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

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

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Conclusion: The conclusion of the study should be highlighted.

Acknowledgements: Any technical or financial support or editorial contributions (statistical analysis, English evaluation) towards the study should appear at the end of the article.

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Editorial

"One day everything will be well, that is our hope.
Everything's fine today, that is our illusion."
Voltaire

Dear JPR Readers,

We are pleased to inform you that the first issue of year 2021 is published.

Globally, as of 10:06 a.m. CET, 29th of January 2021, there have been 100,819,363 confirmed cases of COVID-19, including 2,176,159 deaths, reported by WHO. The rise of the COVID-19 pandemic crisis has put enormous pressure on paediatric health and wellbeing all over the world. According to UNICEF, 99 per cent of children and young people under 18 worldwide (2.34 billion) live in one of the 186 countries with some form of restrictions on movement due to COVID-19. The mitigating measures such as lockdown, isolation, restrictions, and school closures taken against the pandemic crisis were found to exacerbate existing health problems and inequalities thereby putting the lives of many children at serious risk of disease or death. In response to the pandemic measures, there has been an impact on children's health, education, nutrition, parent-child relationships, and peer relationships.

The year 2021 is the year of vaccination for COVID-19.

As healthcare professionals, we will continue to support children and their families who cannot get an equal share of the world's benefits and whose rights are violated...

In this issue, you are going to find 15 articles, including 13 pieces of original research and two case reports representing different disciplines. We hope that our readers will have the opportunity to update their knowledge on some acute and chronic paediatric health problems such as congenital hypothyroidism, celiac disease, carbon monoxide poisoning, rhegmatogenous retinal detachment, Henoch-Schönlein purpura, NAFLD, foreign body aspiration, obesity, trauma, nail diseases, tuberous sclerosis complex, paediatric pain management, recurrent hypersomnia, and heart transplantation. Recently, culturally competent care is one of the most important skills required from health care professionals. By reading one of the articles which focuses on the "neonatal outcomes of Turkish and immigrant pre-terms", our readers will have the chance to be more aware of the impact of cultural diversity in paediatric settings.

Finally, we would like to remind you that The Journal of Pediatric Research is indexed in the Web of Science-Emerging Sources Citation Index (ESCI), Embase, Directory of Open Access Journals (DOAJ), EBSCO, British Library, CINAHL Complete Database, ProQuest, Gale/Cengage Learning, Index Copernicus, Tübitak/Ulakbim TR Index, TurkMedline, J-GATE, IdealOnline, ROOT INDEXING, Hinari, GOALI, ARDI, OARE, AGORA, EuroPub, Türkiye Citation Index and CABI.

We would like to thank all our authors, reviewers, the editorial board and Galenos publishing house who are contributing to the field of scientific literature.

Prof. Dr. Candan OZTURK
RN, PhD, Section Editor

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Original Article

Etiological Evaluation of Congenital Hypothyroidism in Cases Referred from the National Screening Program

Deniz Tanyeri[1], Ayşe Anık[2], Arzu Cengiz[3], Yasemin Durum Polat[4], Tolga Ünüvar[5], Ahmet Anık[5]

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ABSTRACT

Aim: To evaluate cases referred from the congenital hypothyroidism (CH) new-born screening program.

Materials and Methods: One hundred and thirty-five cases which were referred between January 2017 and July 2019 were included in the study.

Results: Fourty eight of 135 cases (35.6%) were diagnosed as CH. The mean onset of treatment was 17.31±9.92 days. Clinical findings suggesting hypothyroidism were detected in 27 patients (56.2%) and goiter was detected in 2 patients (4.1%). According to imaging findings, 16 (35.5%) patients were diagnosed as dysgenesis, [1 (2.2%) as agenesia, 3 (6.7%) as ectopia, and 12 (26.6%) as hypoplasia], 11 were diagnosed as dyshormonogenesis (24.5%), and 18 were diagnosed as eutopic thyroid (40%). The mean levothyroxine dose was 12.7±2.5 mcg/kg/day and the mean onset of treatment in 30.4% of diagnosed patients was within the first 14 days and 93.3% were within the first 30 days.

Conclusion: Dysgenesis and dyshormonogenesis are the most common detectable causes of CH. The normal localization of the thyroid gland in about half of the patients suggests that transient causes of CH may be more common than expected. Considering that only 1/3 of the patients were treated in the first 2 weeks, it was thought that the referral of patients is still an important problem and it should be done more promptly.

Keywords: Congenital hypothyroidism, neonatal screening program, etiology

Introduction

Congenital hypothyroidism (CH) is defined as the deficiency of thyroid hormones in newborn babies, with an incidence of 1 in 1,400 to 2,800 (1,2). Due to the essential role of thyroid hormones in brain development, its deficiency can have devastating effects on neurocognitive development if not detected and treated early and effectively (1). The lack of obvious clinical manifestations of hypothyroidism in newborns, reinforces the pivotal role of newborn screening in facilitating prompt diagnosis and treatment.

The most frequent method used for screening for CH in the world, as well as in our country, is the measurement

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of thyroid stimulating hormone (TSH) from the heel-stick blood sample between the 2nd and 5th days of life (3). Screening for CH in Turkey was started in 2006 and the incidence of CH in Turkey was reported as 1 in 888 in 2008, 1 in 592 in 2009 and 1 in 469 in 2010 (4). Though the prevalence of CH in our country is not exactly known, various studies reported that transient CH varies between 25 and 65% (5-9). Considering the increasing frequency in recent years, it is becoming more important to determine the etiological factors of CH.

The aim of this study was to evaluate the rate of diagnosis of CH in referred patients from the national screening program; as well as the clinical and laboratory features and etiological distributions of the patients.

Materials and Methods

In this study, cases with high capillary TSH who were referred from the national screening program to our hospital were retrospectively evaluated. This study was carried out in Aydın province located in the Aegean region. The study was approved by the Aydın Adnan Menderes University Faculty of Medicine, Non-Interventional Clinical Research Ethics Committee (date: 22.08.2019, approval number: 2019/125).

CH was diagnosed according to ESPE guidelines (10):

- Venous TSH level >20 mIU/L and fT4 level normal or low (<0.7 ng/dL)

- Patients whose venous fT4 level is within normal limits (0.7-1.48 ng/dL) and TSH level is between 6-20 mIU/L and those with normal fT4 levels and increased TSH levels underwent repeated weekly measurements until postnatal 21st day of life.

The demographic information of the patients, postnatal age, birth week, birth weight, family history of thyroid disease, consanguinity, physical examination and perinatal event details including complaint, anthropometric data, heel-stick blood sample time and results, and laboratory and imaging results were obtained from the hospital recording system. In addition, serum fT4, TSH, thyroglobulin (TG), ultrasonographic features (localization, volume, parenchymal echogenicity of the thyroid gland), and thyroid scintigraphy (localization and activity of the thyroid gland) and serum thyrotropin receptor antibodies (TRB-Ab) level in those patients with maternal thyroid disease were also recorded from the same data.

Laboratory and imaging tests of all patients were performed on the same day. TSH and fT4 were measured by chemiluminometric assay with Abbott Architect i2000. TG levels were measured by two different immunoassay methods (ROCHE cobas 601 and ROCHE cobas E411). The TRB-Ab level was measured by the radioimmunoassay method (STRATEC-GAMA READER and TRAC ETIMAX).

Thyroid ultrasonography was performed by the same pediatric radiologist using the L3-12A broadband high-resolution linear probe with a frequency range of 3-12 MHz with the Samsung Medison RS80A Prestige (Samsung Medison Co. Ltd., Seoul, Korea). The longest longitudinal (D1), anterior-posterior (D2), transverse (D3) diameter and isthmus thickness were recorded separately for both lobes of the thyroid gland. The volume for each lobe and the entire gland in millilitres was automatically calculated according to the formula [width x length x depth x $\pi/6$ (0.523)] in the Child Metrics program (11). Those volumes of thyroid gland between 0.526-1.849 mL for the entire gland, 0.228-0.931 mL for the right lobe, and 0.294-0.959 mL for the left lobe were considered as normal (12). Results below these values were considered as hypoplasia and above as hyperplasia.

Twenty minutes after 500-750 µCi Technetium-99m pertechnetate intravenous injection, thyroid scintigraphy was performed via a Siemens syngo via device and gamma camera and images were recorded for a total of 5 minutes. Anatomical localization of the gland and activity (decreased, increased, or normal) of these images were evaluated by the same nuclear medicine specialist.

Patients with agenesis, ectopia or hypoplasia according to imaging results were classified as dysgenesis; while patients with a history of consanguinity and increased activity in the thyroid gland, or with increased activity and hyperplasia were classified as dyshormonogenesis. The remaining patients were classified as eutopic thyroid, which could be transient CH. The given starting LT4 dose was recorded in mcg/kg/day.

Statistical Analysis

Kolmogorov-Smirnov test was used to test whether the quantitative variables are suitable for normal distribution. The groups were compared with two independent samples t-test for normally distributed variables and Mann-Whitney U test for abnormally distributed variables. Chi-square analysis was used to test whether there is independence between qualitative variables. Descriptive statistics of variables with normal distribution were expressed as "mean ± standard deviation" and descriptive statistics of abnormally distributed quantitative variables as "median (25th-75th percentile)". Descriptive statistics of qualitative variables were expressed in frequency (%). $P<0.05$ values were considered statistically significant.

Results

Of the 135 cases included in the study, 48 (35.6%) were diagnosed with CH, and 87 (64.4%) cases were healthy. The average age at admission was 19.05±9.87 days for the whole study population, and it was 17.3±9.9 days in those babies with CH. The average gestational week of the 48 patients with CH [19 (39.6%) female, 29 (60.4%) male] was 38.7±1.7 weeks, among which, 40 of the cases were term (83.3%) and 8 were preterm babies (16.7%). The mean birth weight was 3,130.1±455.3 g. There was no significant difference between the group diagnosed with CH and the healthy group in terms of age of presentation, birth week, birth weight, term/preterm rate, and gender distribution (p>0.05) (Table I). Body weight, height and head circumference at the time of presentation were similar in both groups.

The average first and second screening times of those patients diagnosed with CH was 6 (4-8) and 10 days (8-14), respectively. The average first screening of TSH level was 10.22 µIU/mL (6.47-17.69) and the second was 20.06 µIU/mL (9.5-25.63) (Figure 1). The average time to start treatment was 17±9 days in those patients with CH.

There was a family history of thyroid disease in 17 (34.4%) of those patients with CH, and history of consanguinity between parents in 11 (22.9%) cases. There were 4 patients with CH whose mother had hypothyroidism and TRB-Ab was negative in all of these babies. No significant difference was found between the group with CH and the healthy group in terms of family history of thyroid disease and consanguinity. Iodine exposure was present in 16 (11.9%) cases in the whole group and in 5 (10.4%) of those patients with CH. This exposure was due to iodine-containing antiseptics that were used for umbilical care in all cases.

