromas may be localized on the genital region and lead to clitoromegaly. Although involvement of the external genitalia in the form of clitoromegaly is extremely unusual, differential diagnosis is necessary for distinguishing the other causes of clitoromegaly to refrain from unnecessary and exhaustive investigations [8].

Here, we will present a patient who applied to our outpatient clinic with clitoromegaly secondary to plexiform neurofibromas.

CASE REPORT

A 10- year-old female patient presented with complaint of painful, and slowly progressive genital swelling. Her past medical history was significant for recent diagnosis of NF type 1. Her mother and seven siblings were being followed up with the same diagnosis. On her physical examination, her weight (20 kg: <3 percentile), and height (126 cm: 3-10 percentile) were measured. She had 15 café-au-lait macules and multiple neurofibromas on her skin, two of them being behind her right ear and one of them on her back. On ophthalmoscopic examination, there were Lisch nodules on both irises. She had ambigious genitalia with rigid 3x1 cm painful clitoris. On labium majus, unlimited, rigid and painful structures which were not seemed as gonads were palpated. Urethra opened behind the clitoris and vaginal opening was intact (Figure 1). Ultrasound imaging demonstrated normal internal female genitalia including uterus, ovaries and cervix. MRI was performed on a 1.5 T superconducting system (EXCELART Vantage, Toshiba Medical Systems, Otawara, Japan). We performed coronal and axial FSE T2 -weighted sequences, precontrast and postcontrast (after IV injection of 0.1 mmol/kg gadolinium) axial T1- weighted gradient echo sequences. Routine abdominopelvic MRI revealed normal adrenal glands and female internal genitalia. Pelvic MRI showed plexiform neurofibroma with dimensions of 8x7x13 cm on the pelvic floor and peripubic region extending to the external genital region and progressing into subcutaneous soft tissue. Plexiform neurofibromas demonstrated a pathognomonic target sign signal intensity. Conglomerate masses similarly exhibited bright signal intensities on T2- weighted images (Figures 2, and 3). Fat-suppressed T1-weighted axial MRI after administration of intravenous gadolinium, intense, homogeneous enhancement of the plexiform neurofibroma. Cranial MRI revealed neurofibromas in the cerebellar region and the basal ganglia, and plexiform neurofibroma in right parietal scalp (Figure 4). Karyotype analysis revealed 46 XX male syndrome.

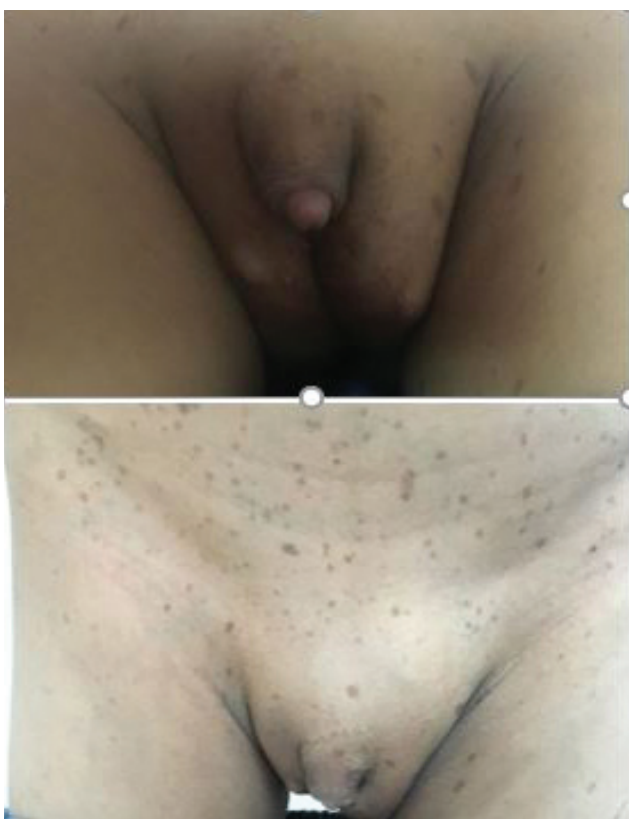

Figure 1. Neurofibromas and Clitoromegaly with pseudopenis appearance and cafe-au lait spots.

