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Journal of Dr. Behcet Uz Children's Hospital is a peer-reviewed open-access official scientific publication of the Izmir Children's Health Society and Izmir Dr. Behcet Uz Children's Hospital. The publication frequency of the journal is 3 times a year (April, August, November). Journal of Dr. Behcet Uz Children's Hospital accepts publications in English as of 2020 and published electronically.

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The journal of Dr. Behcet Uz Children's Hospital is devoted to the continuing education of national and international practicing pediatrics and pediatric surgeons, and to provide a forum for social and scientific communication in the field. Studies that emphasize these aims provide the basis for publication, including original articles, case reports, reviews, annual meetings' abstracts, letters to the editor, review of the recently published books, biographies, and social articles. The journal of Dr. Behcet Uz Children's Hospital accepts only invited review articles.

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Journal of Dr. Behcet Uz Children's Hospital is a double-blind peer-reviewed journal which has been started to be published in 2011.

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Ferrari A, Casanova M, Bisogno G, Cecchetto G, Meazza C, Gandola L, et al. Malignant vascular tumors in children and adolescents: a report from the Italian and German Soft Tissue Sarcoma Cooperative Group. Med Pediatr Oncol. 2002;39(2):109-14. doi: 10.1002/mpo.10078.

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PEER REVIEW, PUBLICATION ETHICS AND MALPRACTICE STATEMENT

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J Dr Behcet Uz Child Hosp 2022;12(3):205-210

Original Article

Evaluation of Cardiovascular Effects of Methylphenidate in Children with Attention-deficit Hyperactivity Disorder

Çocuklarda Dikkat Eksikliği ve Hiperaktivite Bozukluğunda Metilfenidatın Kardiyovasküler Etkilerinin Değerlendirilmesi

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ABSTRACT

Objective: In patients with attention-deficit hyperactivity disorder (ADHD), methylphenidate (MPH) treatment may lead to serious cardiac problems. Therefore, this study was undertaken to assess cardiac effects and electrocardiographic (ECG) changes regarding risks of ventricular arrhythmia occurring after initiation of MPH treatment in ADHD patients.

Method: Thirty patients (mean age: 8.9±1.93 years) diagnosed with ADHD and 41 healthy subjects (mean age: 9.78±3.07 years) were included in this study blood pressures, heart rates, and ECGs of the patients were evaluated before and third month of treatment. ECG parameters including QRS, QT, corrected QT interval (QTc), QTdispersion (QTdis), Tp-Te, Tp-Te dispersion, and Tp-Te/QTc ratio were also assessed.

Results: Untreated patients with ADHD and healthy subjects had similar systolic blood pressures and heart rates, although ADHD patients had higher diastolic blood pressures. An increase in heart rates, systolic and diastolic blood pressures was observed in the patient group in third month of treatment. Prior to MPH treatment, patients with ADHD and control subjects were compared in terms of ECG parameters: QRS, QT, QTc, QTdis, Tp-Te, Tp-Te dispersion, Tp-Te/QTc ratio but without any intergroup difference. Following MPH treatment, QRS, QT, QTc, QTdis did not change in the patient group but significant increases were observed in Tp-Te, Tp-Te dispersions, Tp-Te/QTc ratios.

Conclusion: Use of the MPH in ADHD patients is associated with alterations in ECG parameters, heart rates, diastolic and systolic blood pressures. Assessment of ECG parameters such as Tp-Te, Tp-Te dispersions, Tp-Te/QTc ratios may prove more beneficial for evaluating the risk of ventricular arrythmia in pediatric patients with ADHD.

Keywords: Attention-deficit hyperactivity disorder, electrocardiography, methylphenidate

ÖZ

Amaç: Dikkat eksikliği hiperaktivite bozukluğu (DEHB) olan hastalarda, metilfenidat (MPH) tedavisi ciddi kardiyak problemlere yol açabilmektedir. Bu yüzden çalışmamız da DEHB tanısı alan ve MPH tedavisi başlanılan hastalarda tedavi öncesi ve sonrasında kardiyak etkileri ve ventriküler aritmi açısından elektrokardiyografik (EKG) değişiklikleri değerlendirmeyi amaçladık.

Yöntem: Çocuk ve ergen psikiyatrisi kliniğinde DEHB tanısı koyulan 30 hasta (yaş ort: 8,9±1,93 yıl) ve 41 sağlıklı kontrol (yaş ort: 9,78±3,07 yıl) çalışmamıza dahil edildi. Kontrol ve hasta grubunun tedavi öncesi ve tedavinin üçüncü ayında kan basıncı, kalp hızı ve EKG, sonuçları kaydedildi. EKG incelemesinde QRS, QT, QTc, QTdispersiyon (QTdis), TpTe, TpTe dispersiyon ve TpTe/QTc oranı belirlendi.

Bulgular: DEHB olan hastaların tedavi öncesi ile kontrol grubu karşılaştırıldığında; sistolik kan basıncı ve kalp hızı arasında fark yok iken, diyastolik kan basıncı daha yüksek idi. DEHB tanılı hastalarda 3 aylık MPH tedavisi sonrasında; kalp hızı, sistolik ve diyastolik kan basıncında artış izlendi. Kontrol grubu ve tedavi öncesi DEHB olan hasta grubu, EKG parametreleri açısından karşılaştırıldığında; QRS, QT, QTc, QTdis, TpTe, TpTe dispersiyon ve TpTe/QTc oranı arasında anlamlı farklılık yoktu. Tedavi sonrasında ise TpTe, TpTe dispersiyon, TpTe/QTc oranında anlamlı artış olduğunu, ancak QRS, QT, QTc, QTdis değerlerinde değişiklik olmadığını izledik.

Sonuç: DEHB olan hastalarda MPH kullanımının EKG üzerinde etkisi olabilmektedir. Bu nedenle tedavi öncesi ve ilaç kullanımını takiben EKG parametreleri çok dikkatli takip edilmelidir. Bu hastaların takibinde ventriküler aritmi açısından TpTe, TpTe dispersiyonu ve TpTe/QTc oranı gibi yeni belirteçlerin kullanılması faydalı olacaktır.

Anahtar kelimeler: Dikkat eksikliği ve hiperaktivite bozukluğu, elektrokardiyografi, metilfenidat

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INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a multifactorial disorder accompanying age-inappropriate behaviors. These patients show increased hyperactivity, inattention, and impulsive behaviors [1]. Prevalence of the ADHD is between 2% and 7% with an average of around 5 percent [2].

The aim of treatment in ADHD patients is to get better functioning in behavioral, social and cognitive domains [3]. Methylphenidate (MPH) is a psychostimulant agent with sympathomimetic effects and the most commonly prescribed pharmacological treatment for ADHD [4]. MPH exerts its sympathomimetic effects through inhibition of catecholamine reuptake and elevation of dopamine and noradrenaline levels in the central nervous system. These sympathomimetic effects have been reported to cause various side effects, such as increases in systolic and diastolic blood pressures as well as pro-arrhythmic effects [5,6]. Thus, patients should be referred for early cardiological assessment in order to identify high-risk individuals.

Use of surface electrocardiography (ECG) and determination of ventricular repolarization heterogeneity may allow identification of high-risk patients. Several ECG parameters including QT interval, corrected QT interval (QTc) and QT dispersion (QTdis) have been used to evaluate the ventricular repolarization heterogeneity, although QT interval, QTc and QTdis are frequently insufficient to determine ventricular repolarization. The T wave in ECG reflects ventricular repolarization, and interval from the peak to the end of the T wave (Tp-Te interval) reflects the dispersion of ventricular repolarization [7,8]. Prolongation of the Tp-Te interval on the 12-lead ECG may indicate a new marker of ventricular arrhythmogenesis [9].

In ADHD patients, MPH treatment may lead to serious cardiac problems. Therefore, this study was undertaken to assess cardiac effects and ECG changes regarding risks of ventricular arrhythmia occurring after initiation of MPH treatment in ADHD patients.

MATERIALS and METHODS

Study Population

This study was conducted between January 01, 2018 and December 31, 2019 and included patients diagnosed with ADHD in the child and adolescent psychiatry clinic. Diagnosis of ADHD was made by child and adolescent psychiatrists according to the DSM-5 criteria [10]. Patients with ADHD who were to be started on drug therapy were evaluated by pediatric cardiology before treatment with MPH. Blood pressures, heart rates, echocardiographic, and ECG parameters of the patients scheduled to receive drug therapy were evaluated before and third month of treatment.

Treatment was started with daily doses of 5 mg MPH and titrated in a month until the therapeutic dose was achieved. The minimum and maximum doses were 5 mg and 40 mg, respectively, and the dose was individualized for each child according to his/her weight.

Age-matched subjects attending to our cardiology outpatient unit for the assessments of cardiac murmurs or for obtaining a health status report to join sports activities comprised the control group, provided that they had no cardiac defects or arrhythmia.

Exclusion criteria included presence of cardiac disease, drug usage which may prolong the QT interval (betamimetics, antihistamines, etc.), electrolyte disorders, and presence of the pulmonary or endocrine disorders.

A written approval was obtained from the Buca Seyfi Demirsoy Training and Research Hospital Non-interventional Research Ethics Committee before this study (decision no: 2021/7-56, date: 28.07.2021) and informed consent was received from all individual participants included in the study.

Electrocardiography

Twelve-lead ECG was taken under similar conditions from patients and the control group. Biocare 12A ECG device was used for ECG recordings at standart velocity and amplitude.

QRS interval was calculated as the time elapsed between the onset of the Q wave to the end point of S wave and the averaged measurements were obtained from all leads.

Duration of QT interval was calculated in leads DII, V5, and V6 and defined as the mean time from the starting point of QRS complex to the end point of T wave on the isoelectric line. We used Bazett's correction formula to measure the QTc interval for heart rate: ($QTc = QT/\sqrt{RR}$ in seconds). QTd was defined, and calculated as the difference between the minimum and maximum QT intervals of the 12 lead ECG. In addition, heart rates, Tpeak-Tend (Tp-Te) intervals, Tp-Te dispersions,

and Tp-Te/QTc ratios were calculated. Tp-Te intervals were measured with the tangent method in precordial leads [9]. A tangential line was drawn where the downward curve of the T wave intersected the isoelectric line. The Tp-Te intervals were calculated by measuring the distance between the two points on the isoelectric line. The difference between the maximum and minimum Tp-Te values in the precordial leads was defined as the Tp-Te dispersion. Systolic and diastolic blood pressures and heart rates were recorded for all groups.

Statistical Analysis

Statistical Package for the Social Sciences version 23 (SPSS Inc, Chicago, IL) was used for data analysis. The Shapiro-Wilk test was used to test for normality. Data with normal and non-normal distribution were examined using the independent t-test, and the Mann-Whitney U test, respectively. Chi-square test was performed to compare categorical variables. The comparisons were made using One-Way ANOVA. Then, post-hoc Tukey and Tamhane's T2 test were used to evaluate multiple comparisons. A value of $p<0.05$ was considered statistically significant.

RESULTS

A total of 30 patients diagnosed with ADHD (18 males, 12 females, mean age 8.9±1.93 years), and 41 healthy subjects (25 males, 16 females, mean age: 9.78±3.07 years) were included in this study. Study groups did not differ significantly regarding age and gender ($p>0.05$).

ADHD patients were receiving MPH treatment for at least 3 months at daily doses ranging between 5 and 40 mg. Both ADHD patients and healthy controls had normal echocardiography findings. Before initiation of treatment, ADHD patients and healthy controls had comparable systolic blood pressures and heart rates, although ADHD patients had higher diastolic blood pressures (67.83±3.21 mmHg vs. 65.17±5.07 mmHg; $p=0.014$). At the third month of treatment increases in systolic blood pressures (106.63±6.01 vs. 102.1±7.1 mmHg; $p=0.049$), diastolic blood pressures (70.30±4.69 vs. 67.83±3.21 mmHg; $p<0.001$), and heart rates (82.23±6.14 vs. 77.60±6.69 : beat per minute; $p=0.025$) were observed in the patient group. The demographic and clinical findings of the patient and healthy control groups are shown in Table 1.

Electrocardiographic Results

Prior to MPH treatment, patients with ADHD and control subjects were compared in terms of ECG parameters: QRS, QT, QTc, QTdis, Tp-Te, Tp-Te dis intervals, and Tp-Te/QTc ratios and any intergroup difference was not observed. Following MPH treatment,

Table 1. Comparison of demographic findings, blood pressure and heart rates values of the patient and the healthy control groups

	Healthy control group n=41	Patients with ADHD n=30		p-value
		pre-MPH treatment	post-MPH treatment	
Age (year) Mean ± SD	9.7±3.07	8.9±1.93	-	0.17
Gender F (n, %) M (n, %)	16 (39%) 25 (60%)	12 (40%) 18 (60%)	-	0.93
Systolic BP (mmHg) Mean ± SD	101.3±8.35	102.1±7.1	106.6±6.01[a,b]	0.011[a] 0.049[b]
Diastolic BP (mmHg) Mean ± SD	65.1±5.07	67.8±3.21 [a1]	70.3±4.69[a2,b]	0.014[a1] <0.001[a2] <0.001[b]
Heart rate Mean ± SD	75.3±7.25	77.6±6.69	82.2±6.14[a,b]	<0.001[a] 0.025[b]

Systolic BP: Systolic blood pressure, Diastolic BP: Diastolic blood pressure, ADHD: Attention-deficit hyperactivity disorder, MPH: Methylphenidate, SD: Standard deviation, F: Female, M: Male

[a]Different from the healthy control group ($p<0.05$)

[a1]Different from the healthy control group ($p<0.05$)

[a2]Different from the healthy control group ($p<0.05$)

[b]Different from the untreated ADHD group ($p<0.05$)

QRS duration, QT intervals, QTc, and QTdis did not change significantly in the patient group (p>0.05) although a statistically significant increase in Tp-Te intervals, TpTe dis, and Tp-Te/QTc ratios was found. ECG results of the patient and the healthy control groups are shown in Table 2.