The average TSH level at the time of diagnosis was 62.94±49.33 µIU/mL in the CH group, and 3.1 µIU/mL (0.77-4.81) in the control group. The average fT4 level was 0.63 ng/dL (0.22-1.22) in the CH group; and 1.09±0.14 ng/dL in the control group. Thirty patients (62.5%) with CH had low fT4 levels (<0.7 ng/dL) at the time of diagnosis. Serum TSH and fT4 levels at the time of admission were statistically significant between the two groups (p<0.001) (Table II).

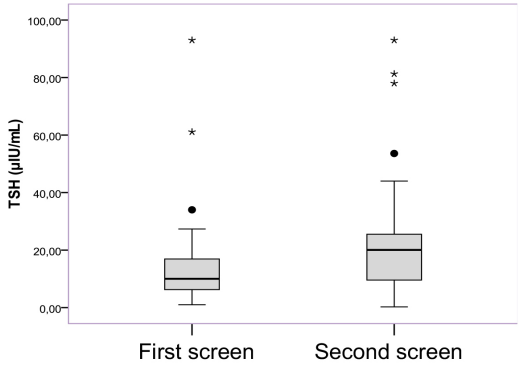

Figure 1. The first and second heel-stick TSH levels in patients with congenital hypothyroidism

TSH: Thyroid stimulating hormone

Table I. Anthropometric, demographic and clinical features of the subjects

		All group n=135 (%)	Congenital hypothyroidism n=48 (%)	Healthy group n=87 (%)	p
Gender	Male	80 (59.3)	29 (60.4)	51 (58.6)	0.984
	Female	55 (40.7)	19 (39.6)	36 (41.4)	
Gestational week	Preterm	30 (22.2)	8 (16.7)	22 (25.3)	0.349
	Term	105 (77.8)	40 (83.3)	65 (74.7)	
Birth week (week)		38.4±1.7	38.7±1.7	38.3±1.7	0.138
Birth weight (gram)		3163.6±474	3130.1±455.3	3182.1±485.6	0.544

Table II. fT4 and TSH levels at admission

	All group n=135	Congenital hypothyroidism n=48	Healthy group n=87	p
TSH (µIU/mL)	24.33±41	62.94±49.33	3.1 (0.77-4.81)	<0.001
sT4 (ng/dL) Low (<0.7 ng/dL) Normal (>0.7 ng/dL)	0.93±0.27 30 (22.2%) 105 (77.8%)	0.63 (0.22-1.22) 30 (62.5%) 18 (37.5%)	1.09±0.14 0 (0%) 87 (100%)	<0.001

TSH: Thyroid stimulating hormone

Thirty three out of 48 patients (68.8%) had symptoms suggesting CH; jaundice in 18 (37.5%), poor sucking in 9 (18.8%), and constipation in 6 cases (12.5%). On physical examination, coarse face was detected in 3 (6.3%), umbilical hernia in 2 (4.2%), jaundice in 18 (60%), and goiter in 2 (4.1%) cases.

Thyroid USG was performed in 44 (91.7%) out of 48 cases, and thyroid scintigraphy in 45 (93.8%) cases. In 4 (9%) cases, the thyroid gland in USG could not be visualized at normal localization. One of them was diagnosed with agenesis; and the other 3 patients were diagnosed as sublingual ectopic thyroid gland according to thyroid scintigraphy. The total volume of the thyroid gland in the other cases was calculated as 1.93±3.7 mL, right lobe 1±1.2 mL, left lobe 1±1.9 mL. Hypoplasia was detected in 11 cases (25%), normal thyroid gland in 20 cases (45.5%), and hyperplasia in 9 cases (20.5%) according to USG. Thyroid scintigraphy showed normal activity in 11 (8.1%), increased activity in 23 (17%), decreased activity in 4 (3%) cases, and 4 (2.9%) cases without gland involvement.

According to etiological classification, 16 patients (35.5%) were classified as dysgenesis [1 agenesis (2.2%), 3 ectopia (6.7%), 12 hypoplasia (26.6%)]; and 11 cases (24.5%) as dyshormonogenesis. The remaining 18 (40%) cases were classified as eutopic thyroid gland (Table III).

The average age at the beginning of the treatment was 17.3±9.9 days and the dose of LT4 was 12.7±2.5 mcg/kg/day.

Discussion

In this study, babies who were referred from the national screening program during a 2-year-period were retrospectively analysed, and CH was diagnosed in 48 (35.6%) out of 135 cases. This rate was reported as 44% in another study conducted in our country, which is compatible with our study (5). In this study, approximately 2/3 of those cases diagnosed with CH were male. In many studies, it has been reported that CH is more common in girls (13,14). However, in recent studies, male dominance has been reported, similar to our study (15-17). Since dysgenesis is known to be more frequent in girls and the rate of dysgenesis is relatively low in our study, it was thought that the higher frequency of males could be related to reasons other than dysgenesis.

Bongers-Schokking et al. (18), reported that neurodevelopmental outcomes of babies with CH that were treated in the first two weeks were similar to a healthy group. In our study, approximately one third of the cases were admitted within the first 14 days of life and the average age of diagnosis was 17 days. In the study of Kor and Kor (15), the average age of admission was found to be 19.87±7.63 (4-51) days and the rate of diagnosis in the first month was 88.4%. Peltek Kendirci et al. (5) reported that the average age of diagnosis was 19.7±8.30 (5-60) days and this is similar to our study. Eren et al. (19) reported the average age of diagnosis before and after the screening program to be 292 and 35 days, respectively. Although the time of diagnosis

Table III. Etiological distribution of patients with congenital hypothyroidism (n=45)

Etiology		Ultrasonography	Scintigraphy
1. Dysgenesis: n=16 (35.5%)			
Agenesis: n=1 (2.2%)		No thyroid gland	No uptake
Ectopia: n=3 (6.7%)		No thyroid gland	Sublingual thyroid gland
Hypoplasia: n=12 (26.6%) Normal: 1		Hypoplasia: 11	Decreased activity: 3 Normal activity: 1 Normal activity: 4 No uptake: 3
		Decreased activity: 1	
2. Dyshormonogenesis: n=11 (24.5%)			
Consanguinity	Yes: 7	Increased activity: 7	
	No: 4	Hyperplasia: 4	Increased activity: 4
3. Eutopic thyroid: 18 (40%)			
n=18 Hyperplasia: 2 Normal: 5		Normal: 10*	Increased activity: 11
		Normal activity: 7	

*One patient with increased activity in scintigraphy had no USG images
USG: Ultrasonography

after the screening program shifts significantly to earlier, according to many studies, the diagnosis rate is still very low in the first two weeks of life.

In this study, the venous TSH value was significantly higher in CH patients compared to the healthy group. In a study by Peltek Kendirci et al. (5), the mean venous TSH level was 55.2±33.5 µIU/mL (0.77-4.81) in patients with CH. Similarly, in a study conducted in 223 patients with CH, it was reported that the mean venous TSH level was 67.26 µIU/mL (15). In our study, venous TSH and fT4 levels at the time of diagnosis were similar to many studies in the literature.

The most common symptom in our patients with CH was jaundice. Similar to our study, Özgelen et al. (20) reported that prolonged jaundice was the most common symptom in patients with CH.

In our study, the most common cause of CH was eutopic thyroid gland (40%), followed by thyroid dysgenesis (35.5%) and dyshormonogenesis (24.5%). In one recent study, the etiological distribution of CH was reported as 33.3% dysgenesis (commonly hypoplasia), 33.3% dyshormonogenesis and 16 (33.3%) as "possible dyshormonogenesis and transient hypothyroidism" (21). In a study conducted in Egypt with 248 patients, 161 (65%) of the cases were diagnosed with dysgenesis (107 ectopic, 28 agenesis, 26 hypoplasia), and 87 (35%) of them with dyshormonogenesis (22). Since the etiological distribution is multifactorial; dysgenesis, dyshormonogenesis and eutopic thyroid rates differs among studies. Methodological differences are thought to be the most important reason for the etiological differences among these studies: (i) some studies used thyroid ultrasonography while others used thyroid scintigraphy for the definition of dysgenesis, and (ii) the diagnosis of dyshormonogenesis was not molecularly confirmed in most studies, hence, these factors significantly affect the etiological distribution. In addition, the frequency of transient hypothyroidism is increasing gradually. In studies published in our country, the frequency of transient hypothyroidism has been reported to be between 25-65% (23). Although the frequency of transient hypothyroidism was not defined in our study, it can be predicted that many cases with eutopic thyroid gland will be transient (24). One of the most important reasons for the increased frequency of transient hypothyroidism in recent years is the lowering of the screening TSH cut-offs. The lowering of the screening TSH cut-offs in these programs has been associated with the doubling of CH incidence, primarily explained by the detection of milder cases. While the whole blood TSH cut-off value in Turkey was 20 µIU/mL in the past, it was determined to be 10 µIU/mL at the start of the screening program, and was lowered to 7.5 µIU/mL in 2009 (4,6,24-26). Accordingly, the frequency of transient CH increased from 27% to 56% in a period of ten years in our country (23).

Study Limitations

There are some limitations in our study: (i) the etiological distribution of CH was made according to the imaging findings, and molecular confirmation tests required for the definitive diagnosis of dyshormonegenesis could not be performed and (ii) Urinary iodine excretion could not be performed, so iodine excess or iodine deficiency could not be documented. The strengths of the article are; (i) it is single centre trial, (ii) the data are complete, (iii) and the imaging methods are standard and were assessed by the same physician.

Conclusion

The most common detectable causes of CH were shown to be dysgenesis and dyshormonogenesis. Considering that the thyroid gland is eutopic in approximately half of the cases, transient causes of CH might be higher than expected. Although the duration until diagnosis and initiation of treatment of CH were markedly reduced with the implementation of the screening program in Turkey compared to before the implementation of the screening program, the targeted and ideal time has not yet been reached for final diagnosis and the initiation of treatment (≤2 weeks).

Ethics

Ethics Committee Approval: The study was approved by the Aydın Adnan Menderes University Faculty of Medicine, Non-Interventional Clinical Research Ethics Committee (date: 22.08.2019, approval number: 2019/125).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Design: T.Ü., A.A., Data Collection or Processing: D.T., A.C., Y.D.P., Analysis or Interpretation: D.T., A.A., A.C., Literature Search: Ay.A., Writing: T.Ü.

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Original Article

Does Celiac Disease Effect Electrocardiographic Markers of Arrhythmic Events in Children?

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ABSTRACT

Aim: Cardiac abnormalities associated with celiac disease (CD) have been reported. However, changes in electrocardiographic (ECG) parameters in children with CD have not been previously evaluated in the literature. In this study, we aimed to evaluate these parameters which may be determinative in the development of atrial and ventricular arrhythmia of children with CD.

Materials and Methods: Patients diagnosed with CD in the gastroenterology clinic were included in the study. ECG measurements of QT, T peak to end (Tp-e) and P intervals were performed. The Tp-e/QT ratio was calculated from these measurements. Echocardiographic and ECG parameters of the patients and controls were compared. Those patients with elevated anti-tissue transglutaminase immunoglobulin A (IgA-tTG) levels were considered positive serology. The patients were divided in three groups and compared with each other according to ECG parameters; namely newly diagnosed patients, patients with seropositive and patients with seronegative who had been on a gluten free diet for at least 6 months.