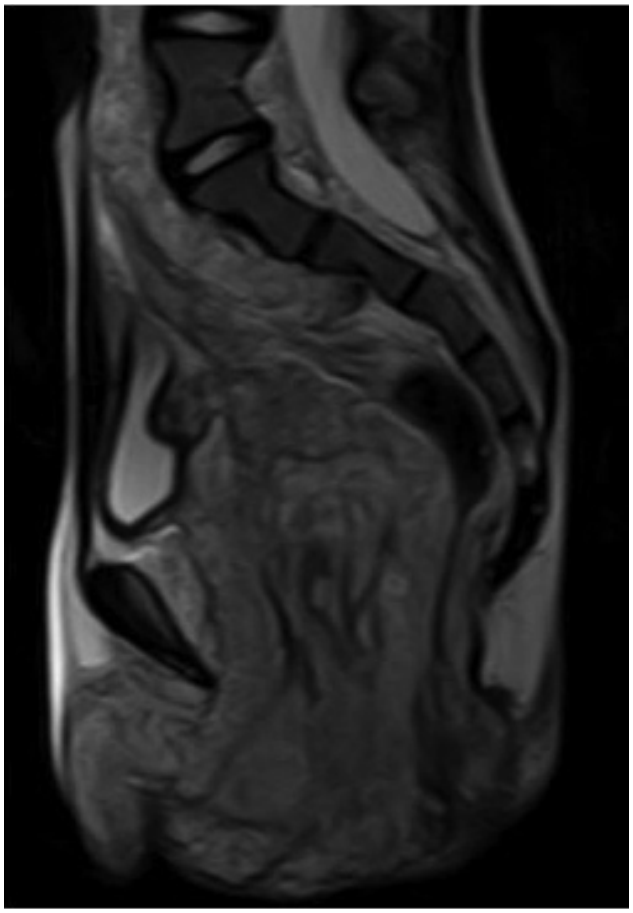

Figure 2. T2 weighted saggital image shows plexiform neurofibroma is found on the pelvic floor and peripubic region, extending to the external genital region and progressing to subcutaneous soft tissue and clitoromegaly.

Some laboratory test results were as follows: serum glucose: 86 mg/dl, serum sodium: 136 mmol/L, serum potassium:4.5 mmol/L, follicle stimulating hormone (FSH): 3.88 U/L , luteinizing hormone (LH): 0.7 U/L, 17 hydroxy progesterone (17-OH-P): 1,21 ng/ml, prolactin: 16 ng/dl, adrenocorticotropic hormone (ACTH): 12.6 pg/ml, cortisol: 19.3 µg/dl, estradiol: 15 ng/dl, total testosterone: 9.5 ng/dl, androstenedione: 0.608 ng/ml, dehydroepiandrosterone sulfate (DHEA-S): 50.5 µg/dl, and all these values were in normal range for this age and sex. The patient underwent nerve sparing reduction clitoroplasty and kept under follow-up for recurrence.

DISCUSSION

NF1 is an autosomal dominant progressive disorder and approximately 30 - 50% of patients with

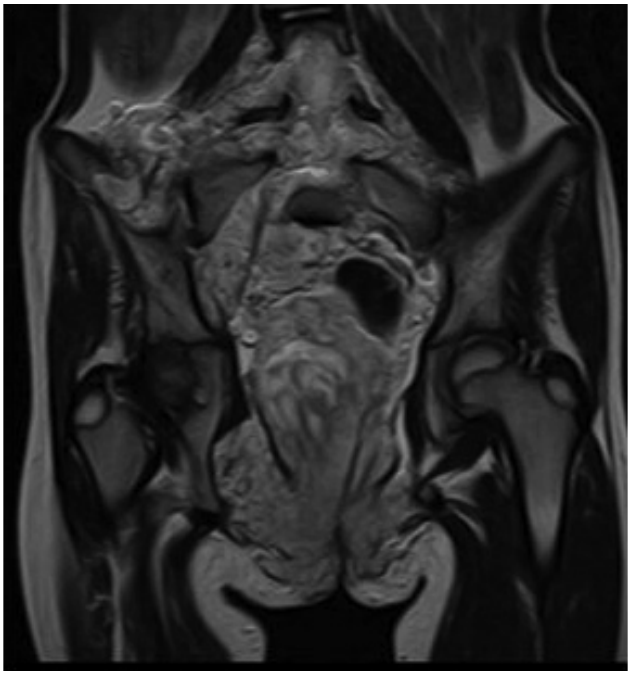

Figure 3. Coronal FSE T2 weighted image characteristic bright signal intensity on these images.