DISCUSSION

Psychostimulant agents, such as MPH, represent the mainstay of pharmacological treatment in ADHD, with class 1 evidence showing their efficacy in this condition [11,12]. However, potential side effects of these agents remain a significant concern. While a large retrospective study did not report any cardiac side effects due to MPH use [13], another prospective study reported increased risks of arrhythmia, cerebrovascular events, and hypertension at rates of 23%, 9%, and 8%, respectively [14]. On the other hand, studies evaluating the cardiovascular effects, and particularly ventricular arrhythmogenic effects of psychostimulants in pediatric patients are limited in number [15-17]. Our study represents one of the few studies examining the effect of MPH treatment on ADHD patients in comparison with healthy subjects. According to our results, although ECG parameters did not differ significantly between ADHD patients and healthy controls prior to treatment, significant increases in Tp-Te intervals, Tp-Te dis, and Tp-Te/QTc ratios as well as systolic and diastolic blood pressures were observed following drug therapy in the MPH group, without any significant changes in QTdis, QTc, and QT intervals.

Tp-Te interval, Tp-Te dispersion and Tp-Te/QTc ratio are among the new trans-myocardial repolarization parameters that define trans-myocardial heterogeneity [9,18]. Amplification of trans myocardial heterogeneity or ventricular repolarization dispersion has long been known to be a substrate for ventricular arrhythmias [9]. In particular, the Tp-Te/QTc ratio serves as a more precise index of arrhythmogenesis, as it provides an estimate of the repolarization dispersion relative to the total repolarization time [9]. In Lamberti et al.'s [15] study examining the acute effects of MPH, any significant differences were not detected between measurements of the acquired Tp-Te intervals, while post-treatment Tp-Te/QTc ratios, though within the normal range, increased compared to the baseline values. However, in contrast with our findings, these authors observed these parameters for only 2 hours following MPH treatment, ECG findings during the long-term follow-up of the patients were not investigated. Another study reported increases in Tp-Te, Tp-Te dis, and Tp-Te/QTc ratios after 3 months of MPH treatment. Similarly, while there were no significant differences between ADHD patients and healthy controls before treatment, post-treatment increases were noted in Tp-Te intervals, Tp-Te dispersions and Tp-Te/QTc ratios among ADHD

Table 2. Comparison of the electrocardiographic parameters between the patient and the healthy control groups

ECG parameters	Healthy control group n=41	Patients with ADHD n=30		p-value
		pre-MPH treatment	post-MPH treatment	
QRS (ms) Mean ± SD	75.21±8.42	77.33±7.54	81.33±7.76[a]	0.007[a]
QT (ms) Mean ± SD	345.80±29.52	358.50±28.04	368.33±13.97[a]	<0.001[a]
QTc (ms) Mean ± SD	390.17±21.55	393.87±16.20	402.17±12.64[a]	0.014[a]
QTc dis Mean ± SD	27.92±8.28	31.83±9.60	32.66±5.83[a]	0.018[a]
Tp-Te (ms) Mean ± SD	72.07±9.41	76.00±8.44	92.67±6.91[a,b]	<0.001[a] <0.001[b]
Tp-Te dispersion (ms) Mean ± SD	10.78±3.84	11.80±2.70	14.83±3.43[a,b]	< 0.001[a] 0.001[b]
TpTe/QTc (ms) Mean ± SD	0.18±0.029	0.19±0.02	0.22±0.019[a,b]	<0.001[a] <0.001[b]

[a]Different from the healthy control group (p<0.05)

[b]Different from the untreated ADHD group (p<0.05)

ADHD: Attention-deficit hyperactivity disorder, MPH: Methylphenidate, SD: Standard deviation, ECG: Electrocardiography

patients [16]. In a large series where the cardiovascular safety among 1,224 patients was evaluated, increased risk of arrythmia, particularly in children with congenital cardiac problems was noted , without any increased risk in other conditions such as myocardial infarction or heart failure [19].

QT represents the interval between the beginning of the Q wave and the end of the T wave and therefore corresponds to ventricular depolarisation and repolarisation. Increased QT, QTdis and QTc intervals are important markers of heterogeneous myocardial repolarization, but they do not always accurately reflect the risk of polymorphic ventricular tachycardia and sudden cardiac death. It has been suggested that a QTc interval higher than 500 ms, and a QTdis interval higher than 100 ms increase the risk of arrhythmia [20]. The QTc interval was not higher than 500 ms and the QTd interval was not higher than 100 ms in any of our patients before and after the treatment. Türkmenoğlu et al. [17] reported no changes in QTc and QTdis intervals following 1 month of MPH treatment. Similarly, MPH treatment was not associated with QTdis, QTc, and QT intervals in our study. Arcieri et al. [6] compared MPH and atomoxetine treatments in children with ADHD, and found that five patients who received MPH had slightly prolonged QTc intervals after six months of drug therapy, but values remained within normal levels. In another study evaluating the acute effects of MPH treatment, Lamberti et al. [15] identified no change in QT, QTc, and QTdis, concluding that this treatment was safe in children.

An increase in heart rate and blood pressure measurements has been previously reported for psychostimulant agents, including MPH [21]. Some other studies in pediatric patients provided similar data [6,15]. In line with these previous observations, systolic and diastolic blood pressures and heart rates increased following MPH treatment in our patient group. In a study, patients receiving MPH were found to have higher blood pressures as compared to controls and ADHD patients who did not receive MPH treatment [16]. Another meta-analysis found that psychostimulants administered for the treatment of ADHD were associated with increased blood pressures and heart rates in all age groups tested [22]. An additional finding in our study was the observation that patients diagnosed with ADHD had significantly higher diastolic blood pressures than controls, even before treatment. Furthermore, these patients experienced slight, and non-significant elevations in their heart rates before treatment. These observations suggest that ADHD patients may have a low level of parasympathetic tone accompanied by a lack of physiological maturation of autonomic function [23].

Study Limitations

The small sample size was the most important limitation of our study. Another limitation of our study is the lack of evaluation with Holter ECG. We believe that further studies with larger sample size and longer follow-up periods are required for safe use of medicines in pediatric patient populations.

CONCLUSION

MPH, a psychostimulant agent used to treat ADHD, had certain effects on ECG parameters used to assess predisposition to ventricular arrhythmia as well as on diastolic, systolic blood pressures and heart rates. Appropriate therapeutic doses of this agent have not been associated with serious cardiovascular effects or fatal arrhythmic effects. However, this assumption does not negate the need to carefully evaluate ECG parameters both before and during treatment in this patient group. Particular care should be taken for children with prolonged QT intervals at baseline ECG. In addition to baseline ECG parameters, other predictive factors assessing the risks of arrhythmia such as TpTe, TpTe dispersion and TpTe/QT ratio, may be useful in pediatric ADHD patients.

Ethics

Ethics Committee Approval: A written approval was obtained from the Buca Seyfi Demirsoy Training and Research Hospital Non-interventional Research Ethics Committee before this study (decision no: 2021/7-56, date: 28.07.2021).

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

Peer-review: Externally and internally peer reviewed.

Author Contributions

Concept: A.Ş., E.A., Design: A.Ş., E.A., Data Collection and/or Processing: A.Ş., E.A., E.G., Analysis and/ or Interpretation: A.Ş., M.A., Literature Search: A.Ş., E.A., E.G., M.A., Writing: A.Ş.

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Original Article

Evaluation of Cases with Pediatric Hydatid Cyst: A 20-years Experience from Turkey

Pediatrik Kist Hidatik Olgularının Değerlendirilmesi: Türkiye'den 20 Yıllık Deneyim

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ABSTRACT

Objective: The aim of the study is to evaluate the demographic features, localizations and pathological features of pediatric cases with hydatid cyst (HC).

Method: We analyzed retrospectively 79 patients that histopathologically diagnosed as HCs between 2000 and 2020. Data such as patients' characteristics, site of lesions were collected from pathology reports.

Results: Patient's mean age was 11.24±4.42 (age range: 2-18 years). Most (51.9%) of the patients (n=41) were female and 48.1% of the patients (n=38) were male. The patients were distributed in the age groups of <6 (n=9) 6-11 (n=29), and >11 (n=29) years, as indicated. There was a male predominance in >11 years group while female predominance was seen in other age groups. HCs were most frequently localized in the liver (54.4%, n=43), and then in the lungs (31.6%, n=25). The other localization sites of HCs were spleen, cerebrum, kidney, orbit, abdomen, bone, and submandibular area. Hepatic HCs were seen mostly in female (25/43; 54.0%), and pulmonary HCs in male (13/25; 52%) patients. Histopatologically all cases shared the same typical microscopic features of HC.

Conclusion: The incidence rate of HCs in pediatric age group was increased by age. It is more common in older children (>11 years). Hepatic HCs were more common in female patients. Pulmonary HCs were more frequently seen in male patients. HCs can be seen in atypical localizations in pediatric age which should always be considered in the differential diagnosis of cystic lesions.

Keywords: Hydatid cyst, echinococcosis, pediatric age, *Echinococcus granulosus*

ÖZ

Amaç: Pediatrik kist hidatik (KH) olgularının demografik özelliklerini, lokalizasyonlarını ve patolojik özelliklerini değerlendirmek amaçlanmıştır.

Yöntem: 2000-2020 yılları arasında histopatolojik olarak KH tanısı alan 79 hasta retrospektif olarak incelendi. Hasta özellikleri, lezyon lokalizsayonları gibi veriler patoloji raporlarından elde edildi.

Bulgular: Hastanın ortalama yaşı 11,24±4,42 (yaş aralığı: 2-18 yıl) idi. Hastaların %51,9'u (n=41) kadın ve hastaların %48,1'i (n=38) erkekti. <6 yaş grubunda 9, 6-11 yaş grubunda 29, >11 yaş grubunda 41 hasta vardı. >11 yaş grubunda erkek, diğerlerinde kadın baskınlığı görüldü. En sık yerleşim yeri karaciğer (%54,4, n=43) iken, bunu akciğer (%31,6, n=25) izlemekteydi. Diğer bölgeler dalak, beyin, böbrek, orbita, abdomen, kemik, submandibular bölgeydi. Kırk üç karaciğer yerleşimli kistin 25'i (%54,0) kadın hastalarda, akciğer yerleşimli 25 KH'nın 13'ü (%52) erkek hastalarda görüldü. Histopatolojik olarak tüm vakalarda KHlerin tipik mikroskobik özellikleri mevcuttu.

Sonuç: Pediatrik yaş grubunda KH insidansı yaşla birlikte artmaktadır. Daha büyük çocuklarda (>11 yaş) daha sık görülür. Karaciğer lokalize kistler kadın cinsiyette, akciğer yerleşimli kistler erkek cinsiyette daha sık görüldü. Pediatrik yaşta atipik lokalizasyonda hidatik kistler görülebilir. Bu her zaman kistik lezyonların ayırıcı tanısında düşünülmelidir.

Anahtar kelimeler: Kist hidatik, ekinokokozis, pediatrik yaş, *Echinococcus granulosus*

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INTRODUCTION

Hydatid cyst (HC) is a zoonosis which causes serious morbidity and mortality in many regions of the world. Its most common pathogen is *Echinococcus granulosus* (EG) that causes cystic hydatid disease followed by *Echinococcus multilocularis* that causes alveolar hydatid disease. The primary hosts for EG tapeworm, are dogs and canines and the intermediate hosts are frequently sheeps. Human infection occurs by oral intake of products contaminated with parasite eggs or contacting with infected dogs [1,2]. EG is endemic in the Mediterranean region, some parts of Russia, Central Asia, China, Australia, some parts of America (especially South America) and North and East Africa [3]. HC is also a serious public health problem in Turkey and endemic especially in animal husbandry areas. Socioeconomic, educational, environmental and agricultural factors contribute to the transmission of infection especially in pediatric age [4,5].

HC is usually asymptomatic. Symptoms or complications are associated with the location and the size of the cyst. It can affect various organs and the progression of disease is different in children and adults [1,6]. The aim of the study is to evaluate the demographic features, localizations and pathological features of pediatric cases diagnosed as HC in an university hospital of Turkey.

MATERIALS and METHODS

The study was ethically approved by the local Ethics Committee of the University of Health Sciences Turkey, Basakşehir Çam and Sakura City Hospital, (protocol number: 2021.08.173, date: 19.08.2021).