Results: Fifty-two patients with CD and 59 healthy volunteers were included. P-wave dispersion, QTd, corrected QT dispersion (QTcd), Tp-e dispersion and TP-e/QT ratio were higher in those children with CD compared to the controls. We did not find any correlation between IgA-tTG levels and P-wave, QT and Tp-e dispersions. There was no difference between the three groups of CD patients for ECG and echocardiographic parameters.

Conclusion: CD is associated with changes in some ECG parameters, which are considered as predictors of atrial and ventricular arrhythmias in special populations. For this reason, children with CD should be evaluated in terms of these parameters, and more electrophysiological studies are necessary to reveal the clinical and prognostic effects of these parameters for CD.

Keywords: Electrocardiography, celiac disease, Tp-e dispersion, Tp-e/QT ratio, ventricular depolarization, arrhythmias

Introduction

Celiac disease (CD) is a chronic immune-mediated disease triggered by gluten, which often results in diffuse inflammatory damage to the small intestinal mucosa (1). Gluten, found in wheat, barley and rye, has this effect only on genetically predisposed people through the interaction of environmental and immunological factors (2). The frequency of CD varies with respect to geographical regions, and different studies report that its prevalence varies between 0.8% and 1% (3,4). In Turkey, this prevalence

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is reported to be 1 in 212 (5). A gluten-free diet is the current treatment for CD (1).

Various cardiovascular abnormalities such as cardiomyopathy, myocarditis, arrhythmias, and premature atherosclerosis have been reported in adult populations with CD (6). Few studies have studied cardiovascular involvement in children with CD, with most of them focusing on clinical and subclinical left ventricular dysfunction (7). Some electrocardiographic (ECG) changes such as P-wave dispersion (PWd), QT dispersion (QTd) and T peak to end (Tp-e) interval, which is the measurement of the interval between the peak and the end of the T-wave, Tp-e/QT ratio and Tp-e dispersion have emerged as markers of transmural dispersion of repolarization (TDR) and it has been reported that they can predict the development of atrial and ventricular arrhythmias (8,9). Although some adult studies have reported on CD patients, these ECG parameters have not been evaluated in children with CD before (10,11). Therefore, we aimed to evaluate PWd, QTd, Tp-e interval and dispersion and Tp-e/QT ratio in children with CD.

Materials and Methods

In this prospective study, those patients with CD admitted to a pediatric gastroenterology outpatient clinic between March 2018-August 2018 were included. The research procedure was approved by the Local Ethics Committee (no: 2018/3-9). The patients signed consent forms which gave information concerning the purpose of this study. Those patients whose celiac serology were positive, who had undergone upper gastrointestinal system endoscopy, and whose duodenum and bulbous specimens were taken and histologically diagnosed as CD were included in this study. CD patients were defined according to the European Society for Pediatric Gastroenterology and Hepatology and Nutrition criteria (12). Healthy volunteers of the same age and gender were included as a control group. These individuals were referred to a pediatric cardiology outpatient clinical for cardiac evaluation due to murmurs but had no structural heart disease detected with echocardiographic examination. CD patients and healthy volunteers with known structural and/or valvular congenital heart disease, thyroid dysfunction or additional chronic disease or those taking any medication that could affect heart rate and ECG parameters were excluded from the study. The patients' clinical and demographic data was determined. Anthropometric measurements of weight, height, and body mass index were obtained.

Echocardiographic examination was performed by a single pediatric cardiologist using the Philips Ultrasound System and S 3-1 probe. Conventional echocardiographic measurements were made in accordance with the standards of the American Echocardiography Association (13). The dimensions of the left ventricle in the parasternal long axis on M mode tracing, and ejection fraction (EF) and fractional shortening were analyzed using the Teichholz formula (14).

ECG measurements of QT, Tp-e and P intervals were performed by a pediatric cardiologist who was blind to patient data. The TP-e interval, QT interval, and P-wave interval were obtained from a minimum of six measurements, at least three of which were from precordial leads. The QT interval was measured from the beginning of the QRS complex to the end of the T-wave and corrected for heart rate according to Bazett's formula (15). The Tp-e interval was defined as the interval from the peak of the T-wave to the end of the T-wave. Measurements of the Tp-e interval were performed from precordial leads (16). The Tp-e/QT ratio was calculated from these measurements. P-wave interval was measured from the beginning of the P-wave to the end of the P-wave. Echocardiographic and ECG parameters of the patients and controls were compared. The patients were divided into three group and compared with each other according to ECG parameters; namely newly diagnosed patients, patients with seropositive and patients with seronegative who had been on a gluten free diet for at least 6 months. Patients with elevated anti-tissue transglutaminase IgA (IgA-tTG) levels were considered positive for celiac serology.

Statistical Analysis

G* Power 3.1 program was used to determine the sample size. In this study, the sample size was determined as follows; patients and the controls to be in a 1-1 ratio, at least 128 patients comprising 64 patients in each group with medium effect size of 0.5, a type-1 error of 5% and the type-2 error of 20% and with 80% power, which was suggested by Cohen (17) in the literature. In this study, a total of 111 individuals, 52 of them being celiac and the remaining being healthy controls who were admitted to our hospital during a 6-months period were enrolled. Accordingly, for QTd values with the use of mean + standard deviation between those patients with celiac and the controls, the effect size was calculated as d=2. At the end of the study, the power of the test was calculated to be 99.9%.

Data were analyzed using the IBM SPSS Statistics 25.0 (IBM Corp., Armonk, New York, USA) statistical package program. Normal distribution of continuous variables was evaluated by Shapiro-Wilk normality test and Q-Q graphs. Whether the group variances were homogeneously distributed or not was examined by Levene test. For the

normal distribution of continuous variables, the t-test for parametric statistical tests was used to compare the two groups, and One-Way ANOVA was used to compare more than two groups. Median (Q1-Q3) values were given as descriptive statistics in the analysis of variables with non-normal distribution. In the comparison of the two groups, the non-parametric statistical test Mann-Whitney U and in the comparison of more than two groups, the Kruskal-Wallis H test were used. Relationships between variables were evaluated by Spearman correlation analysis. The relationships between variables with categorical structure were evaluated by using the Continuity Correction chi-square test in 2x2 tables. P<0.05 was considered as statistically significant (17).

Results

Fifty-two patients with CD and 59 healthy volunteers were included in this study. The baseline clinical characteristics of the patients and controls are shown in Table I. The mean age of the CD patients was 10.24±4.6 years and 58.8% were female. There were no difference in terms of age and gender (p=0.025). The laboratory parameters of CD patients are shown in Table II. The mean follow-up period of CD patients was 29.8±28.4 months.

The ECG and echocardiographic findings of the patient and control groups are given in Table III. There was no significant difference in left ventricular dimensions and EF between groups. PWd, QTd, corrected QTcd, Tp-e dispersion and TP-e/QT ratio were higher in children with CD compared to the controls. We did not find any correlation between IgA-tTG levels and P-wave, QT and Tp-e dispersions (p=0.95, 0.67, 0.97 respectively). When the ECG and echocardiographic parameters of CD patients were compared with each other, we did not find any difference between groups (Table IV). QT and QTcd was found to be significantly higher in seronegative patients who were under celiac diet compared to the controls (p<0.05).

Discussion

In the current study, we have investigated atrial and ventricular depolarization together with ventricular repolarization changes in children with CD. We found that the P-wave, QT and QTc dispersions, Tp-e dispersion and Tp-e/QT ratio were prolonged in patients with CD. However, we did not find any difference in Tp-e/QTc ratios between the groups and we did not find any correlation between IgA-tTG and PWd, QTd, QTc d and Tp-e dispersion.

Different types of cardiovascular diseases in CD such as autoimmune myocarditis, left ventricular dysfunction, congestive heart failure and arrhythmia have been described (6,7). Antibodies specific for CD have been observed in some patients with autoimmune myocarditis (18). Some research revealed subclinical left ventricular systolic dysfunction by using conventional and strain echocardiography in children and adults with CD (19,20). Some theories have been proposed to explain the mechanisms of cardiac involvement in these patients. One of these theories is that nutritional deficiency is triggered by intestinal malabsorption and another is autoimmune is triggered myocardial involvement (20). In our study, although we did not find any systolic dysfunction by using conventional M-mode echocardiography, we think that further studies

Table I. Clinical data of the study population

	Patient group mean ± SD M (Q1-Q3)	**Control group mean ± SD M (Q1-Q3)**	**p**
Age (year)	10.24±4.63 10 (6.25-14.75)	10.47±4.28 11 (7-14)	0.143+
Gender			
Girl (n, %)	31 (59.6)	28 (47.5)	0.318*
Boy (n, %)	21 (40.4)	31 (52.5)	
Body mass index (kg/m^2)	17.42±3.44 16.59 (14.38-19.54)	23.20±39.69 17.85 (15.43-20.77)	0.124+
Heart rate (bpm)	112.37±129.47 90 (80-114)	89.45±16.59 89.50 (76-102.25)	0.201+
Mean sistolic blood pressure (mmHg)	106.91±15.45 109 (100-120)	113.21±11.57 113.50 (106.50-120)	0.082+
Mean diastolic blood pressure (mmHg)	63.66±8.78 60 (60-70)	62.71±9.65 60 (60-70)	0.441+

+Mann-Whitney U test, *Continuity Correction test, SD: Standard deviation

Table II. Laboratory parameters in Celiac disease patients

	Mean ± SD M (Q1-Q3)	**Minimum-Maximum**
Hemoglobin (g/dL)	12.57±1.46 12 (11.6-13.2)	8.6-16.2
WBC (cell/mm³)	7,750±1,797 7,900 (6,500-9,100)	4,900-12,200
Platelet (cell/mm³)	299,780±74,486 303,000 (255,000-366,000)	158,000-487,000
AST (IU/L)	29.4±9.7 31 (23-36.5)	10-57
ALT (IU/L)	17.6±9.5 16 (11-20)	6-58
Ure (mg/dL)	20.8±6.8 19 (14.5-22.5)	10-36
Creatinine (mg/dL)	0.57±0.12 0.5 (0.45-0.6)	0.3-0.9
Sodium (mEq/L)	139±2 139 (137-141.5)	134-144
Potassium (mmol/L)	4.3±0.37 4.2 (4-4.55)	3.5-5.6
Calcium (mg/dL)	9.9±0.3 9.9 (9.6-10)	9.2-10.7
Albumin (gr/dL)	4.39±0.28 4.3 (4.3-4.55)	3.5-5.1
Ferritin (ng/mL)	25.6±16.6 23 (13.5-44)	2-70
Folic acid (ng/mL)	12.4±5.1 13 (8.5-17.85)	5-24
Vitamin D (ng/mL)	20.4±9.57 20 (11-29.7)	6-50
IgA-tTG (RU/mL)	105±82 200 (58-200)	0-200

WBC: White blood cell, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, IgA-tTG: Anti-tissue transglutaminase IgA, SD: Standard deviation

with strain echocardiography with larger numbers of patients are needed to demonstrate the subclinical left ventricular dysfunction in children with CD.