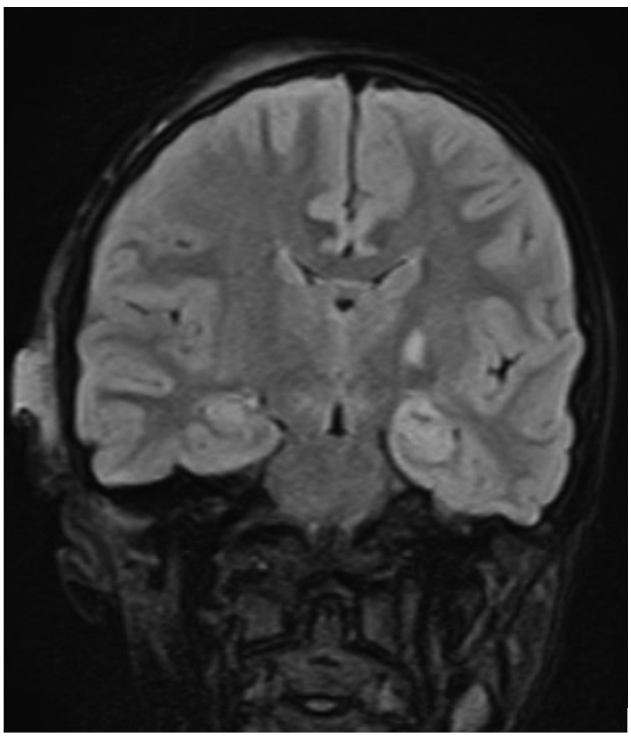

Figure 4. The MRI scan, Coronal FLAIR sequence shows typical hyperintense lesions in the basal ganglia and shows thickening with intermediate signal intensity in the right high parietal scalp.

NF1 have plexiform neurofibromas which usually arise along the course of peripheral nerves [6]. The most frequent presenting sign in external genitalia is clitoromegaly which imitates penis in female and enlarged penis in males. Genital neurofibromas have a propensity for the contiguous involvement of the bladder and ureter. Moreover, plexiform neurofibromas have extremely rare potential to transfer malignancy [9,10]. Therefore, any child with genital neurofibromatosis should be evaluated carefully for malignant potential and involvement of bladder and ureter. Hence, magnetic resonance imaging (MRI) is an important diagnostic tool to evaluate the extension of the lesion.

Clitoral neurofibroma was firstly reported by Haddad and Jones [11]. Since then approximately 30 cases were reported. Progressive, mostly painless, increased genital size as described by our patient is the most common sign in patients with clitoral neurofibroma as described by our patients. Genitourinary signs and symptoms include frequency, urgency, hematuria, and difficulty in voiding, and other rare accompanying complaints can be seen as genital neurofibromas may be associated with lower urinary tract involvement [12]. In previous reports, genital neurofibromas were typically plexiform and surgical resection has been suggested considering the malignant potential and progressive growth [13].

In our case, our patient had painful progressive clitoromegaly. She has been followed up with diagnosis of NF1 and also her mother and seven siblings had the same diagnosis. We performed MRI and 8x7x13 cm plexiform neurofibroma which was originated from the pelvic floor and extended into the external genital area and peripubic region from the pelvic floor was detected. Surgical resection has been chosen as treatment of the lesion because of the potential of progressive growth and risk of malignancy. The patient followed up for recurrence.

When clitoromegaly is detected, endocrinological evaluation should be done carefully. Endocrinological evaluation, family history, physical signs such as cafe au lait spots, neurofibromas which supports the diagnosis of NF provide to differentiate clitoromegaly due to NF1 from adrenogenital syndrome caused by an enzyme defect in the normal pathway of steroid biosynthesis, congenital adrenal hyperplasia, masculinizing tumors, exposure to the androgens. In all cases of clitoromegaly, hormonal, and nonhormonal etiologies should be evaluated in differential diagnosis. After surgical removal of the neurofibromas and clitoroplasty, it must be kept in mind that the patients should be follow up for recurrence of the neurofibromas.

CONCLUSION

Clitoromegaly due to plexiform neurofibromas in NF1 is rare. When painful, progressive clitoromegaly is detected in these patients, differential diagnosis of clitoromegaly due to neurofibromas due to hormonal disorders should be evaluated.

Conflict of Interest: The authors have stated that they have no conflict of interests.
Informed Consent: Informed consent of the patients was not obtained from parents.

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