Case Analysis

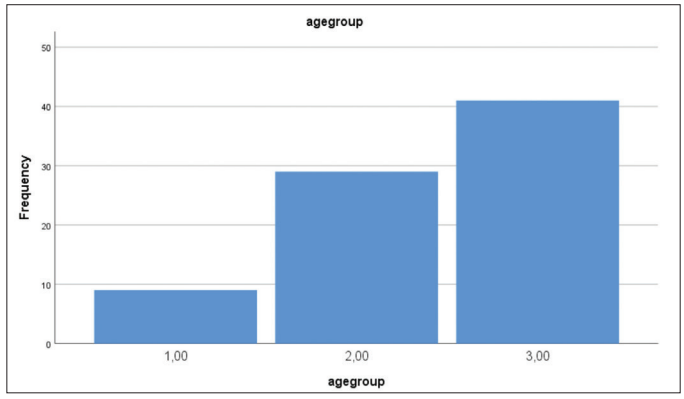
We retrospectively analyzed 503 patients including 79 pediatric cases that were histopathologically diagnosed as HC in İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Pathology between 2000 and 2020. The data including patients' characteristics, site of lesions were collected from pathology reports. Histopathological examinations were done by light microscopic examination of the sections stained with hematoxylin and eosin.

Statistical Analysis

Data analysis was performed using the SPSS 22.0 program. Descriptive statistics of the results were expressed as mean values, while the nominal variables were shown as the number of cases and percentages. Spearman, Pearson correlation and independent samples tests were used for comparison and correlations. A p=0.05 was chosen as the level of statistical significance.

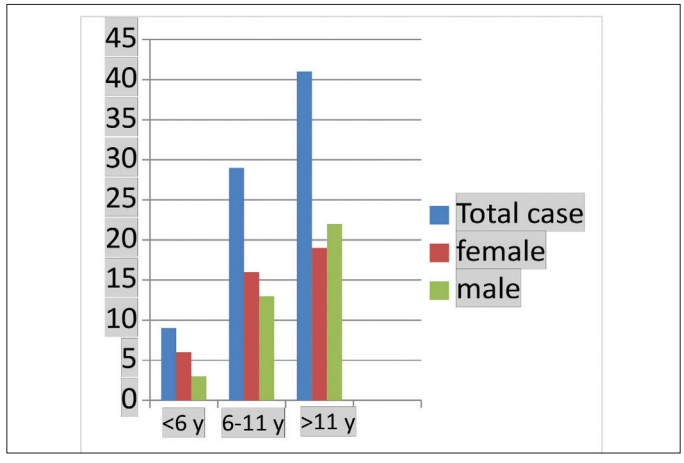
RESULTS

Patient's mean age was 11.24±4.42 years (age range: 2-18 years). Patient's ages were normally distributed. (Sig: >0.05 in the Kolmogorov-Smirnov test). There was a slight female predominance, with a female to male ratio of 41: 38. The patients were distributed in the age groups of <6 (n=9) 6-11 (n=29), and >11 (n=41) years, as indicated. The incidence increased with age (Graphic 1). The gender distribution by age is shown in Graphic 2. There was a female predominance in the age groups of <6 and 6-11 years while male predominance was seen in the age group of >11 years. However there was no significant difference between groups (p>0.05 for each group).



Graphic 1. The frequency of hydatid cyst according to age groups

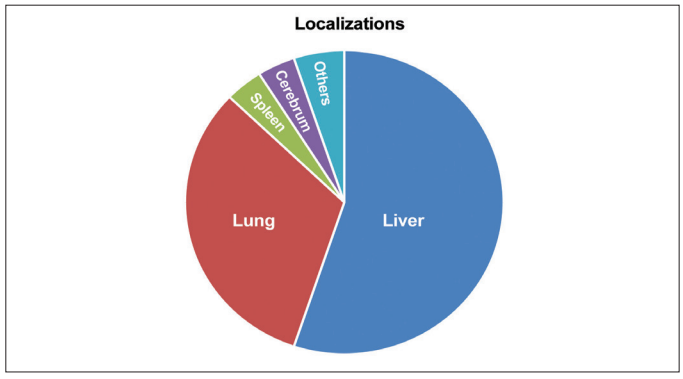
(1: <6 years, 2: 6-11 years, 3: >11 years)



Graphic 2. The gender distribution by age

HCs were most frequently localized in the liver (54.4%, n=43), and then in the lungs (31.6%, n=25). The other localization sites were spleen (n=3), cerebrum (n=3), kidney (n=1), orbit (n=1), abdomen (n=1), bone (n=1), and submandibular area (n=1) (Graphic 3). Hepatic HCs were seen mostly in female (25/43; 54.0%), and pulmonary HCs in male (13/25; 52%) patients without any significant difference between genders (p=0.470).

Histopatologically all cases shared the same microscopic features of HCs such as; presence of an avascular, eosinophilic, refractile, chitinous, thin laminated membrane, germinal layer, with or without scolex surrounded by a dense fibrous tissue (Figure 1).



Graphic 3. The localization sites of the lesions

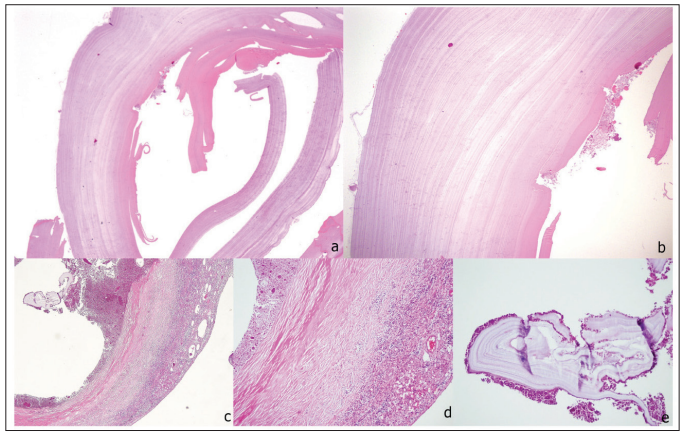


Figure 1. A- and b- Histologic appearance pulmonary HC. Avascular, eosinophilic, chitinous laminated membrane and a few scolexes. (a- H&Ex100, b- H&Ex200); c, d and e- Histologic appearance of a hepatic HC. The germinal layer with scolexes, laminated membrane, surrounded by dense fibrous tissue and atrophic liver tissue (c- H&Ex40, d- H&Ex100, e- H&Ex200)

HC: Hydatid cyst

DISCUSSION

Cystic *echinococcus* (CE) is a more common disease in adults but it is known that it is acquired in childhood.

Pediatric cases constitute 10-20% of all cases [7]. In our study; 15.7% of total cases with HCs consisted of pediatric cases. In children the most common site for CE is the lung. On the contrary hepatic cysts are mostly seen in adults.

It is suggested that because of relatively higher elasticity of children's lungs HCs grow faster in the lungs than in the liver in pediatric cases [4,5,7-9]. A study from Diyarbakır, indicated that not only in children but also in adult cases cystic pulmonary hydatidosis was found more frequently than other sites [10]. But in another study which investigated HC of children; most of cysts were located in the liver [11]. In our study the most common site was liver (54.4%), followed by lung (31.6%). Pulmonary HCs are more common in males whereas hepatic cysts are more frequent in females [12]. However some other studies showed contrary results [13,14]. Similar to literature in our study hepatic HCs were more common in females and pulmonary HCs in males. However there was no significant difference between genders regarding this issue.

HCs can be seen in atypic locations especially in pediatric age. Splenic HC is very rare and generally develops by or intraperitoneal spread from a ruptured liver cyst or systemic dissemination [15]. In our study there were 3 splenic HC cases. One of them was primarily localized in spleen however 2 of them occurred after the rupture of a hepatic HC.

Incidence of cerebral CE is 0.8-4%, and 50-75% of them are seen in the pediatric age [15,16]. Renal involvement is also very rare (0.4-4%) [15-17]. In our study rates of cerebral and renal CE were 3.8% and 1.2%, respectively.

CE also rarely involves bones (0.5-2.4%). It is most commonly seen in spine (35%), pelvis (21%), femur (16%), tibia (10%) and other sites [15-18]. In our study one case with sacral bone involvement had a history of operations due to spinal bone HC.

Peritoneal HCs are almost always secondary to hepatic involvement but a few primary peritoneal HC cases have been described [18]. In our study in one case HC was localized in abdomen without hepatic involvement.

HCs of the head and neck are also rare. Only a few cases of submandibular HC with submandibular gland involvement have been described [19,20]. In our case HC

was located in the submandibular area which expanded to tonsils without a relationship with the salivary gland.

Histopathological examination play a significant role in HC diagnosis. There are three cyst layers consisting of a fibrous outermost pericyst layer, laminated, hyalinized and acellular middle ectocyst layer and the inner endocyst or germinative layer which contains daughter cysts and scolices [15,18].

Differential diagnosis is related to the site of the lesion. Lymphangioma, hemangioma, epidermoid cyst, abscess, hematoma and posttraumatic pseudocyst should be considered in the differential diagnosis of splenic HC. Renal HCs can be misdiagnosed as simple renal cysts, renal abcess, or cystic variants of renal cell carcinoma. A spinal HC can mimic tuberculous spondylitis or chronic osteomyelitis. Benign bone cysts, fibrous dysplasia and also osteosarcoma should be evaluated in the differential diagnosis [15,18,21]. HC can be seen in atypical sites especially in pediatric age such as cardiac localizations [22].

Therapeutic management of CE hydatid disease includes medical treatment, surgical treatment and use of minimally invasive methods [23]. Our cases consisted of surgically treated patients, and HC was diagnosed histopathologically.

Study Limitations

The study has also limitations. Although the cases of a reference center with a wide patient profile have been examined, the number of cases is limited. Larger case series from multiple centers may provide more data for childhood HC.

CONCLUSION

The incidence rate of HC in pediatric age group increases with age. It is more common in older children (>11 years). Hepatic HCs were more common in female patients. Pulmonary HCs were more frequently seen in male patients. HC can be found in all parts of the body and it can be especially seen in atypical localizations in pediatric age. HC should be into account in the differential diagnosis of cystic lesions.

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Ethics

Ethics Committee Approval: The study was ethically approved by the local Ethics Committee of the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, (protocol number: 2021.08.173, date: 19.08.2021).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer reviewed.

Author Contributions

Surgical and Medical Practices: Ş.E., Concept: Ş.E.D., N.K., Ş.E., Design: Ş.E.D., N.K., Data Collection and/or Processing: Ş.E.D., C.T., Analysis and/ or Interpretation: Ş.E.D., C.T., N.K., Ş.E., Literature Search: Ş.E.D., C.T., Writing: Ş.E.D.

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Original Article

Evaluation of the Clinical, Laboratory and Etiological Characteristics of the Patients with Congenital Hypothyroidism

Konjenital Hipotiroidi Tanılı Hastaların Klinik, Laboratuvar ve Etiyolojik Özelliklerinin Değerlendirilmesi

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ABSTRACT

Objective: In this study, we aimed to determine the frequency and etiology of transient and permanent congenital hypothyroidism (CH), and to investigate the role of laboratory data in predicting permanent and transient hypothyroidism.

Method: A total of 217 patients (111 girls, 106 boys) on L-thyroxine (LT4) therapy who were diagnosed with CH and followed up for at least 3 years were included in the study. The files of the patients were scanned retrospectively. Thyroid stimulating hormone (TSH), free thyroxine (fT4) levels, thyroid ultrasonography results and treatment doses were noted at the time of diagnosis and 4-6 weeks after treatment was discontinued.

Results: Permanent CH was found in 59%, and transient CH in 41% of the cases. The most common causes of permanent, and transient CH were dysgenesis (77.3%), and dyshormonogenesis or unexplained etiology (51.6%), respectively. TSH level at the time of diagnosis was found to be statistically significantly higher in the permanent group, while fT4 levels at the 3rd year were significantly higher in patients with transient CH (p<0.0001, and p=0.002, respectively). LT4 doses were significantly lower in the transient CH group (p<0.0001).

Conclusion: Most frequently permanent hypothyroidism due to dysgenesis was detected. It has been shown that high TSH levels at the time of diagnosis, low fT4 levels in the 3rd year of treatment, and LT4 doses at the time of treatment discontinuation are determinative factors in the differential diagnosis made between permanent and transient CH.

Keywords: Congenital hypothyroidism, permanent hypothyroidism, transient hypothyroidism

ÖZ

Amaç: Bu çalışmada, konjenital hipotiroidi (KH) tanısıyla takip edilen olgularda geçici ve kalıcı hipotiroidi sıklığının saptanması, KH olgularında etiyolojinin belirlenmesi ve kalıcı-geçici hipotiroidiyi öngörmede laboratuvar verilerinin rolünün araştırılması amaçlanmıştır.

Yöntem: Çalışmaya KH tanısı konularak L-tiroksin tedavisi başlanmış ve en az 3 yıl takip edilen 217 hasta (111 kız, 106 erkek) alındı. Hastaların dosyaları geriye dönük olarak tarandı. Tanı anında ve tedavi kesildikten 4-6 hafta sonra bakılan tiroid stimülan hormon (TSH), serbest tiroksin (sT4), tiroid ultrasonografileri ve tedavi dozları not edildi.

Bulgular: Olguların %59'unda kalıcı KH, %41'inde ise geçici KH saptandı. Kalıcı hipotiroidilerin en sık sebebi disgenezi (%77,3) iken, geçici konjenital hipotiroidide en sık sebep dishormonogenezis veya açıklanamayan etiyoloji (%51,6) idi. Tanı anındaki TSH seviyesi kalıcı grupta istatiksel olarak anlamlı düzeyde yüksek saptanırken, 3. yıldaki sT4 seviyeleri geçici KH hastalarında anlamlı yüksekti (sırası ile p<0,001 p=0,002). L-tiroksin (LT4) dozları geçici KH grubunda anlamlı ölçüde daha düşüktü (p<0,001).