Recent studies have shown that PWd is an ECG marker which reflects the homogenous distribution of atrial conduction. Its predictive value has been shown in different clinical situations such as atrial flutter and fibrillation in patients with CD (16). Inflammation may trigger fibrosis and structural changes that results in arrhythmogenic substrate for atrial fibrillation in CD patients. In a study, Karadeniz et al. (21) showed prolonged P-wave duration and dispersion in children with low iron stores. Secondary iron deficiency anemia is more common in CD patients due to malabsorption. Although we did not study the correlation between ferritin level and PWd in the CD group, low iron stores may explain the prolonged PWd in our study group.

Both QT and QTc dispersion reflects inhomogeneity of ventricular repolarization and is used as a marker tendency for ventricular arrhythmia and sudden cardiac death. Previous studies have shown that increased QT and QTc dispersions are significantly correlated with the burden of ventricular premature contractions in children with structurally normal hearts (22,23). Besides QT and QTc dispersions, prolonged QT interval is another ECG marker for malignant ventricular arrhythmia which reflects delayed heart repolarization. Corazza et al. (24) reported that 33% of CD patients had prolonged QT interval. Similar to Corazza et al. (24), we found increased QT and QTc dispersions in children with CD.

Studies have shown that the last part of the T-wave represents the arrhythmogenic tendency for malignant ventricular arrhythmias (25). The interval between the

Table III. Electrocardiographic and echocardiographic characteristics in patients with Celiac disease and healthy controls

	Patient group Mean ± SD M (Q1-Q3)	**Control group Mean ± SD M (Q1-Q3)**	**p**
QTmax (ms)	0.35±0.04 0.34 (0.32-0.36)	0.34±0.03 0.34 (0.32-0.36)	0.075+
QTmin (ms)	0.29±0.04 0.28 (0.26-0.32)	0.32±0.04 0.32 (0.3-0.34)	**<0.001+**
QTcmax (ms)	0.44±0.03 0.43 (0.42-0.45)	0.42±0.02 0.41 (0.39-0.43)	**<0.001+**
QTcmin (ms)	0.37±0.02 0.39 (0.37-0.40)	0.39±0.02 0.38 (0.35-0.4)	**<0.001***
QTdisp (ms)	0.06±0.02 0.05 (0.04-0.08)	0.02±0.02 0.02 (0.02-0.03)	**<0.001+**
Pmax (ms)	0.11±0.02 0.1 (0.09-0.12)	0.1±0.02 0.1 (0.09-0.12)	0.834+
Pmin (ms)	0.05±0.01 0.06 (0.04-0.06)	0.06±0.01 0.06 (0.06-0.07)	**0.015+**
Pdisp (ms)	0.05±0.02 0.05 (0.04-0.06)	0.04±0.01 0.04 (0.04-0.06)	**0.024+**
TP-emax (ms)	0.09±0.02 0.09 (0.08-0.1)	0.09±0.02 0.08 (0.08-0.1)	0.151+
TP-emin (ms)	0.05±0.01 0.06 (0.05-0.06)	0.06±0.01 0.06 (0.05-0.06)	0.272+
TP-edisp (ms)	0.04±0.01 0.04 (0.02-0.05)	0.03±0.01 0.03 (0.02-0.04)	0.180+
TP-e/QTmax	0.27±0.04 0.27 (0.24-0.28)	0.26±0.04 0.25 (0.23-0.28)	0.378+
TP-e/QTmin	0.19±0.03 0.19 (0.17-0.21)	0.18±0.03 0.18 (0.15-0.2)	**0.039***
TP-e/QTcmax	0.21±0.05 0.20 (0.18-0.24)	0.21±0.04 0.21 (0.18-0.24)	0.297+
TP-e/QTcmin	0.15±0.03 0.16 (0.13-0.17)	0.15±0.03 0.15 (0.12-0.17)	0.162+
RR (ms)	637.69±156.76 630 (500-742.5)	691.61±138.51 675 (567.5-765)	**0.031+**
LVEF%	67.71±11.18 68 (64.5-73)	69.58±6.18 70 (64.75-74)	0.738+

*Independent sample t-test, +Mann-Whitney U test, LVEF: Left ventricular ejection fraction, ms: Milliseconds, QTc: Corrected QT interval, SD: Standard deviation, TP-e: T peak to end

peak and the end of the T-wave (Tp-e interval) and Tp-e dispersion have emerged as novel ECG markers of increased dispersion of ventricular repolarization. These parameters are more useful markers than QT dispersion for TDR. Previous studies have shown prolonged Tp-e interval and Tp-e dispersion in long QT syndrome, Brugada syndrome, hypertrophic cardiomyopathy and myocardial infraction (26,27). Unlike Tp-e interval, Tp-e/QT is not affected by heart rate and body weight; thus, it has been used as a more sensitive marker rather than Tp-e and QT intervals. The Tp-e/QT ratio is an important index of arrhythmogenic tendency in acquired and congenital channelopathies (9). Demirtas et al. (10) showed that the Tp-e interval and Tp-e/QT ratio are higher in patients with CD compared to controls. Additionally, they reported significantly increased Tp-e/QT ratios in parallel to disease duration. Given that the Tp-e interval, Tp-e dispersion and Tp-e/QT ratio have not been evaluated in children with CD before, in the present study, we found prolonged Tp-e dispersion and increased Tp-e/QT ratios in children with CD. However, we could not

Table IV. Electrocardiographic and echocardiographic characteristics in the groups of the patients with Celiac disease

	Seronegative under gluten free diet Mean ± SD M (Q1-Q3)	**Seropositive under gluten free diet Mean ± SD M (Q1-Q3)**	**New diagnosis Mean ± SD M (Q1-Q3)**	**p**
n (%)	**23 (44.2)**	**13 (25)**	**16 (30.8)**	
QTdisp (ms)	0.05±0.03 0.05 (0.04-0.08)	0.06±0.03 0.06 (0.04-0.08)	0.06±0.02 0.05 (0.04-0.08)	0.707+
Pdisp (ms)	0.05±0.02 0.05 (0.04-0.06)	0.06±0.02 0.05 (0.04-0.08)	0.05±0.02 0.05 (0.04-0.06)	0.649*
TP-edisp (ms)	0.04±0.02 0.04 (0.02-0.05)	0.04±0.01 0.04 (0.03-0.05)	0.04±0.01 0.03 (0.02-0.04)	0,643+
TP-e/QTmax	0.26±0.05 0.26 (0.25-0.28)	0.27±0.05 0.28 (0.23-0.32)	0.26±0.04 0.27 (0.24-0.29)	0.614+
TP-e/QTmin	0.19±0.04 0.19 (0.16-0.21)	0.2±0.04 0.19 (0.17-0.21)	0.19±0.03 0.19 (0.17-0.21)	0.915+
TP-e/QTcmax	0.22±0.05 0.21 (0.18-0.25)	0.22±0.04 0.21 (0.18-0.26)	0.19±0.04 0.18 (0.17-0.21)	0.187*
TP-e/QTcmin	0.16±0.03 0.17 (0.14-0.17)	0.16±0.03 0.16 (0.13-0.17)	0.14±0.02 0.13 (0.11-0.16)	0.115*
RR (ms)	676.96±147.54 680 (540-760)	656.92±154.24 700 (510-750)	565.63±156.12 520 (440-660)	0.079*

+Kruskal-Wallis analysis, *One-Way ANOVA, Data are given as mean ± SD, SD: Standard deviation, LVEF: Left ventricular ejection fraction, ms: Milliseconds, QTc: Corrected QT interval, TP-e: T peak to end

find any difference in terms of Tp-e interval, and we did not demonstrate any correlation between disease duration and these parameters. Additionally, when we compared the seropositive, seronegative patients practicing a gluten free diet and those patients with a new diagnosis, we did not find any difference between the groups in terms of ECG parameters. The short follow-up period may be the major reason for these results. Nutritional deficiency and autoimmune triggered myocardial involvement may have led to the increased QT, QTc and Tp-e dispersions and Tp-e/QT ratio in our study. Furthermore, when seronegative patients with celiac diet were compared to controls, QT and QTc dispersions were significantly higher in the celiac patients. These results suggest that CD patients continue to have a cardiac risk despite diet and that autoimmunity may lead to this situation. Due to the lack of studies evaluating these ECG parameters in children with CD, our study may be the starting point for further electrophysiological studies to evaluate potentially fatal atrial and ventricular arrhythmias in this patient population.

Study Limitations

Our study has some limitations that need to be considered. First, its relatively small sample size is the foremost limitation of our study. Second, we could not evaluate the ventricular functions by strain echocardiography to demonstrate subclinical left ventricular dysfunction. Third, it is possible that we did not find any correlation between ECG parameters and disease duration due to the short follow-up period. Finally, we could not perform 24-hour ECG monitoring on patients with CD and evaluate future arrhythmic events.

Conclusion

Our study showed that CD is associated with changes in some ECG parameters such as prolonged PWd, QT, QTc and Tp-e dispersions and increased Tp-e/QT ratio, which are considered as predictors of atrial and ventricular arrhythmias in special populations. Due to the long-life expectancy in children, pediatric patients with CD may be considered to be at risk of developing arrhythmias. For this reason, these parameters should be evaluated carefully in children with CD. Longer prospective electrophysiological studies are needed to demonstrate the long-term clinical and prognostic results of these ECG parameters.

Ethics

Ethics Committee Approval: The research procedure was approved by the Local Ethics Committee (no: 2018/3-9).

Informed Consent: The patients signed consent forms which gave information concerning the purpose of this study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: T.D., Data Collection or Processing: Y.Ç.A., B.A., Echocardiography: B.G., Writing: T.D., N.N., C.K., Critical Revision: M.B.

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Original Article

Neonatal Outcomes of Immigrant and Turkish Preterm Infants Treated in a Level-3 Neonatal Intensive Care Unit: A Retrospective Study

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ABSTRACT

Aim: To evaluate the neonatal outcomes of immigrant preterm babies and compare them with Turkish preterm babies in a Neonatal Intensive Care Unit (NICU).

Materials and Methods: The present study was conducted using a retrospective design in the NICU of Necmettin Erbakan University between October 2015 and October 2019. Antenatal, natal and postnatal outcomes of the premature infants were evaluated and compared.

Results: Maternal age (p<0.001), antenatal follow-up (p<0.001), antenatal steroid use (p<0.001), patent ductus arteriosus (PDA) (p=0.03) and bronchopulmonary dysplasia (BPD) (p=0.05) were statistically higher in the Turkish patients. Additionally, the rates of breastfeeding (p<0.01) and kangaroo mother care (p<0.01) were found to be higher among Turkish mothers. On the other hand, the necrotizing enterocolitis (NEC) rate (p=0.002) was found to be higher among immigrant babies. Duration of mechanical ventilation and oxygen supply were similar for both groups; however, the duration of nasal-continuous positive airway pressure use was longer in the Turkish patients (p=0.01).