Sonuç: KH'nin en sık nedeninin disgenezise bağlı kalıcı hipotiroidi olduğu görülmüştür. Tanı anındaki yüksek TSH seviyelerinin, tedavinin 3. yılındaki sT4 düşüklüğünün ve tedavi kesimi sırasındaki LT4 dozlarının kalıcı ve geçici KH ayırımında belirleyici olduğu gösterilmiştir.

Anahtar kelimeler: Konjenital hipotiroidi, kalıcı hipotiroidi, geçici hipotiroidi

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INTRODUCTION

Congenital hypothyroidism (CH) is characterized by thyroid hormone deficiency in newborns and is seen in one in 2,000-4,000 live births. CH, which is the most common endocrine problem of the neonatal period, causes permanent mental retardation if not treated in the early period [1,2]. When CH is evaluated in terms of its underlying cause(s) and disease duration, it is divided into two main subgroups as permanent and transient CH. Permanent CH occurs as a result of thyroid dysgenesis, which is a developmental defect of the thyroid gland, or dyshormonogenesis, which is a defective thyroid hormone production [3]. Transient CH is a condition characterized by the improvement of thyroid hormone deficiency over time and the normalization of thyroid hormone synthesis. The main causes of transient CH are iodine deficiency, prenatal-perinatal iodine overload, maternal thyroid stimulating hormone (TSH) receptor blocking antibodies that can cross the placenta, maternal or neonatal exposure to radioactive iodine or anti-thyroid drugs, and transient dyshormonogenesis [3-5]. Moreover, determining the etiology of CH is important for the duration of the treatment [6]. In permanent CH cases, the treatment is lifelong thyroid hormone replacement. Although treatment can be discontinued earlier in some cases of transient hypothyroidism, treatment of these patients up to 3 years of age and their evaluation at that age are recommended [7-9].

The aim of our study was to determine both the frequency of permanent and transient hypothyroidism in cases diagnosed with CH in our clinic, and the etiology in cases of permanent CH, and to investigate the role of laboratory data in predicting permanent and transient CH.

MATERIALS and METHODS

Patients who were diagnosed with CH in the neonatal period, treated with L-thyroxine (LT4) and followed up regularly for at least three years in University of Health Sciences Turkey, Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital were included in the study. Patients who started treatment in other centers, cases with unknown thyroid function test results at the time of diagnosis, and those who received the diagnosis of CH in our center but continued their treatment in another clinic were not included in our study. Patients that did not attend their follow-up visits for three years for various reasons, and cases that did not reach the age limit of 3 at the time of the study were also excluded. The files of the patients were reviewed retrospectively. The age at diagnosis, gender, gestational week, maternal thyroid disease status, findings at the time of diagnosis, iodine exposure, weight, height, weight and height deviation scores, free thyroxine (fT4), TSH levels, LT4 doses at the time of diagnosis, and at the third year of the treatment and 4-6 weeks after the treatment was discontinued, thyroid ultrasonography (USG) results were recorded retrospectively from their medical records. Patients diagnosed with permanent CH by thyroid USG and/or thyroid scintigraphy were classified as cases with thyroid agenesis, ectopic thyroid gland, and thyroid hypoplasia according to imaging results. Thyroid volumes were calculated and those found below 2 standard deviation score (SDS) were accepted as thyroid hypoplasia. Treatment of the cases was discontinued at the age of three, and serum thyroid hormones were measured 4 weeks after drug discontinuation and the cases with TSH values >10 mIU/L received the diagnosis of permanent hypothyroidism [10].

Approval of Scientific Research Ethics Committee of University of Health Sciences Turkey, Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital was obtained (approval number: 639, date: 09.12.2021).

Statistical Analysis

Analyses were performed using the Statistical Package for the Social Sciences 18.0 (SPSS). Fitness of quantitative variables to normal distribution was tested with the single-sample Kolmogorov-Smirnov test. Mann-Whitney U test was used to compare data that were not normally distributed, and the chi-square test was used for intergroup comparisons of categorical data. Receiver operating characteristic analysis method was used to determine the threshold value of the LT4 dose at the time of treatment discontinuation as a predictive criterion for making a distinction between permanent and transient CH, and the sensitivity and specificity values were calculated for this threshold value. Descriptive statistics for the data were given as median (minimum-maximum) for non-normally and mean ± SDS for normally-distributed parameters. A p-value of <0.05 was considered as statistically significant.

RESULTS

A total of 217 patients, 106 (48.8%) males and 111 (51.2%) females, were included in the study. The male/female ratio was 0.95. Transient CH was detected in 89 (41%) (35 girls, 54 boys), and permanent CH in 128 (59%) patients (76 girls, 52 boys). The mean ages of the patients at diagnosis

were 24.61±19.05 days in patients with transient CH and 24.02±22.82 days in patients with permanent CH. There was no statistically significant difference according to age between two groups (p=0.706). Clinical and laboratory findings of the patients with CH are shown in Table 1. Thyroid dysgenesis was detected in 99 (77.3%) of the patients with permanent CH. Among the patients with thyroid dysgenesis, thyroid agenesis was found in 28 (28.2%), thyroid hypoplasia in 63 (63.6%), and ectopic thyroid gland in 8 (8.08%) patients. In addition, among patients with transient CH, iodine exposure due to umbilical wound care was detected in 14.6% (9 female, 4 male; total 13 patients), isolated TSH elevation in 14.6% (7 female, 6 male; total 13 patients) history of maternal anti-thyroid medication in 10.1% (6 female, 3 male; total 9 patients), prematurity in 8.9% (2 female, 6 male; total 8 patients), dyshormonogenesis or unknown etiology in 51.6% of the cases. Two of the premature cases were born by normal vaginal delivery and the rest of the premature babies were born by cesarean section. Thyroid gland dimensions were within normal limits in all premature cases based on thyroid USG findings L-T4 dosage at diagnosis was 8.95±3.19 mcg/kg/day in patients with transient CH and 10.93±2.56 mcg/kg/day in patients with permanent CH. LT4 dosages used in 3-year-old (mcg/kg/day) patients with transient CH and permanent CH were 1.25±0.45; 2.76±0.93; respectively (p<0.001). Clinical and laboratory findings of patients with permanent and transient CH are shown in Table 2.

Table 1. Clinical and laboratory findings of patients with congenital hypothyroidism

Clinical and laboratory findings	n=217
Gender (n, %) Female Male	 111 (51.2%) 106 (48.8%)
Age at Diagnosis (days)	24.6±21.3
TSH (at diagnosis) (mIU/L) (n=0.51-4.30)	86.9±32.8
fT4 (at diagnosis) (ng/dL) (n=0.93-1.77)	0.57±0.58
LT4 dosage at diagnosis (mcg/kg/day)	10.8±2.9
TSH (at 3 years old) (mIU/L) (n=0.51-4.30)	4.46±7.6
fT4 (at 3 years old) (ng/dL) (n=0.93-1.77)	1.32±0.4
LT4 dosage at 3 years old (mcg/kg/day)	2.64±1.07

TSH: Thyroid stimulating hormone, fT4: Free T4, LT4: L-thyroxine

A LT4 dose of 1.90 mcg/kg/day was found to be the best cut-off value as a predictive criterion for distinguishing between permanent and transient CH (89.1% sensitivity and 91.0% specificity) with a discriminative ability of 0.948±0.15 (95% confidence interval: 0.919-0.977, p<0.001).

DISCUSSION

CH is the most common endocrine problem in the neonatal period, and early diagnosis and treatment are important in terms of preventing mental retardation and motor dysfunction. Moreover, differential diagnosis made between permanent and transient CH will prevent unnecessary treatment in patients with transient CH, and will avoid inadequate treatment in patients with permanent CH [11].

Various prevalence rates of permanent CH (Gaudino et al. [12]: 62%, and Hashemipour et al. [13]: 59.8%), and

Table 2. Clinical and laboratory findings of patients with permanent and transient congenital hypothyroidism

	Transient congenital hypothyroidism (n=89)	Permanent congenital hypothyroidism (n=128)	p-value
Gender (n, %) Female Male	 35 54	 76 52	-
Age at diagnosis (days)	24.6±19.1 (min-max: 4-90)	24.0±22.8 (min-max: 3-150)	0.524
TSH (at diagnosis) (mIU/L) (n=0.51-4.30)	55.12±33.33	90.34±23.46	<0.001
fT4 (at diagnosis) (ng/dL) (n=0.93-1.77)	0.80±0.44	0.56±0.65	0.550
L-T4 dosage at diagnosis (mcg/kg/day)	8.95±3.19	10.93±2.56	<0.001
TSH (at 3 years old) (mIU/L) (n=0.51-4.30)	3.09±1.91	4.60±9.47	0.160
fT4 (at 3 years old) (ng/dL) (n=0.93-1.77)	1.52±0.55	1.31±0.35	0.002
L-T4 dosage at 3 years old (mcg/kg/day)	1.25±0.45	2.76±0.93	<0.001

TSH: Thyroid stimulating hormone, fT4: Free T4, LT4: L-thyroxine, min: Minimum, max: Maximum

transient CH (Messina et al. [14]: 36.5%, and Ghasemi et al. [15]: 79.4%), have been reported. On the other hand, Park et al. [16] determined the frequency of transient CH in children without dysgenesis as 65%. In various studies conducted in our country, the incidence rates of permanent CH ranging between 25-75% have been reported [11,17-22]. In our study, in line with the literature, we determined the rate of permanent CH as 59%. The frequency of transient and permanent CH differed between studies in our country. The variations in the frequency of consanguineous marriages by region, inclusion criteria (term vs preterm), the use of different TSH threshold values in the definition of transient CH, and iodine deficiency, iodine overload, or transmission of TSH receptor-blocking antibodies from the mother to the fetus can play an important role in these different frequency rates reported regarding transient and permanent CH. In the literature, thyroid dysgenesis (85%) is reported as the most common while thyroid dyshormonogenesis (10-15%) as the second most common cause of permanent CH [3]. In studies conducted in our country, thyroid dysgenesis was found in 34-55.6% of permanent CH cases [11,17,21]. In our study, we detected thyroid dysgenesis in 77.3% (n=99) of patients with permanent CH. Among the patients with permanent CH, thyroid hypoplasia was the most common cause, with a frequency of 63%. On the other hand, in the current study, the female-male ratio was 111/106 in all cases diagnosed with CH, consistent with previous studies in our country [11,18,22]. In addition, transient CH was found more frequently in male and permanent hypothyroidism in female cases.

The mean age at diagnosis has been reported to be between 11 and 18 days, and the mean age at diagnosis in our study was 24.6±21.3 [3,22-24] days. This difference in age at the time of diagnosis in this study may be due to premature cases, isolated TSH elevations, iodine exposure, and the inclusion of cases with CH due to maternal hypothyroidism.

In the literature, levels of TSH, and fT4 at diagnosis and follow-up have been studied and different results have been obtained in transient and permanent CH groups. Studies on TSH, fT4, fT3 and LT4 levels at the time of diagnosis and during follow-up have been conducted to differentiate between patients with permanent CH and transient CH and different results have been obtained [11,13,16,17,18,20-22,25-27]. In our study, serum TSH levels at the time of diagnosis were found to be significantly higher in the permanent CH group, but without any difference in fT4 levels. While there was no difference between the two groups in terms of TSH levels in the third year of treatment, fT4 was found to be significantly higher in the patients with transient CH. According to these results, we think that higher TSH levels at the time of diagnosis can be evaluated in favor of permanent CH, while higher fT4 levels in the third year of treatment may be evaluated in favor of permanent CH.

Many studies have determined that the dose of LT4 used in the treatment is higher in patients with permanent CH than in cases with transient CH [11,17,18,21,28-30]. In our study, in line with the literature, we observed that patients with permanent CH used higher LT4 doses during follow-up. In the literature, different cut-off values for LT4 doses ranging between 1.6-2.1 mcg/kg/day have been reported during treatment cessation [11,14,16,22,31]. In our study, the threshold value for LT4 dose during treatment discontinuation, which was determined as a predictive criterion for the differential diagnosis between permanent and transient CH, was 1.90 mcg/kg/day.

Study Limitations

The most important limitations of our study are its retrospective design and the relatively low number of cases. In addition, we failed to evaluate iodine deficiency or excess that may affect thyroid functions, trans-placental transmission of maternal thyroid autoantibodies, and maternal drug use that may affect thyroid functions.

CONCLUSION

In summary, in our study, the frequency of transient CH was 59%, and the most common cause of permanent CH was dysgenesis. Among the predictive criteria in the differential diagnosis between transient and permanent CH, TSH value at the time of diagnosis, fT4 and LT4 doses at the 3rd year of the treatment were found to be statistically significant.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital, Ethics Committee (approval number: 639, date: 09.12.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer reviewed.

Author Contributions

Surgical and Medical Practices: Ö.N., B.Ö., Concept: Ö.N., B.Ö., Design: Ö.N., B.Ö., Data Collection and/or Processing: Ö.N., B.Ö., Analysis and/ or Interpretation: Ö.N., B.Ö., Literature Search: Ö.N., B.Ö., Writing: Ö.N., B.Ö.

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Original Article

Evaluation of Detailed Fetal Renal Sonographic Findings and the Early Neonatal Outcomes of the Patients with Fetal Pelviectasis Whom Referred After 24th Weeks of Pregnancy

Gebeliğin 24. Haftasından Sonra Fetal Pelviektazi Saptanarak Perinatoloji Kliniğine Refere Edilen Hastaların Detaylı Renal Ultrason ve Erken Neonatal Sonuçlarının Analizi

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ABSTRACT

Objective: Analysis of detailed renal sonographic findings in the patients whom referred to our tertiary center with the diagnosis of renal pelvic dilatation (RPD) after 24 weeks of gestation.

Method: The study group consisted of the patients who have referred by their doctors to our perinatology center with a diagnosis of pelviectasy. Maternal age, gestational week, right and left renal pelvis diameter, bladder diameter, amniotic fluid index, other sonographic findings and antenatal diagnosis were analysed.

Results: Bilateral hydronephrosis were detected in 19 (44.18%) patients. Unilateral left hydronephrosis were found in 10 (23.25%) patients while right hydronephrosis were found in 6 (13.95%) patients. Mearn left renal pelvis diameter was 11.20 (4-32) mm and mean right renal pelvis diameter was 7.89 (4-18) mm. Antenatal diagnosis was vesicoureteral reflux in 16 (37.20%) patients, ureteropelvic junction obstruction in 9 (20.93%) patients, posterior urethral valves in 5 (11.62%) patients. The antetanal diagnosis was renal agenesia in one patient, renal cortikal cyst in one patient, policyctic renal disease in one patients and multiple dysplastic renal disease in 3 patients.

Conclusion: When RPD is detected in the fetal ultrasound of during pregnancy, directing the patients to the perinatal centers for advanced evaluation is important, since it can prevent the progressive renal damage that may develop in the later years of life.

Keywords: Pelviectasy, renal pelvic dilatation, detailed fetal ultrasound, renal anomalies

ÖZ

Amaç: Renal pelvik dilatasyon (RPD) ön tanısıyla üçüncü trimesterde perinatoloji kliniğine refere edilen gebelerin tersiyer merkezde yapılan ayrıntılı renal ultrasonlarının analizi.

Yöntem: Gebelik takibi sırasında birinci düzey ultrasonda pelviektazi saptanarak perinatoloji kliniğimize refere edilen üçüncü trimesterdeki gebeler çalışmaya alınmıştır. Gebelerin yaşı, gestasyonel haftası, sol ve sağ renal pelvis çapları,mesane çapları, amniotik sıvı indeksi, ultrasonda ek bulgu varlığı ve sonografik antenatal tanıları analiz edildi. Genetik anomali şüphesi olanlar ve daha önce tanı almış olanlar çalışmaya alınmadı.

Bulgular: On dokuz (%44,18) hastada bilateral hidroüreteronefroz saptanırken 10 (%23,25) hastada sol hidroüreteronefroz, 6 (%13,95) hastada sağ hidroüreteronefroz saptandı. Geriye kalan hastaların 1'inde renal agenezi, 1'inde renal kortikal kist, 6 hastada ise böbrekte kistik genişleme tespit edildi. Ortalama sol renal pelvis çapı 11,20 (4-32) mm iken ortalama sağ renal pelvis çapı 7,89 (4-18) mm idi. On altı (%37,20) hasta antenatal takiplerde veziko üretral reflu ön tanısı aldı. Dokuz (%20,93) hastada antenatal ön tanı ureteropelvik bileşke darlığı idi. Beş (%11,62) hastada posterior üretral valv düşünüldü. Bir hastada renal agenezi. Bir hastada renal kortikal kist, 1 hastada polikistik böbrek, 3 hastada multiple displastik böbrek ön tanısı konuldu.

Sonuç: Gebelik takibinde birinci düzey ultrasonda RPD saptandığında ileri düzeyde değerlendirme için hastaların perinatal merkezlere yönlendirilmesi hayatın ilerleyen yıllarında gelişebilecek ilerleyici böbrek hasarının önüne geçebileceğinden önem taşımaktadır.

Anahtar kelimeler: Pelviektazi, renal pelvik dilatasyon, ayrıntılı fetal ultrason, renal anomaliler

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INTRODUCTION

Renal pelvic dilatation (RPD) is one of the most common anomalies detected in antenatal ultrasound and is seen in 1% to 5% of all pregnancies [1,2]. RPD can be seen unilaterally or bilaterally, but incidence of unilateral pelviectasis is generally higher [3,4]. It is also more common in male fetuses than female fetuses [5].

RPD may occur due to many urological and nephrological conditions, or it may be purely physiological. Ultrasound findings accompanying RPD are also important in the differential diagnosis of this condition. RPD is also considered an aneuploidy marker, especially when detected in the 2nd trimester ultrasound [5,6]. Although this clinical condition, which may be evaluated in a wide spectrum, is described under a single title, clearer results can be obtained when the limitation is made according to the time of its occurrence and accompanying findings.

In this study, we have planned to analyze the detailed renal ultrasound findings and antenatal diagnoses of pregnant women in the 3rd trimester who were referred to our clinic with a diagnosis of pelviectasis based on level 1 (screening) ultrasound findings.

MATERIALS and METHODS

This retrospective study evaluated the patients between November 2015 and November 2018 who were referred to the Perinatology Department of the Faculty of Medicine of Trakya University. The ethical approval was obtained from Trakya University Faculty of Medicine Scientific Research Ethics Committee (decision number: 04/11, date: 05.03.2018). The patients referred after 24th weeks of gestation with a diagnosis of fetal pelviectasis were included in the study. The diagnosis of pelviectasis was made when the anteroposterior (AP) diameter of the renal pelvis was 7 mm or greater. The pregnant women who had a detailed ultrasonographic examination in our clinic before the study period were also excluded from the study. All women in the study group were selected from the pregnants who were examined firstly in the 3rd trimester in our clinic. Pregnant women who did not reach 24 weeks of gestation were not included in the study. Pregnant women who were found to be in a high risk category in screening tests were also excluded from the study.

All ultrasonographic examinations were performed using a 2-MHz convex abdominal probe of a GE Voluson 730 Expert ultrasound machine (Voluson 730; General Electric, Tiefenbach, Austria).

Age, gestational week, AP diameters of both renal pelvises, and bladder, bladder thickness, renal echogenecity, state of ureters, amniotic fluid index, additional ultrasonographic findings and sonographic antenatal diagnoses of the referred pregnant women were analyzed.

Hydronephrosis was defined based on the measurements of the AP diameter of the pelvis as mild (7-9 mm), moderate (9-15 mm), and severe (≥15 mm) hydronephrosis.

Presence of renal cysts, abnormal renal echogenicity or dimensions, oligohydroamnios, thickened bladder wall, abnormal bladder volume, state and dilatation of the ureters, and genital organs, urethral widening, and key hole signs were used as the sub-diagnostic criteria but all of the diagnoses were made after repeated sonographic examinations to exclude transient changes or sonographic pitfalls.

Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007&PASS (Power Analysis and Sample Size) 2008 Statistical Software (NCSS, Kaysville, UT, USA) program was used for statistical analysis. Kruskal-Wallis test and Mann-Whitney U test were used in the evaluation of the results of the study data. In the results of three or more in the normal examination in the reasons for voter, standard, proportionality, minimum, maximum preferences, rank quantitative selections, and in the aspects of different approaches. Pearson's chi-square test and Fisher-Freeman-Halton's Exact test were used to compare the data. Statistical significance was evaluated at $p<0.01$ and $p<0.05$ levels.

RESULTS

A total of 43 pregnant women were included in the study. The mean age of the pregnants was 31.52 (19-41) years. The mean gestational week of the pregnants was 28.83 (24-38) weeks. Bilateral hydroureteronephrosis was detected in 19 (44.18%), left hydroureteronephrosis in 10 (23.25%), and right hydroureteronephrosis in 6 (13.95%) patients. Renal agenesis was found in 1, renal cortical cyst in 1, and renal cysts in 6 patients. The mean AP diameters of the left and the right renal pelvises were 11.20 (4-32) mm, and 7.89 (4-18) mm respectively (Figure 1). The pelviectasis were classified as mild (7-9 mm) in 11 (25.5%), moderate (10-15 mm) in 22 (51.1%) and severe (>15 mm) in 10 (23.2%) patients. The bladder were larger than normal in 7 (16.27%) patients, and 5 (11.62%) of these patients had also thickened bladder wall (>2 mm). The

bladders of 3 (6.97%) patients were smaller than their age-adjusted normal sizes. Thirty (69.76%) male, and 13 (30.23%) female fetuses were evaluated. Male fetuses were significantly higher than female fetuses (p=0.001).

Additional ultrasonographic findings were detected in 10 (23.25%) patients. The most common accompanying ultrasonographic findings were hyperechoic cardiac foci (40%), followed by choroid plexus cysts, growth retardation and gallbladder agenesis in order of decreasing frequency (Table 1).

The patients were monitored up to term. Seven (16.27%) patients were excluded from follow-up because of the stabilization of the pelviectasis at 7 mm or the disappearance of ultrasonographic findings. Sixteen (37.20%) patients received the antenatal diagnosis of vesicoureteral reflux (VUR) in antenatal follow-ups. Antenatal diagnoses were posterior urethral valves (PUV) in 9 (20.93%), ureteropelvic junction obstruction in 9 (20.93%), renal cortical cyst in 5 (11.62%), polycystic kidney in 1, and multiple dysplastic kidney in 3 patients. All antenatal diagnoses were confirmed postnatally.

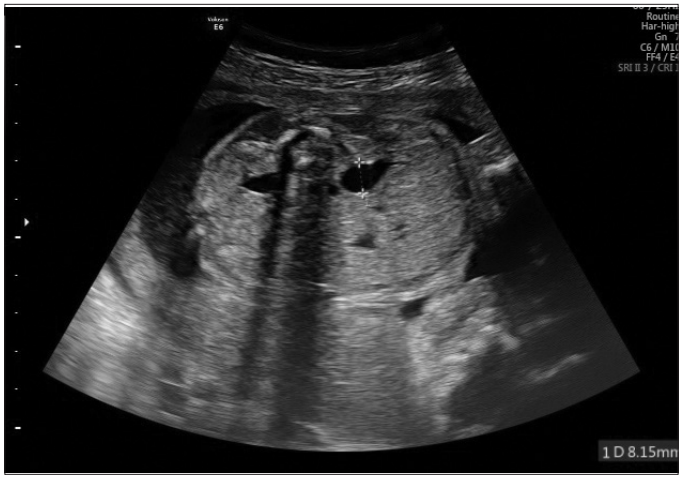

Figure 1. Fetal pelviectasis

DISCUSSION

The incidence of antenatal hydronephrosis is 1 in 500 pregnancies. They are often transient in 50-70% of the cases, but ureteroropelvic junction obstruction,vesicoreteric reflux, ureterovesical junction obstruction, multicystic dysplastic kidney, posterior urethral valve, ureterocele, ectopic ureter, duplex system, urethral atresia, cysts also lead to urinary tract dilatation. Criteria of normality are defined as normal ultrasonographic echogenicity, non-visible hydronephrosis, and ureters, visible but not enlarged bladder, and also normal amniotic fluid after 16 gestational weeks.

Fetal pelviectasis as a ultrasonographic finding at the first line sonography is one of the most common indications of referrals to the high-risk pregnancy and maternofetal units for detailed ultrasonographic evaluation. The diagnosis of fetal pelviectasis is usually made by measuring ultrasonographically the diameters of the renal pelvis in the antero-posterior plane in suspected cases of enlarged renal pelvis.

There are different approaches to the definition of fetal pelviectasis. In addition to the approaches

Table 1. Ultrasonographic findings

	Ultrasonographic findings
Gestational week at admission	28.8 (24-38) weeks
Hydroureteronephrosis	19 (44.18%) bilateral 10 (23.25%) left 6 (13.95%) right
Mean renal pelvis AP diameters	left 11.20 (4-32) mm right 7.89 (4-18) mm
Bladder	7 (16.27%) increased bladder volume 5 (11.62%) thickened bladder wall (>2 mm) 3 (6.97%) small bladder
Amniotic fluid index	4 (9.30%) oligo/anhydramnios 39 (90.69%) normal
Fetal gender	30 (69.76%) male 13 (30.23%) female

AP: Anteroposterior

that accept 4-7 mm as AP diameter of renal pelvis between 24 and 32 weeks of gestation, some authors have suggested that pelviectasis should be mentioned when it is measured above 5 mm regardless of the gestational week [6,7]. However, fetal pelviectasis is commonly mentioned when the renal pelvis diameter is measured higher than 7-10 mm in the 3rd trimester [8-10]. According to Society for Fetal Urology grading system, hydronephrosis is classified as mild, moderate, and severe when AP diameters of renal pelvises are 7-9 mm, 9-15 mm, and >15 mm, respectively [11].

In our cases, we observed regression or stabilization in the following weeks of pregnancy in almost all of the patients with renal pelvic AP diameters measuring between 7-9 mm in the 3rd trimester, and we defined them as benign pelviectasis. Benign, in other words, physiological pelviectasis develops depending on maternal hydration and pregnancy hormones [12]. Especially considering our own data, we think that the pelviectasis with AP diameters measuring between 7-9 mm with no additional finding is usually a benign condition if it would not progressively increase during follow-up. It is clear that evaluation and follow-up in advanced perinatal centers will be beneficial, especially considering the serious pathologies that may underlie the measurements above 10 mm. In our cases some of the underlying causes were ureteropelvic junction obstruction, posterior ureteral valve and VUR. Establishment of these perinatal diagnoses is very important to improve the postnatal management [13].