Conclusion: In this study, immigrant mothers were younger than their Turkish counterparts and their antenatal follow-ups were insufficient. The rate of hospitalization in a NICU and NEC rates were higher in immigrant preterm infants, respiratory distress syndrome, PDA and BPD were more commonly encountered in Turkish preterm infants.

Keywords: Newborn, migration, refugees, preterm, Turkey

Introduction

The number of refugees who leave their home country due to civil wars in Middle Eastern countries has been increasing gradually over the years. In parallel with low socioeconomic status, unhealthy living conditions and an increased birth rate among these immigrants, health issues are also increasing. There have been many studies that investigated the perinatal status of the global immigrant population, and their findings revealed that having an immigrant status is related to insufficient antenatal care, perinatal mortality, prematurity, low birth weight (BW) and congenital anomalies (1-4). In addition to individual/patient-associated factors in host and immigrant populations, inequality and variability in healthcare access are factors that contribute to the poor perinatal outcomes of the immigrant population.

In the literature, studies that describe perinatal outcomes of immigrant populations have been published.

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However, to our knowledge, there is no research to date that evaluates the outcomes of the neonatal period of premature babies treated solely in intensive care units. The present study evaluates neonatal outcomes of immigrant preterm babies and compares them with those of Turkish preterm babies.

Materials and Methods

Study Design and Study Population

The present study was conducted using a retrospective design in the Neonatal Intensive Care Unit (NICU) of Necmettin Erbakan University, Meram Faculty of Medicine Ethics Committee between October 2015 and October 2019. A total of 240 preterm infants with a gestational age (GA) ≤32 weeks were enrolled. Patients with major congenital anomalies and stillborn infants were not included in the study.

The demographic characteristics of the immigrant and Turkish newborns including nationality, gender, GA, maternal age, maternal or gestational disease, mode of delivery, BW, BW according to GA (small for GA/SGA), antenatal steroid usage and antenatal follow-up were collected from the medical records. Neonatal morbidities were defined as resuscitation in the delivery room, respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH) (grade >3), sepsis, hemodynamically significant patent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD), respiratory support [duration of mechanical ventilation, nasal continuous positive airway pressure (nCPAP) and supplemental oxygen], necrotizing enterocolitis (NEC), severe retinopathy of prematurity (ROP) and kangaroo mother care, breastfeeding and catch-up time of birth weight.

GA was determined by either prenatal ultrasound examination, date of last menstrual period or new Ballard. SGA was defined as infants with a BW below the 10th percentile for their GA (5). Sepsis was defined via positive blood culture. Hemodynamically significant PDA was defined according to echocardiography parameters. Left atrium-to-aortic root diameter ratio ≥1.4 in the parasternal long-axis view, ductal diameter ≥1.4 mm/kg body weight, left ventricular enlargement, and reversed diastolic flow in the descending aorta indicating a significant ductal shunt (6). The antenatal steroid was considered to have been administered if betamethasone therapy was completed 24 hours before delivery. First eye examination was performed at 4 weeks of the chronological age for infants with GA ≥27 weeks, or at 31 weeks of the postmenstrual age (PMA) for infants with GA between 24 and 26 weeks. All assessments for ROP were made by the same pediatric ophthalmologist throughout the study. The staging of ROP was recorded according to the international classification of ROP. The criteria for treatment were: zone 1 any stage of ROP with a plus disease or zone 1 stage 3 without plus and zone 2 stages 2 or 3 with the plus disease as defined by early treatment for the ROP cooperative group (7); severe ROP was defined as ROP requiring treatment. BPD was defined as oxygen requirement at 36-weeks PMA for an infant who was born at ≤32 gestational weeks (8). IVH was based on cranial ultrasonography evaluation in the first week of life according to Volpe criteria (9). Stage 3 patients according to Bell's criteria were defined as NEC. Women who had antenatal examinations at least three times during their pregnancies were followed up antenatally.

Statistical Analysis

The calculation of the sample size for statistical analysis was performed by taking 20 patients per each variable.

The demographics and incidences of neonatal morbidity among Turkish and immigrant patients were calculated with categorical variables given as frequencies and percentages, and were compared using chi-square or Fisher's tests. The mean and standard deviations or median and first and third quartiles of continuous variables were provided. Continuous variables were compared using the t-test or the Mann-Whitney U test, where appropriate. The garnered data were analyzed using SAS university edition package version 9.4 (SAS Institute Cary, NC, USA). A p-value of <0.05 was considered significant.

Results

A total of 240 babies aged ≤32 weeks were included in this study, among which, 64 (26.6%) were immigrant and 174 (73.4%) were Turkish. The demographic and clinical data of the patients are summarized in Table I. Maternal age (p<0.001), antenatal follow-up (p<0.001) and antenatal steroid use (p<0.001) were significantly higher in Turkish patients than in those who were immigrants. GA and BW were similar for the two groups. Incidences of SGA (p=0.04) and gestational diabetes (p=0.01) were found to be higher among Turkish babies. The postnatal outcomes of the patients are presented in Table II. RDS (p=0.04), PDA (p=0.03) and BPD (p=0.05) were statistically higher in the Turkish patients compared to the immigrant patients (Table II). Rates of breastfeeding (p<0.01) and kangaroo mother care (p<0.01) were found to be higher among Turkish mothers. On the other hand, the NEC rate (p=0.002) was

found to be higher among immigrant babies. The duration of mechanical ventilation and oxygen supply were similar for both groups; however, the duration of nCPAP use was longer in the Turkish patients (p=0.01).

Discussion

The number of international immigrants has been increasing over recent years. In the broader context of globalization, the increasing volume and complexity of

Table I. Antenatal and natal outcomes of prematurity infants

	Turkish citizen n=176	Immigrant n=64	p
Maternal age (mean ± SD)	28.2 (6.29)	23.4 (4.8)	<0.0001
Gestational age (week) (mean ± SD)	29.4 (2.48)	29.9 (2.16)	0.16
Birth weight (gr) (mean ± SD)	1435.1 (424.4)	1446.6 (356.8)	0.85
Assisted reproductive technigus; n (%)	3 (1.17)	2 (3.17)	0.61
C/S n (%)	118 (67.43)	41 (65.08)	0.73
SGA n (%)	16 (9.14)	12 (19.05)	0.04
Sex (male) n (%)	93 (53.14)	38 (60.32)	0.33
Multiple pregnancy n (%)	52 (29.71)	26 (41.27)	0.09
No or low frequency of antenatal care n (%)	125 (71.43)	28 (43.75)	<0.0001
Antenatal steroid n (%)	52 (29.71)	5 (7.94)	0.0005
Preeclampsia n (%)	17 (9.71)	5 (7.94)	0.68
Gestational diabetes mellitus n (%)	15 (8.57)	0 (0)	0.01
Resuscitation n (%)	51 (29.14)	22 (34.92)	0.39
Stillbirth[1]	8.8 (95/10740)	15.2 (45/2960)	0.003

[1]: Per 1000 births
C/S: Cesarean/sexio, SGA: Small gestational age, SD: Standard deviation

Table II. Postnatal outcomes of prematurity infants in neonatal intensive care unit

	Turkish citizen n=176	Immigrant n=64	p
RDS n (%)	111 (63.43)	31 (49.21)	0.04
IVH n (%)	4 (2.68)	1 (1.79)	1.00
PDA n (%)	21 (14.09)	2 (3.57)	0.03
NEC n (%)	1 (0.67)	6 (10.71)	0.002
ROP n (%)	32 (21.48)	8 (14.29)	0.25
BPD n (%)	30 (20.13)	5 (8.93)	0.05
Early onset neonatal sepsis n (%)	3 (2.00)	2 (3.57)	0.61
Late onset neonatal sepsis n (%)	15 (10.07)	6 (10.71)	0.89
Breastfeeding n (%)	116 (77.33)	17 (30.36)	<0.001
Kangaroo mother care (mean ± SD) (d)	114 (70.51)	8 (14.29)	<0.0001
Catch-up time of birth weight (mean ± SD) (d)	10.05 (5.00)	9.73 (5.26)	0.69
Oxygen support (median Q1-Q3) (d)	10.0 (4.0-31.0)	7.0 (2.50-24.0)	0.28
MV time [median (Q1-Q3)] (d)	0.0 (0.0-4.0)	0.0 (0.0-3.5)	0.70
nCPAP time [median (Q1-Q3)] (d)	2.0 (1.0-5.0)	1.0 (0.0-2.0)	0.01

BPD: Bronchopulmonary dysplasia, MV: Mechanical ventilation, NEC: Necrotizing enterocolitis, nCPAP: Nazal-continue positive air way pressure, PDA: Patent ductus arteriosus, RDS: Respiratory distres ROP: Retinopathy of prematurity syndrome, SGA: Small gestational age, SD: Standard deviation IVH: Intraventricular hemorrhage

flows of migration have led to a wide range of problems in fields including human rights, public health, illness and border control (10). Particularly, the migration of women has been an important component of international migration. The biological status of these women is closely associated with nutrition, reproductive life, the presence of some infections and smoking or alcohol consumption. Statuses of inequalities that cause psychosocial stress such as economic inequality, gender inequality and, in multiethnic societies, ethnic inequality determine the emotional status of these women. All of these influence perinatal health, regardless of why they have become an immigrant (11).

Rates of multiparity, pregnancy-associated complications and negative perinatal outcomes have been reported to be higher among refugees when compared to native populations in some publications (12-15). Raimondi et al. (11) revealed in their study that native mothers have lower birth-weight newborn infants, primiparity, and adolescent pregnancy. They also reported that a larger population of native women in the study compared to the immigrants was effective in this situation (11). However, as an epidemiological paradox, in this research are reported to be better in refugees, although immigrant women tend to face greater demographic and socio-economic risk factors (16).

Group B streptococcal screening during pregnancy in the United States and consequently intrapartum antibiotic prophylaxis reduced the incidence of early-onset sepsis with GBS by 65% (17). However, the quality of healthcare provided to immigrants living in developed countries has been reported to be inferior to that provided to native populations (2,18). Similar healthcare services are provided for Turkish and immigrant mothers and their babies in Turkey. Antenatal follow-up of immigrant mothers has been observed to be insufficient in the present study. It is likely that the reason for this is not due to the presence of obstacles that prevent immigrant patients from accessing healthcare, but rather due to communication problems and lack of knowledge about antenatal follow-up among patients. In addition, other factors that cause poor antenatal follow-up in the immigrant population are the absence of any problems encountered in the prior pregnancies of multiparous mothers and the absence of a caregiver or a relative to look after other children in the family while their mother attends hospital for follow-up visits. Poor antenatal follow-ups and lack of antenatal corticosteroid use among immigrant mothers brought about a rise in stillbirth rates, requirements for neonatal resuscitation and admission to NICUs consistent with findings which have been reported in the previous literature (3).

Clinical and demographical findings, such as birth weight, week of pregnancy, multiparity and cesarean section birth, were found to be similar in both groups. The number of cesarean section births has been reported to be lower in immigrant patients than in the host citizens in some studies (19,20). However, the cesarean section rate in those studies was calculated including all modes of delivery. In our study, we calculated the rate of cesarean sections only among at-risk babies in neonatal care and found similar rates between the two groups. The maternal age of immigrant patients was found to be lower in the present study, which is compatible with the findings in previous literature (19). Marriage at a young age as a result of conventional family structure, and the desire to escape from the civil war are thought to be related to low maternal age.