If pelviectasis with AP diameters measuring over 10 mm worsens during pregnancy, it is recommended that these patients should be followed up in tertiary centers that also have pediatric urology and pediatric nephrology clinics [14]. We included patients whose detailed ultrasonographic examinations were not performed by us and pelviectasis was detected for the first time in the 3rd trimester and referred to us in our study. One of our aims here was to reveal the correlations or contrasts with the preliminary diagnosis of the patients by disclosing the findings of the ultrasonographic examinations performed in a tertiary health care center and sent to us with the diagnosis of pelviectasis. Only 16.27% of the patients referred to us were evaluated as benign pelviectasis. Potentially serious renal pathologies were diagnosed during antenatal period in 83.72% of the cases. VUR was detected in 11-24% of the cases with antenatal pelviectasis [15,16].

In our study group, 37.20% of the patients had the antenatal diagnosis of VUR during antenatal follow-up. Antenatal diagnosis was ureteropelvic junction stenosis in 20.93% of the patients. Suspicion of these two most common diagnoses in the antenatal period and appropriate follow-up after birth are of great importance as it can prevent progressive kidney damage that may occur in the future. The antenatal diagnosis of PUV is also important because it has been shown that it may improve postnatal management [13]. Critical diagnoses leading to termination of pregnancy were less frequently seen by us, because we included only pregnancies diagnosed in the 3rd trimester in our study. Genetic diseases are diagnosed earlier. Severe pathologies like polycystic kidney are usually diagnosed until the 3rd trimester. Third trimester diagnoses usually include pathologies for which follow-up conveys paramount importance.

When the patients referred to us were evaluated, a correlation was found with the findings detected in level 1 ultrasound which signifies that when in doubt referral of the patients to perinatal centers is a medically correct approach.

When fetal pelviectasis is detected in the first level ultrasound, the findings will be evaluated more precisely and it will be easier to enlighten the patient before referral to a tertiary health care center if the state of the bladder and sex of the fetus are known. In general, when pelviectasis below 10 mm is detected, and in the absence of additional finding(s), the patient should be told that a good prognosis is expected and the possibility of serious underlying disease is low. However, any pelviectasis greater than 7 mm, regardless of whether it is accompanied with additional findings or not, should be referred to advanced perinatal centers where pediatric urology consultations is possible. Particular attention should be paid to progressive and bilateral pelviectasis.

One week and one month after birth, renal ultrasound should be performed to all these fetuses to confirm the antenatal diagnosis and to plan for follow-up and treatment [17].

Study Limitations

This was a retrospective study with a small sample size. We examined pregnant women who applied to a tertiary center with the diagnosis of pelviectasis. We evaluated the sonographic findings and postnatal diagnoses of the fetuses. We also confirmed our prenatal

diagnoses in the postnatal period. Although it is very important to follow these babies up to the age of 2 after birth, this study included the postnatal data of babies from birth to one month.

CONCLUSION

Apparently, the follow-up, which can prevent progressive kidney damage, starts in the antenatal period. Therefore, it is of great importance to determine whether there is a noticeable enlargement of the kidneys of the fetus during ultrasonographic examination performed in the 3rd trimester evaluation as a routine pregnancy follow-up.

Ethics

Ethics Committee Approval: The ethical approval was obtained from Trakya University Faculty of Medicine Scientific Research Ethics Committee (decision number: 04/11, date: 05.03.2018).

Informed Consent: Retrospective study.

Peer-review: Externally peer reviewed.

Author Contributions

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

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Case Report

A 30-day-old Infant with Meningitides due to Invasive Methicillin-sensitive *Staphylococcus aureus* Infections: A Case Report

İnvaziv Metisilin Duyarlı Staphylococcus aureus'un Neden Olduğu Menenjitli 30 Günlük İnfant: Olgu Sunumu

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ABSTRACT

One-month-old girl was referred to our hospital because of ongoing fever and methicillin-sensitive *Staphylococcus aureus (S. aureus)* (MSSA) positivity in blood cultures, despite the administration of antimicrobials for 14 days. Although there was, no immunodeficiency or underlying disease that could be a risk factor for infection, on the 14th day of the cefotaxime for MSSA meningitides, the persistence of leukocytosis in cerebrospinal fluid (CSF) analyses also was continued. After administration 30 days of treatment, the patient was discharged from the hospital with a normal CSF analysis and clinic. Central nervous system infections caused by *S. aureus* are uncommon in pediatric patients. The treatment of *S. aureus* meningitis is challenging because of the lack of established management guidelines, difficulty in achieving therapeutic drug concentrations in CSF, and presence of resistant strains. Therefore, it has a high clinical importance. This case is presented to emphasize that meningitis due to *S. aureus* difficulty in the treatment management, and need for further examination.

Keywords: *Staphylococcus aureus*, meningitides, cerebrospinal fluid culture

ÖZ

Dış merkeze ateş nedeni ile başvuran ve kan kültüründe metisiline duyarlı *Staphylococcus aureus (S. aureus)* (MSSA) üremesi saptanan 1 aylık kız hasta, 14 günlük antibiyograma uygun tedaviye rağmen klinik iyileşme olmaması ve kan kültürü pozitifliğinin devam etmesi üzerine hastanemize sevk edildi. Başvurusunda beyin omurilik sıvısı (BOS) kültüründe de MSSA saptanan ve altta yatan immün yetmezlik veya komorbiditesi olmayan hastanın, 14 gün süre ile antibiyograma uygun sefotaksim tedavisi sonucu BOS bakısında lökositozun sebat ettiği görüldü. Otuz günlük tedavinin ardından hastanın BOS bulguları ve klinik bulguları tamamen normal olarak taburcu edildi. Pediyatrik hastalarda *S. aureus*'un neden olduğu merkezi sinir sistemi enfeksiyonları nadirdir. *S. aureus* menenjitinin tedavisi, yayınlanmış rehberlerin olmaması, BOS'de terapötik ilaç konsantrasyonlarına ulaşmanın zorluğu ve dirençli suşların varlığı nedeniyle zordur. Bu nedenle klinik önemi yüksektir. Bu olgu, *S. aureus*'a bağlı menenjitin tedavi yönetiminde güçlüğü ve ileri tetkik gerekliliğini vurgulamak amacıyla sunulmuştur.

Anahtar kelimeler: *Staphylococcus aureus*, menenjit, beyin omurilik sıvısı kültürü

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INTRODUCTION

Invasive methicillin-sensitive *Staphylococcus aureus (S. aureus)* (MSSA) infections contribute significantly to public health burden and cause substantial morbidity and mortality [1]. Central nervous system (CNS) infections caused by *S. aureus* are uncommon in pediatric patients [2]. In Schlech et al.'s [3] study published about 20 years ago [3], the incidence of bacterial meningitis caused by *S. aureus* in children in the United States has been reported as less than one percent, while studies published in recent years have indicated an increase in its incidence [4,5]. Usually, these infections occur as a complication of invasive neurosurgical procedures or as a consequence of disseminated *S. aureus* infection [6]. In recent years, although the number of cases with CNS infections caused by *S. aureus* has increased, relevant large series have not been reported [2,4]. We presented an infant with long-term MSSA positivity in both blood and cerebrospinal fluid (CSF) cultures, despite administration of appropriate antibiotherapy.

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CASE REPORT

A one-month-old girl was referred to our hospital for further evaluation due to recurrent MSSA positivity in blood cultures. Despite ampicillin and gentamicin antibiotherapies for 14 days in a tertiary healthcare center, she was referred to us with persistent fever. The patient was born at term without any history of chorioamnionitis or another maternal infectious disease. It was revealed that the patient, who had been hospitalized for five days in the postnatal period due to jaundice, had not undergone any additional invasive procedures.

She had been suffering from loss of appetite before her admission to the hospital physical examination revealed a lethargic infant with a suspect tense fontanel. Her weight and height were in the 75th percentile and head circumference was 38 cm (50-75th p). The remaining physical examination findings were within normal limits. Laboratory tests showed elevated white blood cell (WBC: 13,920/µL) count with lymphocytic predominance (6,770/µL; 48.6%), C-reactive protein (6.44 mg/dL; normal value: <5 mg/dL), and procalcitonin (0.27 ng/mL; normal value: <0.1 ng/mL), acetyl transferase (122 IU/L; normal range: 15-60 IU/L), alanine transaminase (76 IU/L; normal range: 13-45 IU/L) were elevated. Electrolytes, and the results of renal function and coagulation tests were within their normal ranges. Transfontanel imaging and lumbar puncture of the patient was performed, because of the findings of tense fontanel, signs of lethargy, and persistent MSSA positivity in blood cultures. The transfontanel ultrasonography scan was normal. CSF examination revealed leukocytosis with neutrophilic predominance, an elevated protein content (1,227 mg/dL; normal range: 20-80 mg/dL), low glucose levels (14 mg/dL; normal range 60-80 mg/dL). Any microorganism was not observed during microscopic examination of Gram stained specimens. After obtaining blood, urine, and CSF cultures, intravenous cefotaxime (300 mg/kg/day), ampicillin (300 mg/kg/day) and vancomycin (60 mg/kg/day) were initiated empirically. The fever persisted for only one day after hospitalization. Viral reverse transcription-polymerase chain reaction (PCR) tests performed in CSF samples were negative for herpes simplex virus 1-2, varicella zoster virus, enterovirus and paraechovirus. MSSA had been detected in both blood and CSF cultures obtained on admission. Antibiotherapy with clindamycin and cefotaxime was initiated based on antibacterial susceptibility test results which revealed *S. aureus* growth both in blood and CSF cultures. After detection of MSSA in blood and CSF, cranial magnetic resonance imaging and transthoracic echocardiography were performed, and any foci of metastatic infection was not found.

The patient developed neutropenia (absolute neutrophil count: 320/10^3 µL) during the follow-up and she was consulted to hematology and immunology departments. A follow-up protocol for neutropenia was recommended. An immunological screening was recommended in consideration of long-term reproduction of MSSA and the results of an evaluation of cellular immunity, humoral immunity, and complement levels. Although all immunological parameters evaluated were within normal limits, immunology recommended outpatient follow-up.

Results of the control analysis of the CSF at the 14th day of antibiotherapy were as follows: WBC: 120/mm^3, protein: 146.8 mg/dL, and glucose: 30 mg/dL. For differential diagnosis, tuberculosis tests, were also performed in addition to the culture obtained, due to the persistence of leukocytosis and high protein levels in the CSF. *Mycobacterium tuberculosis* was not detected in CSF based on Ehrlich-Ziehl-Neelsen staining a PCR assay and culture obtained. CSF and blood cultures were also negative for *Mycobacterium tuberculosis.*

Clindamycin was discontinued on the 14th day and cefotaxim was given for a total of 30 days. Lumbar puncture was performed again before the discontinuation of antibiotic treatment and CSF examination results were within normal limits. And she was discharged on the 32th day of hospitalization.

During a 6-month follow-up period, no sequela due to meningitis developed in the patient.

Consent was obtained from the patient during the formation of the case report.

DISCUSSION

Here we presented an infant with bacteremia and meningitis caused by MSSA. Although she previously received appropriate treatment for 14 days in a hospital she had been admitted, blood and CSF cultures were still positive for MSSA. There was no immunodeficiency or underlying disease that could be a risk factor for infection. Therefore, the patient's advanced imaging and immunological evaluations were performed, and her treatments were arranged according to the antimicrobial susceptibility test results. The treatment was continued for 30 days as a result of persistent leucocytosis in CSF. Since there is no clear information in the literature regarding the duration of treatment for *S. aureus*

meningitis and invasive infections, we maintained the treatment until both peripheral and CSF cultures were sterile and no cells were seen in CSF.

CNS infections caused by *S. aureus* are uncommon in previously healthy children [2]. Most cases of *S. aureus* meningitis occur in patients with a history of neurosurgical procedures, trauma and had CSF shunt devices implanted. Other important etiologic factors include hematogenous dissemination of *S. aureus* secondary to bacteremia, and presence of additional underlying diseases. In our case, blood culture was positive for MSSA. Similar to the literature, the case in our study was evaluated as meningitis due to hematogenous dissemination of *S. aureus* secondary to bacteremia.

The choice of antimicrobial agent for *S. aureus* meningitis should be determined by the susceptibility profile of the agent [7]. Any relevant large series and any established management guidelines for pediatric cases with *S. aureus* meningitis have not been reported so far [4]. The treatment is challenging because of difficulty in achieving therapeutic drug concentrations in CSF, and the presence of resistant strains. Usually, for the treatment of MSSA meningitis, a parenteral B-lactam antibiotic such as oxacillin, nafcillin, or cephalosporins is recommended [7]. Although the duration of treatment is controversial, the guidelines recommend the use of antibiotics for at least 2 weeks [2]. In an adult study by Aguilar et al. [4], the authors observed that CSF had been cleared of MSSA in a mean time of 7.7 days. In this case, on the 14th day of the cefotaxime and clindamycin treatments, CSF culture-negativity was achieved but cefotaxime treatment was maintained for one month due to the persistence of leukocytosis in CSF. Despite high mortality rates in infants with MSSA meningitis [8], our patient was discharged without sequelae.

MSSA should be considered as a causative agent in previously healthy patients whose clinical findings did not improve despite appropriate antibiotic therapy, and treatment should be managed according to the CSF findings and culture positivity.

Informed Consent: Consent was obtained from the patient during the formation of the case report.

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Author Contributions

Surgical and Medical Practices: E.C., Concept: E.C., Design: E.C., Data Collection and/or Processing: E.C., E.K., E.B., Ş.Ş., Analysis and/or Interpretation: E.C., M.Y.Ç., M.D., A.A.K., Literature Search: E.C., M.Y.Ç., M.D., Writing: E.C.

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Case Report

Transient Hyperphosphatasemia Associated with Human Bocavirus Infection

Human Bocavirüs Enfeksiyonu ile İlişkili Geçici Hiperfosfatazemi

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ABSTRACT

Transient hyperphosphatemia is a rare benign condition in children characterized by elevated serum alkaline phosphatase levels in infancy and childhood without metabolic bone or liver disease. As it can occur with many different conditions, temporary hyperphosphatasia can be seen especially in gastrointestinal, ear, urinary and respiratory tract infections. It is believed to be triggered by a viral infectious disease. It is important to raise the awareness of clinicians on this issue in terms of facilitating the diagnosis and not requiring additional research. Here, a case of transient hyperphosphatasemia with acute bronchiolitis caused by human bocavirus infection is presented.

Keywords: Alkaline phosphatase, transient hyperphosphatasemia, acute bronchiolitis, infant

ÖZ

Geçici hiperfosfatemi, metabolik kemik veya karaciğer hastalığı olmaksızın bebeklik ve çocukluk döneminde yüksek serum alkalin fosfataz seviyeleri ile karakterize, çocuklarda nadir görülen iyi huylu bir durumdur. Birçok farklı durum ile ortaya çıkabileceği gibi özellikle gastrointestinal, kulak, idrar ve solunum yolu enfeksiyonlarında geçici hiperfosfatazemi görülebilmektedir. Viral bulaşıcı bir hastalık tarafından tetiklendiğine inanılır. Klinisyenlerin bu konuda bilinçlendirilmesi tanıyı kolaylaştırması ve ek araştırmalar gerektirmemesi açısından önemlidir. Burada human bocavirüs enfeksiyonu ile ilişkili akut bronşiolit ile birlikte geçici hiperfosfatezemi saptanan olgu sunulmaktadır.

Anahtar kelimeler: Alkalen fosfataz, geçici hiperfosfatazemi, akut bronşiolit, bebek

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INTRODUCTION

Transient hyperphosphatasemia is characterized by elevated serum alkaline phosphatase (ALP) levels in infancy and childhood without metabolic bone or liver disease [1]. It can be seen concomitantly with many viral infections, especially gastroenteritis and upper respiratory tract infections [2]. Here, a case of transient hyperphosphatasemia with acute bronchiolitis caused by human bocavirus (HBoV) infection is presented.

CASE REPORT

Eight-month-old boy (who was healthy) was admitted to pediatric emergency service with complaints of cough and wheezing. He was admitted with a diagnosis of acute bronchiolitis. At admission his head circumference 43.5 cm was [-1.28 standard deviation (SD)], body weight 9,600 gr (0.5 SD), body length 74 cm (0.82 SD), body mass index 17.5 (0.01 SD) and growth and development was normal. From laboratory findings, ALP level was 4647 IU/L (age-adjusted normal range: 110-302 IU/L). Aspartate aminotransferase, alanine aminotransferase, glutamine transferase, bilirubin and serum creatinine levels were within normal ranges, therefore hepatic and renal pathology was excluded. One month ago, the patient had a serum ALP level of 149 IU/L. No rachitic changes were detected in the wrist X-ray of the patient. Serum calcium level was 10.3 mg/dL (reference range:

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8.9-10.9 mg/dL), serum phosphate 4.8 mg/dL (reference range: 4.5-6.7 mg/dL), serum 25-hydroxyvitamin D [25(OH)D] 25 ng/mL (reference range: 25-80 ng/mL) and serum parathyroid hormone (PTH) 29 pg/mL (reference range: 11-67 pg/mL). Thus, rickets and other bone metabolism disorders were also ruled out. HBoV was identified in respiratory specimen by means of reverse transcription-polymerase chain reaction. The patient, who was followed up with oxygen and fluid therapy with a simple mask in our emergency department, was discharged home with the recommendation of control. On the 14th day of follow-up, ALP level decreased to 576 U/L and other laboratory values were within normal ranges. Without any treatment, serum ALP concentration returned to age-adjusted normal values in the first month of follow-up (Figure 1). Verbal consent was obtained from the patient's family.

DISCUSSION

ALP is an enzyme with different isoenzymes secreted from many tissues such as bone, liver, kidney and intestines [1]. Serum ALP concentration increases in conditions such as hepatopathy (cholestasis, malignancy), metabolic bone diseases (rickets, osteomalacia), diseases with high bone turnover (bone tumors), chronic renal failure, tubulopathies, and during treatment with some medications (cotrimoxazole, antiepileptics) [1,3]. ALP elevation in children can also present as a benign condition known as transient hyperphosphatasemia.

Transient hyperphosphatasemia is most common in young children, especially between 6 and 24 months of age [2]. Its prevalence in children younger than 24 months (previously healthy) has been reported to range from 2.8 to 6.2 percent (between 400 and 1,000 units/L) [4-6]. Often, an isolated elevation in serum ALP can be detected incidentally during laboratory testing for routine health care or as part of an evaluation for a particular complaint. Although various theories have been proposed regarding the etiology of benign hyperphosphatasemia, the pathogenesis of this clinical condition is not clear. It is a benign condition thought to be triggered by viral agents. In a study of 21 cases, it has been shown that temporary hyperphosphatasemia can be seen in especially gastrointestinal tract infections [7]. In addition, it can be seen in conditions such as ear, urinary and respiratory tract infections, failure to thrive or gastrointestinal disturbances and coeliac disease [7,8]. Pathogens such as rotavirus, echo 22, enterovirus, coxsackies, adenovirus have been associated with transient benign hyperphosphatasemia [9]. It was thought that the transient hyperphosphatasemia in our patient might be associated with acute bronchiolitis caused by HBoV. Serum ALP concentration typically rises 4 and 5 times the upper reference limit [2,10]. Rarely, elevations up to 20 times the upper reference limit have also been described in the literature. In our patient, ALP level increased 30 times compared to the ALP levels measured 1 month previously, while other laboratory values [including 25(OH)D and PTH] remained at normal levels during hospitalization and follow-up. On the 30th day of his admission, his ALP level also returned to normal limits.

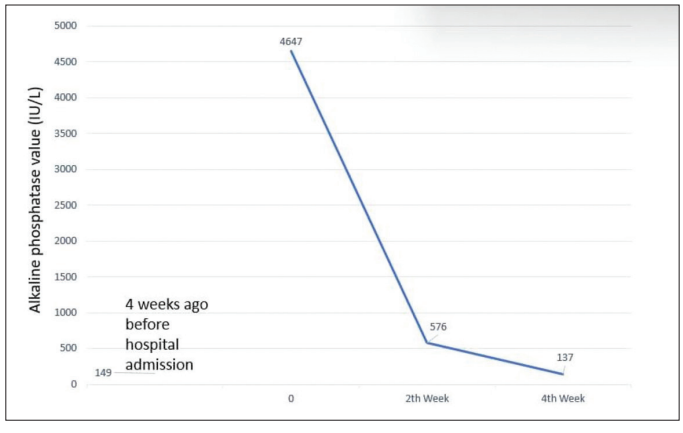

Figure 1. The time course of alkaline phosphatase elevation

CONCLUSION

Transient hyperphosphatasemia is a benign condition that accompanies many different diseases characterized by elevated serum ALP levels during infancy and childhood without metabolic bone or liver disease. It is important to raise the awareness of clinicians on this issue. In this case, recognizing the presence of transient hyperphosphatasemia may facilitate rapid diagnosis, and minimize anxiety for both the clinician and the patient's family.

Informed Consent: Verbal consent was obtained from the patient's family.

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Author Contributions

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Case Report

A Case of Severe Poisoning due to Oral Hydrofluoric Acid Ingestion that Could Survive with Timely Effective Treatments

Zamanında Etkili Tedavilerle Hayatta Kalabilen, Oral Hidroflorik Asit Alımına Bağlı Ciddi Bir Zehirlenme Olgusu

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ABSTRACT

Hydrofluoric acid (HFA) is one of the most corrosive inorganic acids. Systemic toxicity usually occurs after ingestion or inhalation. It can lead to hypocalcemia, hypomagnesemia, hypokalaemia, hyperkalaemia, shock, metabolic acidosis, and ventricular dysrhythmias. A 13-month-old male patient was hospitalized after drinking an unknown amount of unbranded rust remover that contained HFA. Following his admission to the hospital, the patient suffered a sudden cardiac arrest with ventricular fibrillation in the pediatric emergency department. Cardiopulmonary resuscitation and defibrillation were carried out. Subsequently, continuous veno-venous hemodiafiltration (CVVHDF) was applied for twelve hours in the pediatric intensive care unit and he was discharged with a recovery. To the best of our knowledge, this case is the first pediatric case in the literature to survive after oral exposure and to receive successful CVVHDF.

Keywords: Hemodiafiltration, hydrofluoric acid, pediatric emergency department, pediatric intensive care, poisoning, ventricular fibrillation

ÖZ

Hidroflorik asit (HFA), en korozif inorganik asitlerden biridir. Sistemik toksisite genellikle yutma veya soluma sonrasında ortaya çıkar. Hipokalsemi, hipomagnezemi, hipokalemi, hiperkalemi, şok, metabolik asidoz ve ventriküler disritmilere yol açabilir. On üç aylık erkek hasta, bilinmeyen miktarda HFA içeren markasız pas sökücü içtikten sonra hastaneye kaldırıldı. Hastaneye kabulünün ardından hasta çocuk acil servisinde ventriküler fibrilasyon ile ani kalp durması yaşadı. Kardiyopulmoner resüsitasyon ve defibrilasyon yapıldı. Ardından çocuk yoğun bakım ünitesinde 12 saat sürekli veno-venöz hemodiyafiltrasyon (CVVHDF) uygulandı ve şifa ile taburcu edildi. Bildiğimiz kadarıyla, bu vaka literatürde oral maruziyetten sonra zamanında CVVHDF uygulanıp hayatta kalan ilk pediatrik vakadır.

Anahtar kelimeler: Hemodiyafiltrasyon, hidroflorik asit, çocuk acil servis, çocuk yoğun bakım, zehirlenme, ventriküler fibrilasyon

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INTRODUCTION

Hydrofluoric acid (HFA) is used in various industrial fields and can be absorbed by skin/eye contact, inhalation, and ingestion. Although local effects such as burns are mostly seen in skin, eyes, gastrointestinal tract or respiratory tract, systemic poisonings are mostly caused by inhalation or ingestion [1]. Fluoride ions bind calcium and magnesium, disrupting potassium channels, leading to cell dysfunction and death. Hypocalcemia and hypomagnesemia manifest themselves as tetany, QT prolongation, ventricular dysrhythmias leading to cardiac arrest. Especially in systemic toxicity, rapid correction of electrolyte disturbances, hemodynamic stabilization and clearance of fluoride ions from the circulation convey critical importance in treatment.

Although many cases of local poisoning have been reported in the literature, only a limited number of pediatric patients with systemic poisoning have been presented. Unfortunately, most of these systemic poisonings resulted in death [2,3]. With this case, we aim to draw attention to the rarely seen fatal oral HFA poisoning. We have also emphasized that the

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rapid intervention in the emergency department and early term treatment with continuous veno-venous hemodiafiltration (CVVHDF) can be lifesaving.

CASE REPORT

A previously healthy 13-month-old male infant presented to emergency department with acute onset of vomiting. The patient had been playing with his older brother and drank unknown amount of a clear liquid in a plastic bottle. His brother thought it was water. When the family realized that it was a cleaning agent, the patient was brought to our emergency department 2 hours after ingestion of this toxic substance. Firstly, the family was questioned in detail in order to understand the content; of the original package they brought. In 20 minutes, by contacting the manufacturer, it was learned that the solution contained 15% HFA. At the first examination in emergency department, the patient's general condition was poor. He looked sluggish and drowsy. The patient's body temperature was 36.6 °C, respiratory rate 50/min, SpO_2 98%, heart rate 150/min, manual blood pressure was measured as 100/70 mmHg in the emergency room. His oral mucosa, lips and oropharynx retained their natural appearance. Oxygen support was provided. A H1 receptor antagonist, and a proton pump inhibitor were administered. The laboratory findings were as follows: pH: 7.19, pCO_2: 44; HCO_3: 15.2, base deficiency: -10.1; lactate: 3.5; ionized calcium: 0.76; serum calcium: 5.7 mmol/L; magnesium: 1.45 mg/dL, and potassium 4.1 mmol/L. Maintenance fluid at daily dose of 1500 mL/m^2 was initiated after a loading dose of saline at a dose of 20 mL/kg. Also 10% calcium gluconate (1 mL/kg/dose) and 15% magnesium sulfate (50 mg/kg) were administered. In the electrocardiography (ECG), the rhythm was normal, QTc interval was calculated as 0.42 ms.