Kangaroo mother care results in increased growth and breastfeeding rates of preterm babies (21). Major immunologic components in human milk, such as secretory immunoglobulin-A and growth factors, have a known role in regulating gut barrier integrity and microbial colonization, and therefore, it is protective against the NEC (22). In our study, Kangaroo mother care and breastfeeding rates were found to be quite low among immigrant mothers. This can be attributed to the unwillingness of mothers to participate in baby care, and inefficiency in the evaluation of the importance of breast milk and nursing among immigrant mothers, which could not be improved due to communication problems such as their inability to speak Turkish. Since they have little faith that their preterm babies, admitted to the intensive care unit, will survive, these mothers desire to become mothers again. Furthermore, they may not want to breastfeed their children, as they believe that milking and continuing breastfeeding are methods of birth control.

The adverse neonatal outcomes of <32 gestation week preterm babies, including IVH, RDS, neonatal sepsis and BPD, have been reported to be associated with ethnic variability (23), although it is difficult to define the effects of ethnicity and race, and this is still a controversial issue (24). The risk of adverse neonatal outcomes after preterm birth among African, Mediterranean and Eastern Asian women is reported to be lower when compared to preterm births among Caucasian European women (23). Incidences of NEC were found to be higher in immigrant babies in the present study, which is considered to be due to the low rate of breastfeeding among immigrant mothers (25). Antenatal follow-up was found to be better, and the rate of antenatal corticosteroid application was higher in Turkish patients. However, incidences of RDS, PDA and BPD were higher in

Turkish patients when compared to immigrants, which could be attributed to ethnicity and intrauterine stress factors, although further studies are needed to account for the association between ethnicity and neonatal outcome.

Study Limitations

The retrospective design and small sampling size are the limitations of our study.

Conclusion

Short-and long-term morbidities of preterm infants in our study differed among Turkish and immigrant patients. We are of the opinion that further studies are needed to determine their association with standards of living, sociocultural status or race.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from Necmettin Erbakan University, Meram Faculty of Medicine Ethics Committee (approval number: 2019/1989, date: 12.07.2019).

Informed Consent: Informed consents were not required because the study was conducted retrospectively.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.T., Concept: N.T., F.H.Y., Design: N.T., Data Collection or Processing: F.H.Y., Analysis or Interpretation: N.T., Literature Search: N.T., H.A., Writing: N.T., F.H.Y.

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Original Article

Clinical Characteristics and Neurological Findings of Pediatric Patients with Acute Carbon Monoxide Intoxication

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ABSTRACT

Aim: The aim of this study is to analyze children with acute carbon monoxide (CO) poisoning and to present two patients with rare neuroradiological findings.

Materials and Methods: We identified and reviewed the medical records of pediatric patients diagnosed with acute CO intoxication who were hospitalized in our department during a 10-year period. Epidemiologic and clinical data were collected and analyzed.

Results: A total of 326 children (166 girls, 160 boys; age range 1 to 17.8 years) with CO poisoning were identified. Their ages ranged from 1 to 17.8 years, with a mean of 8.3±4.8 years. Improperly vented coal or wood stoves were the most common (80.7%) cause of intoxication. The most common presenting symptoms were nausea/vomiting and headache. Seizure was seen in 32 patients (9.8%). Two patients died and the mortality was 0.6%. All patients received normobaric oxygen therapy until their carboxyhemoglobin (COHb) levels were decreased below 2% and their symptoms resolved. One hundred of the 326 patients (30.7%) also were treated with hyperbaric oxygen (HBO) therapy as indicated by the signs and symptoms or COHb levels. Brain imaging was performed in 19 patients (thirteen magnetic resonance imaging and six computerized tomography), and was normal in 15. Acute brain stem demyelination related to water pipe smoking developed in one patient. All patients showed complete recovery without neurological sequelae except one who had mild right hemiparesis at discharge.

Conclusion: Acute CO intoxication is an important health problem in our country, especially in winter, because of poorly functioning heating systems. The clinical spectrum including neurological findings varies during childhood. We suggest that HBO therapy could be used safely in children. We believe that the combined administration of pulse methylprednisolone and HBO treatment might reduce cerebral damage caused by CO poisoning in selected pediatric patients.

Keywords: Acute carbon monoxide intoxication, clinical features, neurological findings, children

Introduction

Carbon monoxide (CO) causes direct cellular damage and tissue hypoxia by shifting the oxyhemoglobin dissociation curve to the left as it competes with oxygen for binding to hemoglobin. As a result, tissue oxygen extraction is hampered and oxidative stress causes tissue damage and clinical symptoms. CO is highly toxic for cardiac and cerebral tissue as these tissues have a higher metabolic

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rate and thus are sensitive to hypoxia (1). Symptoms of mild CO intoxication such as fatigue, headache, nausea and vomiting are non-specific. Visual disturbances, confusion, ataxia, seizure, loss of consciousness and death have also been reported in cases of moderate or severe exposure. Children are more sensitive to the toxic effects of CO and become symptomatic earlier than adults since their blood volume is lower, basal metabolic rate is higher and tissue oxygen demand is greater (2). There are few studies on CO poisoning in children, especially concerning neurological and neuroradiological findings. The purpose of this study is to describe and analyze the clinical features, treatment, neuroradiological findings and outcomes in children who were admitted with CO intoxication.

Materials and Methods

This study was performed retrospectively among pediatric patients who were admitted to the Emergency Department of Dr. Sami Ulus Training and Research Hospital due to CO poisoning between January 2007 and December 2017. Clinical and laboratory data were obtained from electronic hospital records retrospectively. Carboxyhemoglobin (COHb) levels higher than 2% were considered as abnormal. A child having manifest symptoms of CO intoxication but a normal COHb level was accepted as acute CO poisoning if the child or family members had a history of CO exposure. Children with chronic pulmonary, cardiac, neurological or metabolic disease were excluded from this study. The age and gender of the patients, source of CO exposure, vital signs, Glasgow Coma scale (GCS) scores, laboratory results, treatment modalities, total hospital stay, results of computerized tomography (CT) and cranial magnetic resonance imaging (MRI) were recorded. Neurological abnormality was defined as altered consciousness, seizure, ataxia, or abnormal neurological examination findings at presentation. Cardiological abnormality was defined as changes in electrocardiography (ECG) and an increase in Troponin I or creatine kinase-myocardial band (CK-MB) levels and severe metabolic acidosis was defined as an arterial blood pH lower than 7.15.

All patients were treated with normobaric oxygen (NBO) therapy at a rate of 10 L/min with a non-rebreathing face mask. The indications for hyperbaric oxygen (HBO) therapy were positive neurological symptoms (seizures, coma, lethargy, syncope) at presentation, refractory neurological symptoms after NBO therapy, COHb level greater than 25% or cardiac abnormality. A military based HBO therapy center in our city was consulted in cases of HBO requirement as our center lacks a HBO chamber.

This study was approved by the ethics committee of Ankara Training and Research Hospital Local Ethics Committee. Informed consent was obtained from the parents/care givers of the patients.

Statistical Analysis

Data analyses were performed using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, United States). Whether the distribution of continuous variables was normal or not was determined by Kolmogorov-Smirnov test. Levene test was used for the evaluation of homogeneity of variances. Unless specified otherwise, continuous data were described as mean ± standard deviation for normal distributions, and median (range) for skewed distributions. Categorical data were described in terms of the number of cases (%). Statistical analysis differences in normally distributed variables between two independent groups were compared by Student's t-test, Mann-Whitney U test was applied for comparisons of non-normally distributed data. While the differences in normally distributed variables among more than two independent groups were analyzed by One-Way ANOVA, otherwise, Kruskal-Wallis test was applied for comparisons of the non-normally data.

Results

A total of 326 children (160 males and 166 females) with CO poisoning were included in this study. They were between 1 month and 17.8 years old, with a mean of 8.3±4.8 years. The majority of poisonings happened during colder seasons (78.8%). The distribution of the patients according to the source of intoxication is summarized in Table I.

One hundred and forty-four of the patients (44.1%) arrived at the hospital on their own while 182 (55.8%) patients were brought by an ambulance. Before admission, 49.4% of the patients had been given NBO therapy and 6.7% had received HBO therapy in another center. COHb levels varied between 0.1% and 47.5% with a mean value of 15.4±9.6%. Fifty-one (15.6%) patients had an initial CO level greater than 25%. Forty-eight (14.7%) patients were asymptomatic but were accepted as possible poisonings

Table I. The distribution of the patients according to source of intoxication (n=326)

Source of exposure	Number of patients (%)
Coal or wood stoves	263 (80.7)
Natural gas	57 (17.5)
House fires	5 (1.5)
Hookah	1 (0.3)

since other family members had overt CO poisoning. The distribution of initial symptoms and COHb levels are given in Table II.

While most patients had normal physical examination findings (n=310, 95.1%), 9 patients were lethargic, 6 patients were in coma and 1 patient had internuclear ophthalmoplegia. It was observed that asymptomatic cases had lower COHb levels with statistical significance than all findings except altered mental status ($p<0.05$). Twenty-one patients were admitted to the intensive care unit with a mean stay duration of 111.3±106.7 hours (range: 10-480 hours). All patients with abnormal neurological examination and 5 patients with normal examination were followed up in the intensive care unit. One of these patients was a 1-month-old who had a plasma CO level of 19.4 and had seizures. Therefore, he was admitted to the intensive care unit for follow-up. The other 4 patients had a COHb level of over 25, and they had seizures prior to admission. Arterial blood gas measurements were performed in 281 patients, the mean pH level was 7.372 (range: 6.823-7.540); 3 children had severe metabolic acidosis. Lactate levels were elevated in 24 patients, CK-MB in 39 patients, troponin I in 30 patients and lactate dehydrogenase in 8 patients. No ECG abnormalities were detected except sinus tachycardia in two patients. Disseminated intravascular coagulation developed in five patients. Inhalation pneumonitis and acute respiratory distress syndrome developed in two of the five house fire victims. Two patients died because of sepsis and multiple organ failure. All surviving patients were discharged without sequelae except one patient with cerebrovascular ischemia.

All patients were treated with NBO therapy and 30.7% (n=100) with HBO therapy. The number of HBO treatment sessions varied between 1 and 16, with a mean of 2 and the mean COHb level was 17.2±13.1 (range: 0.1-47.5). The symptoms of patients who needed HBO therapy were syncope (n=42), a decreased level of consciousness (n=32), seizures (n=26), headache (n=19), nausea/vomiting (n=19) and vertigo (n=11). No HBO treatment related complications were observed.

Cranial imaging was performed in 19 patients (13 MRIs and 6 CTs) and 15 were normal. Abnormal findings in cranial scans were cerebellar tonsillar herniation due to severe brain edema in 2 patients, cerebrovascular ischemia in 1 patient, and brainstem demyelination with thalamic involvement in 1 patient. Detailed clinical information and cranial imaging findings are presented in Table III.

Two acute CO intoxication cases of interest along with their neurological and radiological findings are presented below.

Case 1

A 16-year old male was brought to the emergency department with headache and diplopia. Headache and nausea had begun after smoking two hookahs (water-pipes used to smoke tobacco) in a closed environment 24 hours earlier. He noticed that he had diplopia when he woke up the next morning. Neurological examination revealed impairment of adduction in the left eye and nystagmus in the right eye on the rightward gaze. His COHb level was 39% and NBO treatment was initiated. Cranial MRI scan performed at the 24th hour revealed high intensity lesions at the left paramedian section of the pons, the medial segment of the left thalamus and left middle cerebellar peduncle on T2 sequences which showed mild contrast enhancement on T1 weighted sequences. The lesion at the left paramedian portion of the pons showed restricted diffusion on diffusion-weighted images. (Figure 1A-C). When cranial MRI and neurological examination findings were evaluated together, internuclear ophthalmoplegia due to CO intoxication was considered. HBO treatment with

Table II. Symptoms and signs of the patients on admission and COHb levels

Symptoms and signs*	Number of patients (%)	Mean COHb% level (range)**
Nausea/vomiting	133 (39.9)	16.1 (0.1-39.5)
Headache	121 (37.1)	16.3 (0.7-39.9)
Syncope	69 (21.2)	17.9 (0.1-47.5)
Vertigo/dizziness	47 (14.4)	17.4 (0.3-30.8)
Altered mental state	42 (12.9)	12.7 (0.1-47.5)
Seizure	32 (9.8)	19.1 (0.3-45)
Asymptomatic	48 (4.7)	11.4 (3-26)

*Many patients had more than one presenting symptom, **Most of the patients received oxygen therapy (NBO or HBO) prior to admission to our center, COHb: Carboxyhemoglobin, NBO: Normobaric oxygen, HBO: Hyperbaric oxygen

Table III. Clinical characteristics of patients performed brain imaging

Patient	Age (year)/sex	Source of exposure	Initial presentation	Treatment before admission	First COHb level	Neurologic examination	Laboratory results	Brain imaging	Treatment/ outcome
1	16/male	Water pipe	Headache diplopia	NBO	33.1	Internuclear ophthalmoplegia	Normal	MRI: High signal intensity in left paramedian portion of the pons, in left middle cerebellar peduncle and in the medial segment of left thalamus on T2-weighted image,and showed restricted diffusion on diffusion-weighted imaging	HBOT and IV Pulsed Methylprednisolone/ discharged without sequelae
2	6/male	Coalor wood stoves	Coma	3 seans HBO	3	Coma (GCS=3)	Increased liver function tests, CK, CK-MB, Troponin I	MRI: Bilateral asymmetrical (left predominant) hyperintensity in the anterior and posterior border zone feeding areas on T2-weighted and diffusion-weighted image, consistent with acute border zone infarctions	HBOT/discharged with a little weakness in the right hand fingers
3	15/female	Natural gas	Syncope	NBO	20	Normal	Normal	MRI: Normal	NBOT/discharged without sequelae
4	Two and a half/male	Coalor wood stoves	Syncope and consciousness disturbance	HBO	0.7	Normal	Normal	CT: Normal	NBO/discharged without sequelae
5	13/female	Coalor wood stoves	Syncope	No treatment	22.9	Normal	Normal	MRI: Normal	HBO/discharged without sequelae
6	5/female	Coalor wood stoves	Consciousness disturbance	NBO	17.9	Lethargy (GCS=12)	Normal	MRI: Normal	HBO/discharged without sequelae
7	15/male	Coalor wood stoves	Coma	NBO	0.5	Coma (GCS=3)	Severe metabolic acidosis, increased liver function tests, CK, CK-MB, Troponin I	MRI: Normal	HBO/discharged without sequelae

Table III. contiuned

8	10/female	Coalor wood stoves	Syncope	No treatment	16	Normal	Normal	CT: Normal	NBO/discharged without sequelae
9	3/female	House fire	Coma	2 seans HBO	1.6	Coma (GCS=3)	Severe metabolic acidosis, increased liver function tests, CK, CK-MB, Troponin I	CT: Brain edema and cerebellar tonsillar herniation	Died
10	3/female	Coalor wood stoves	Seizure	NBO	16	Normal	Normal	MRI: Normal	HBO/discharged without sequelae
11	16/female	Natural gas	Consciousness disturbance	NBO	28.2	Lethargy (GCS=12)	Increased iver function tests, CK, CK-MB, Troponin I	MRI: Normal	HBO/discharged without sequelae
12	5/female	House fire	Coma	NBO	39	Coma (GCS=3)	Increased liver function tests, CK, CK-MB, Troponin I	MRI: Normal	HBO/discharged without sequelae
13	16/female	Coalor wood stoves	Consciousness disturbance	1 seans HBO	1	Normal	Increased CK, CK-MB, Troponin I	MRI: Normal	HBO/discharged without sequelae
14	15/female	Coalor wood stoves	Syncope headache	NBO	3.7	Normal	Increased Troponin I	CT and MRI: Normal	HBO/discharged without sequelae
15	12/male	House fire	Coma	1 seans HBO	0.1	Coma (GCS=3)	Increased CK, CK-MB, Troponin I	CT: Brain edema and cerebellar tonsillar herniation	Died
16	12/male	Coalor wood stoves	Coma	1 seans HBO	0.3	Coma (GCS=3) and ARDS	Increased CK, CK-MB, Troponin I	CT: Normal	HBO/discharged without sequelae
17	5/female	Coalor wood stoves	Coma	NBO	21	Coma (GCS=3)	Increased CK, CK-MB, Troponin I	MRI: Normal	HBO/discharged without sequelae
18	17/male	Coalor wood stoves	Seizure	NBO	10.6	Normal	Normal	CT: Normal	HBO/discharged without sequelae
19	16/male	Natural gas	Seizure	NBO	30.1	Normal	Increased CK, CK-MB, Troponin I	MRI: Normal	HBO/discharged without sequelae

NBO: Normobaric oxygen treatment, HBO: Hyperbaric oxygen treatment, GCS: Glasgow coma scale, ARDS: Acute respiratory distress syndrome, CT: Computed tomography, MRI: Magnetic resonance imaging, CK: Creatine kinase, CK-MB: Creatine kinase-myocardial band

simultaneous pulsed methylprednisolone (30 mg/kg/day for 5 days) was initiated. On the third day of steroid and HBO treatment, double vision resolved and the impairment of adduction in the left eye was significantly reduced. The patient was discharged without any sequelae after 7 days of hospitalization. MRI performed on the third week of follow-up revealed that the left cerebellar and left thalamic lesions had completely resolved and the size of the pontine lesion had significantly diminished. The patient's neurological examination at the third week was completely normal.

Case 2

A 6-year-old male patient had been found in an unconscious state in a room with a coal heater and was immediately taken to a local hospital. His GCS score was 5. He was immediately intubated and was given high-flow oxygen therapy. His COHb level was 25.5%. The patient was transferred to our center after one session of HBO treatment at another center in the same city. Upon arrival at our intensive care unit, his GCS score was 7 and he was being ventilated mechanically. His COHb level was 0.3% after 1 session of HBO treatment. Creatine phosphokinase was 41537 IU/L, CK-MB was 9605 U/L, aspartate aminotransferase was 605 U/L, alanine aminotransferase was 260 U/L, blood urea nitrogen was 33 mg/dL, creatinine was 0.84 mg/dL, lactate was 27.3 mg/dL, troponin I was 47 ng/L, prothrombin time was 15.6 seconds, international normalized ratio was 2.29, D-dimer was 3373 ng/mL. ECG and echocardiography were normal. After 72 hours, he gradually awakened and was extubated. On the 5th day of follow-up, his muscle strength in upper extremity was 3/5. Cranial CT revealed no abnormalities but MRI revealed bilateral asymmetrical (predominantly on the left) hyperintense lesions in the anterior and posterior border zones of the watershed areas of the middle cerebral arteries on T2-weighted and diffusion weighted sequences, consistent with acute watershed infarcts (Figure 2A-F). HBO treatment was administered in 16 sessions and physical therapy and rehabilitation were initiated. After 20 days, the patient was discharged from the hospital with physical therapy and rehabilitation recommendations. On the second year of follow-up, brain MRI was normal and neurologic examination revealed a slight weakness in the right-hand fingers. The patient was able to walk without support and did not have any difficulties at school.

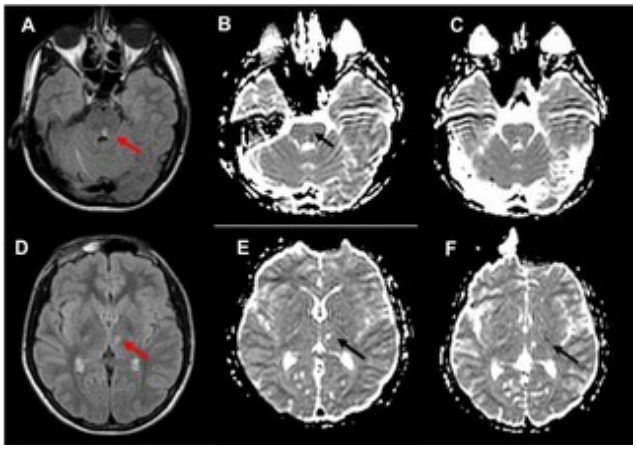

Figure 1. Initial 24 hr cranial MR scan of a 16-year old male with CO poisoning secondary to water pipe smoking shows high signal intensity lesion in the left paramedian section of the pons on Flair (A) (red arrow) which also shows diffusion restriction on ADC (black arrow) and is resolved on 3rd week control MR (C). Another lesion at the medial segment of the left thalamus on initial scan shows high signal on Flair (D) (red arrow) but no diffusion restriction on ADC initially (E) or on follow-up (F) (black arrows)
MR: Magnetic resonance, CO: Carbon monoxide, ADC: Apparent diffusion coefficient

Discussion

The incidence of CO poisoning depends on the region, geographical conditions, socio-economic status and seasons and it is more common in winter and in colder climates which are directly proportional to the need for heating. Stoves have been reported as the most common source of CO intoxication (3-5). Improperly vented coal or wood stoves were the most common (80.7%) source of CO intoxication in our study.

Interestingly, one patient had double vision following hookah smoking and internuclear ophthalmoplegia was detected in neurologic examination. The hookah, also known as nargileh, shisha, water-pipe or hubble-bubble is used to smoke tobacco. In recent years, it has become increasingly popular among adolescents and young adults. A widespread misconception is that the water purifies the smoke, thereby rendering it harmless. However, this type of smoking produces the same harmful substances as cigarette smoking (tar, nicotine, CO, etc.) and involves a serious risk of CO poisoning (6). A number of cases associated with

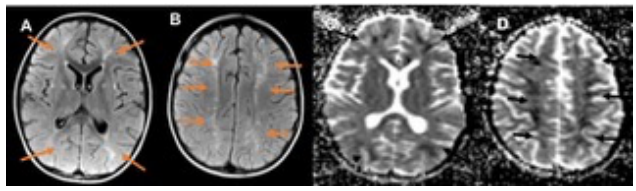

Figure 2. Cranial MRI of a 6-year old male intoxicated from stove shows bilateral asymmetrical hyperintensities in the anterior and posterior border zones on T2-weighted images (A-B) (red arrows) corresponding to areas of diffusion restriction on ADC images (C-D) (black arrows), consistent with acute border zone infarctions
MRI: Magnetic resonance imaging, ADC: Apparent diffusion coefficient

hookah smoking have been previously reported (7-9). To the best of our knowledge, this is the first patient in the literature with internuclear ophthalmoplegia secondary to CO intoxication secondary to hookah smoking.