At the 50th minute of the follow-up, ventricular fibrillation (VF) was noted on the monitor and no pulse (Figure 1A). Cardiopulmonary resuscitation (CPR) was started immediately afterwards. A defibrillation device was set up, and defibrillation was performed at 2J/kg immediately and CPR was maintained. Since the patient's VF persisted, he was defibrillated at 4J/kg (50J) two more times with an interval of 2 minutes. After the third defibrillation, his cardiac rhythm returned to normal (Figure 1B). CPR was continued for a short time and terminated after his heart rate returned to normal ranges. To protect respiratory tract, he was intubated. In the control ECG after defibrillation, QTc was 0.34 msn. After initiation of an IV loading dose of amiodarone (5 mg/kg) IV infusion from 5 mcg/kg/min was begun. The patient was transferred to the pediatric intensive care unit (PICU) at the 4th hour after ingestion of the toxic substance for immediate hemodialysis (HD).

At the admission of the patient to the PICU; the body temperature was 35.8 °C, heart rate 166/min, arterial blood pressure 87/56 mmHg, respiratory rate 48/min, SpO_2 98% with 50% FiO_2, capillary filling time was 3 seconds. The ECG was consistent with the sinus

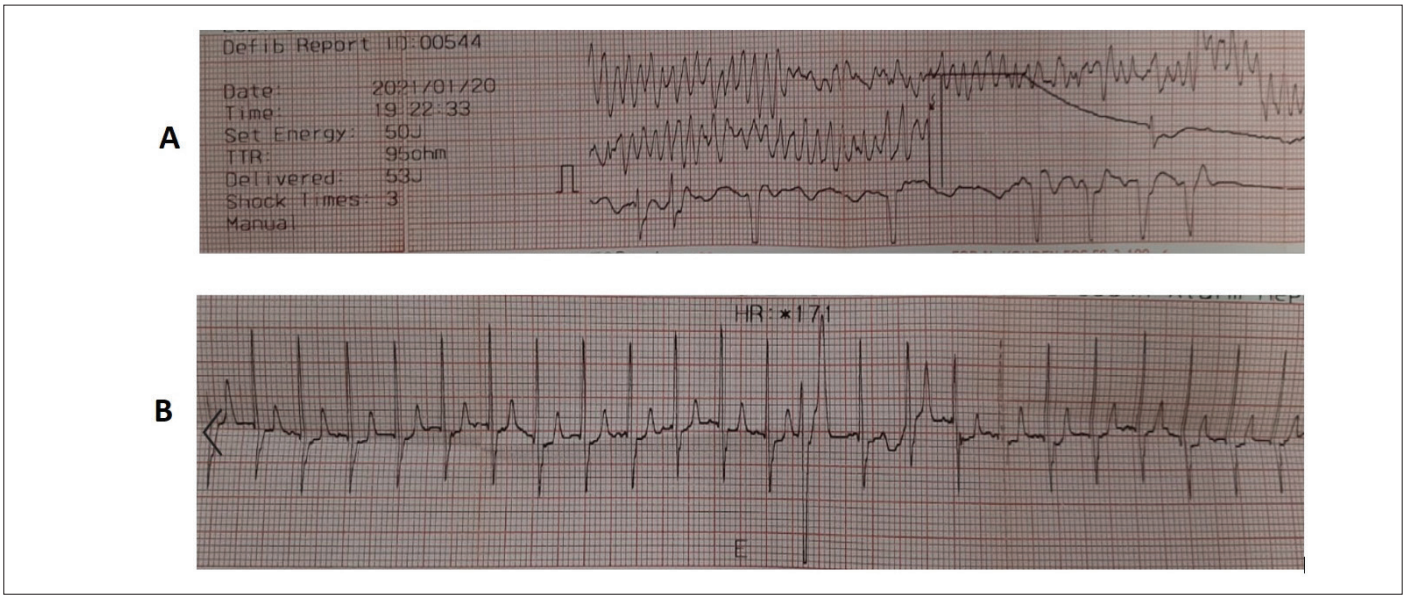

Figure 1. Electrocardiogram of the patient before (A) and after (B) defibrillation

tachycardia and the QTc was 0.38 msn. His chest X-ray, abdominal ultrasonography findings, and hemogram values were within normal ranges. Other parameters of the patient are indicated in Table 1.

Amiodarone infusion was maintained at 5 mcg/kg/min. Sodium bicarbonate was administered at a dose of 1 mEq/kg IV delivered in 1 hour for the correction of metabolic acidosis (Table 2). At the 5th hour after ingestion of the toxic substance, CVVHDF was initiated for the patient who had signs of severe systemic toxicity. His metabolic acidosis resolved at the 5th hour of follow-up in PICU, and lactate levels returned to normal at 8th hour (Table 2). Four doses of 10% calcium gluconate (1 mL/kg/dose), and 2 doses of 15% magnesium sulfate (50 mg/kg/dose) were administered to provide normal serum levels (Figure 2). Adrenaline infusion was initiated at a dose of 0.1 mcg/kg/min because of the development of hypotension despite administration of a bolus dose of saline and maintenance fluid support in the follow-up. When the QTc was 0.44 ms on the ECG, the amiodarone infusion was tapered and eventually stopped at the end of the 12-hours. Then as an antiarrhythmic, propranolol at a daily dose of 1 mg/kg was initiated. There was no pathological finding on echocardiography. After the patient's cardiac, clinical and laboratory findings were stabilized and urine output became normal, the CVVHDF treatment was stopped at the end of the 12th hour. On the 3rd day he had a generalized tonic clonic seizure, consequently midazolam was administered, levetiracetam IV treatment was started. No repetitive seizure activity was observed. On the 4th day, the patient was stable and extubated. On the 6th day, short-term hypertension and bradycardia was observed, and following administration of 3% NaCl at a dose of 3 mL/kg the patient recovered. The cranial CT was normal, and

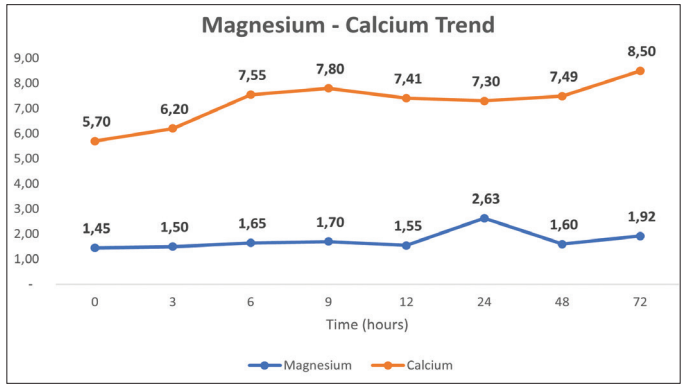

Figure 2. Note the gradually increasing levels of calcium and magnesium during the follow-up

Table 1. Evaluation of laboratory tests during PICU follow-up of the patient

Laboratory	At admission	1st day	2nd day	5th day	10th day
Urea (mg/dL) (10-38)	30	29	13	36	21
Creatinine (mg/dL) (0.5-1.2)	0.5	0.56	0.34	0.45	0.4
Sodium (mmol/L) (135-145)	136	134	135	141	138
Potassium (mmol/L) (3.5-5.5)	4.1	3.3	3.6	4.4	4.1
Calcium (mmol/L) (8.8-10.8)	5.7	7.3	7.49	8.5	8.8
Magnesium (mg/dL) (1.5-2.6)	1.45	2.63	1.6	2	2.1
[1]AST (U/L) (0-50)	78	587	1015	103	48
[2]ALT (U/L) (0-50)	22	112	194	142	83
Troponin (ng/mL) (0-0.6)	11.640	10.887	3000	0.29	0.1
[3]INR (0.8-1.2)	1.1	1.48	1.46	1.07	1

[1]AST: Aspartate transaminase, [2]ALT: Alanine transaminase, [3]INR: International normalized ratio, PICU: Pediatric intensive care unit

Table 2. Evaluation of acid base status

Venous blood gas	At admission	1st hour	2nd hour	5th hour	8th hour
pH	7.19	7.09	7.26	7.35	7.42
pCO_2 (mmHg)	44	55	40.1	36	41
HCO_3 (mmol/L)	15.2	13.9	17.5	21.3	22.4
BE (mmol/L)	-10.1	-11.2	-8.4	-2	-1.8
Lactate (mmol/L)	3.5	3.1	3.1	2.9	1.7

the cranial MR revealed diffusion restriction, possibly due to the hypoxic involvement at the border zone level in the left parietooccipital cortex. On the 10th day, the patient had a Glascow Coma Scale score of 15 points. He was hemodynamically stable and transferred to the pediatric ward. On the 14th day of hospitalization, he was discharged with recovery. Informed consent was received from the family.

DISCUSSION

Despite its infrequency, HFA ingestion can result in death. Emergency physicians should consider HFA poisoning in patients who have drunk a colorless, transparent liquid. HFA toxicity is caused by three mechanisms; 1- at high concentrations (>50%), the HFA acts as a strong acid causing corrosive burns, 2- at lower concentrations, the fluoride penetrates the dermal layer causing tissue destruction, and 3-fluoride can enter the blood streams chelating calcium and magnesium ions causing hypocalcemia and hypomagnesemia but also toxicity by itself [1]. HFA is rapidly absorbed by the gastrointestinal system and may cause vomiting, dysphagia, abdominal pain and ultimately bleeding and perforation [4]. With ingestion of a solution at 15% HFA concentration the patient had a vomiting. Any corrosive effect of the solution was not seen but it caused systemic toxicity. A Haddon matrix can be used to determine pre-event, event and post-event strategies in cases of HFA ingestion (Table 3). In our study, post-event strategies were successfully applied in accordance with this matrix.

HFA can cause VF with electrolyte disturbances and direct cardiotoxicity with myocardial damage in several hours after its ingestion or dermal exposure. These conditions require immediate intervention and systemic toxicity requires urgent dialysis. Hypocalcemia, hypomagnesemia, hypokalaemia or hyperkalaemia, metabolic acidosis, and coagulation disorders may develop in systemic toxicity [5,6]. Hypocalcemia is considered to be one of the main factors that triggers heart rhythm disturbances. Therefore, calcium supplementation is the main treatment against fluoride toxicity [7]. Prolonged QTc and lethal dysrhythmias are also related with hypomagnesemia and should be corrected by IV magnesium sulfate infusion [8-10]. In this case, hypocalcemia and hypomagnesemia were present. These electrolyte disturbances were corrected with appropriate replacement therapies.

Free fluoride ions may cause refractory VF with myocardial irritability. As reported in one pediatric case [2] and several adult cases [1,6,9,11] sudden cardiac arrest and death may occur in severe fluoride poisoning. In the case of VF, defibrillation should be done and repeated as often as necessary [12]. In this case, VF developed, but

Table 3. Haddon matrix: Host, agent and environmental factors affecting the likelihood of death due to hydrofluoric acid ingestion

	Host	**Agent (hydrofluoric acid)**	**Environment (physical and social)**
Pre-event	Knowledge about lethality of cleaning agent Raising awareness in children and parents against all kinds of poisoning hazards	Concentration (15%) and quantity of available chemical formulations	Safe storage Accessibility of toxic chemicals
Event	To work with personnel who can do what is necessary against the substance that caused the toxicity Level of intent	Ingested dosage unknown Toxicity of agent is lethal Additives affecting absorption Taking action to reduce the consequences as soon as the danger of poisoning is noticed	After eliminating the source of the accident, to inform the necessary centre (poisoning centre, emergency call, hospital) and people
Post-event	Ability to take first aid after poisoning	Speed of poisoning onset Effectiveness of treatmen IV calcium gluconate and magnesium sulphate Saline bolus, IV sodium bicarbonate, cardiopulmonary resuscitation, defibrillation, IV amiodarone, hemodialysis	First aid Access/transport to hospital care Elimination of environmental and housing problems

the patient was successfully treated with the application of CPR for 6 minutes, and defibrillation for 3 times.

Cardiotoxicity due to high levels of fluoride in serum is thought to be the reason of recurrent VF in spite of normalized serum electrolyte levels and oxygenation. With early HD, Björnhagen et al. [13] successfully treated a patient who experienced recurrent VF attacks despite correction of electrolyte disorder after dermal exposure to a high concentration of fluoride. As indicated in a study performed with small number of adult cases, continuous renal replacement therapy, HD, and hemodiafiltration can be effective and potentially lifesaving for patients with severe systemic toxicity after dermal exposure [1,14,15]. We think that administering CVVHDF after HFA exposure reduces the effects of toxicity. CVVHDF was started because acidosis and shock persisted despite calcium, magnesium, amiodarone, fluid and bicarbonate supplements. Although, the fluoride level could not be measured in our hospital, CVVHDF was applied for 12 hours until hemodynamic stability was achieved.

In case of acute exposure to HFA, the functionality of the neuromuscular system may be affected because of electrolyte imbalance. Anxiety, headache, confusion, convulsion, paresthesia, paresis, and paralysis, carpopedal spasm and generalized tetany may develop. Cerebral edema and then deep coma may occur when exposed to high doses [5,11,16]. This patient experienced convulsion and cerebral edema in the long term which suggested that they were caused by the hypoxic process due to CPR rather than HFA intoxication, as demonstrated by MR.

CONCLUSION

HFA may result in systemic toxicity leading to ventricular dysrhythmia and death, especially among young children, even with very little oral intake. The patient may survive using timely effective treatment methods including close cardiac monitorization, rapid correction of electrolyte disturbances, CVVHDF and providing hemodynamic stability. To our knowledge, our patient is the first pediatric case with evidence of severe systemic poisoning that was successfully treated with CVVHDF.

Informed Consent: Informed consent was received from the family.

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Author Contributions

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