Children are more susceptible to the toxic effects of CO since they have fewer compensatory mechanisms against hypoxia and they need more oxygen due to their higher basal metabolic rate. Therefore, children become symptomatic earlier in the course of CO poisoning. Symptoms in pediatric patients are often non-specific, such as nausea and vomiting, and may be easily misdiagnosed as a viral infection (10,11). In our study, we found that symptoms such as nausea, vomiting, headache, syncope and impaired consciousness were the most common symptoms. The prevalence of seizures in CO poisoning in children has been reported at rates ranging from 2.1% to 23.3% in the literature (5,12,13). Seizures were observed in 32 cases (9.8%) in our study. We observed that the mean COHb levels of the patients presented with syncope and seizure were relatively higher than the others. Lower COHb levels were detected compared to all findings except for altered mental status in asymptomatic patients. However, no definite clinical relationship was found between the CO levels and clinical symptoms of the patients. This finding had a correlation with previous studies. This is why our hospital is a tertiary center so that patients with neurological symptoms such as syncope, seizures and altered mental status will highly referred.

COHb levels were greater than 25% in 51 (15.6%) patients and were normal in 23 (7%) patients. Before admission to our center, 49.4% of the patients had been given NBO therapy and 6.7% had been given HBO therapy in another center. The half-life of COHb is 4-5 hours in room air, and this decreases to 60 minutes when breathing 100% oxygen and further decreases to 15-30 minutes during HBO therapy (14). We believe that those patients who applied to the emergency department with normal CO levels had longer transportation times while receiving 100% oxygen treatment with a mask in the ambulance and thus, the measured values did not reflect the actual COHb levels. Therefore, we think that the presence of normal CO levels in children does not exclude the diagnosis of severe intoxication.

Tissue hypoxia is the main consequence of CO intoxication, so the basis of treatment is to give oxygen through the mask or in a hyperbaric chamber (15). HBO increases the dissolved oxygen level in the plasma thus enhancing oxygen delivery to the tissues. HBO also modulates mitochondrial oxidative metabolism, lipid peroxidation and neuronal apoptosis (16-19). Generally accepted indications for HBO treatment in children with acute CO poisoning are severe neurologic symptoms at presentation, continued neurologic symptoms after NBO therapy, myocardial ischemia and cardiac dysrhythmias, abnormal neuropsychiatric findings, high COHb levels and infants under six months with symptoms such as lethargy, irritability or poor feeding (20-22). It is recommended that the first session of HBO treatment be administered within 4-6 hours of poisoning and the recommended number of sessions is at least two (23,24). In our study, all patients were treated with NBO and 100 patients (30.7%) were treated with an average of 2 sessions of HBO treatment. HBO therapy was initiated within the first 24 hours and the most frequent indication for HBO treatment was syncope and altered mental status. HBO treatment is not free of side effects which include painful barotrauma, decompression sickness, pulmonary edema and hemorrhage, seizures and oxygen toxicity (25,26). In our study, almost all patients who received HBO treatment were discharged in a healthy condition.

The nervous system is highly sensitive to the toxic effects of CO. Some brain regions including the cerebral cortex, the white matter, the basal nuclei and the cerebellar Purkinje cells are highly sensitive to hypoxic damage. The globus pallidus is more prone to injury due to its high concentrations of heme-iron bound to CO and weak collateral blood supply (27,28). Nineteen patients (5.6%) underwent brain imaging and 13 patients had normal imaging. The typical globus pallidus involvement was not seen in any of the patients. One patient (Case 1) had acute brainstem demyelination, and 1 patient (Case 2) had acute watershed infarctions.

CO intoxication triggers inflammation and activation in N-methyl-D-aspartate neurons, and the subsequent overactivity of neuronal nitric oxide synthase causes perivascular changes that cause neutrophil sequestration/activation (29,30). Xiang et al. (31) stated that inflammation plays an important role in delayed encephalopathy induced by acute CO poisoning in rats and can be attenuated by dexamethasone by protecting myelin from inflammatory damage. In a recent study with adult patients, it was found that the combined application of dexamethasone and HBO therapy could yield better efficacy for patients than HBO therapy as a monotherapy (32). Pulse methylprednisolone therapy can be given with various indications such as acute demyelinating disorders, cerebral vasculitis and encephalopathy. High doses of steroid is believed to suppress inflammation, edema and demyelination. The

patient with internuclear ophthalmoplegia and acute brainstem demyelination was given pulse steroid therapy combined with HBO treatment. On the third day of this treatment regime, we observed that the patient's double vision disappeared and the impairment of adduction in the left eye had significantly subsided. We believe that the combined administration of corticosteroid and HBO treatment might reduce cerebral damage caused by CO poisoning.

Study Limitations

The study center is a research and education center, and some of the patients were referred from other hospitals. The patients referred from other hospitals were treated with oxygen during the transfer. Therefore, these patients' measured COHb values may be lower than their actual COHb values. Also, the absence of an institutional protocol of HBO therapy is another limitation of our study.

Conclusion

In this study, we presented our clinical experience in childhood CO poisonings with a large number of cases. In conclusion, acute neurologic manifestations following CO exposure are common in children. Detailed history, physical examination and a high level of suspicion are important in the diagnosis of CO poisoning. HBO therapy can be safely used in children who have CO poisoning. A combined treatment regime consisting of pulse methylprednisolone and HBO treatment may have a more therapeutic potential to prevent neuronal damage in selected pediatric patients with CO poisoning.

Ethics

Ethics Committee Approval: This study was approved by the ethics committee of Ankara Training and Research Hospital Local Ethics Committee.

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ü.Ö., Design: Ü.Ö., D.Y., N.T., Data Collection or Processing: Ü.Ö., Ö.Y.K, E.A., Analysis or Interpretation: Ü.Ö., Ö.Y.K, E.A., D.Y., Radiological Evaluation: A.S.E., Literature Search: Ü.Ö., A.D., E.A., Writing: Ü.Ö., Ö.Y.K.

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Original Article

Paediatric Rhegmatogenous Retinal Detachment: Clinical Features and Surgical Outcomes

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ABSTRACT

Aim: To evaluate the clinical characteristics, predisposing factors and surgical outcomes of rhegmatogenous retinal detachment (RRD) in paediatric patients.

Materials and Methods: This retrospective consecutive case series included 79 paediatric patients diagnosed with RRD who were treated by surgical intervention. Demographic data, predisposing factors, the status of macular involvement, presence of proliferative vitreoretinopathy (PVR), the type of initial surgery, and the surgical anatomical and visual outcomes of the patients were recorded.

Results: The study included 79 eyes of 79 children with a mean age of 11.63±4.36 years. There were 59 (74.7%) male and 20 (25.3%) female patients in the study group. The mean follow-up period was 18.65±6.04 months. Trauma (45%) was found to be the most common predisposing factor associated with RRD. Other common predisposing factors were myopia (42%), congenital/developmental anomaly (9%), and history of ocular surgery (4%). Macular detachment was present in 56 eyes (70.8%). At the initial examination, the mean VA (VA) was 1.72±1.01 logMAR (n=60). As a primary surgical treatment, 48 eyes (60.7%) had undergone pars plana vitrectomy (PPV), 11 eyes (13.9%) had scleral buckle (SB), and 20 (25.3%) eyes had PPV combined with SB procedures. Reattachment was achieved in 50 (63.2%) eyes after the first surgery. The final mean VA was improved to 1.58±0.87 logMAR, and the anatomical success rate was 74.6%.

Conclusion: This study demonstrated that paediatric RRD is commonly associated with trauma and myopia. Successful outcomes were obtained in both groups after RRD surgery. Although associated with poor visual outcomes, careful ophthalmologic assessment and surgical management can preserve visual functions in children with RRD.

Keywords: Pars plana vitrectomy, paediatric rhegmatogenous retinal detachment, scleral buckle

Introduction

Retinal detachment in the paediatric population is a rare clinical condition as compared to adults (1). Rhegmatogenous retinal detachment (RRD) in children constitutes 3 to 7 percent of all RRDs (2,3). Myopia, trauma, prior surgery, and congenital or developmental anomalies are defined as predisposing factors for RRD occurrence in children (4,5). Previous studies have shown that clinical features, surgical outcomes, and prognosis of RRD in children differ from adults (1,6,7). Systemic and ocular comorbidities, severe developmental disorders, macular involvement and proliferative vitreoretinopathy (PVR) are associated with poor prognosis in paediatric RRD (7-9).

Decreased vision is the most common complaint in all RRDs, however, the disease is often diagnosed at a later stage in the paediatric age group compared to adults (1).

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The lack of self-expression capacity and immature cognitive functions of children may cause the late diagnosis of RRD. Previous studies reported that 40-70% of patients had visual disturbances at the time of diagnosis (10,11). Owing to late diagnosis, paediatric patients are more likely to present with a higher percentage of macular involvement and PVR (4,11). Despite improvements in instruments and surgical techniques, paediatric RRD treatment remains a challenge for surgeons. In this study, we presented the clinical features and surgical outcomes of paediatric RRD patients from our tertiary referral centre. Herein, we also aim to provide contemporary data to prevent and detect this socially significant condition earlier.

Materials and Methods

We retrospectively reviewed the charts of paediatric patients (age <18 years) treated for a diagnosis of RRD at Beyoglu Eye Training and Research Hospital from February 2015 to April 2018. The study was approved by the Hamidiye Ethics Committee of the University of Health Sciences and conducted in adherence to the tenets of the Declaration of Helsinki. The exclusion criteria were active retinopathy of prematurity, retinoblastoma, persistent foetal vasculature, or a follow-up period of less than six months.

Age, gender, laterality, etiology, macular status, refractive status, presence of PVR (grade C or worse), presenting and final (VA), duration of follow-up, and anatomic success after initial surgery and at the end of follow-up were recorded. Patients were divided into groups according to predisposing factors as; the myopia group consisting of patients with a refractive error greater than -4 diopters, the traumatic group (history of open and closed globe injury), the congenital/developmental anomaly group consisting of patients presenting with ocular structural and developmental anomalies and the previous ocular surgery group consisting of patients with prior ocular surgery history.

Data related to operations were recorded, including the type of initial surgical procedure, endotamponade use, and the overall number of surgical interventions, including silicone oil removal procedures. Data of the initial surgery were recorded as follows; the scleral buckle (SB), pars plana vitrectomy (PPV), or combined procedure (both SB and PPV). Scleral buckling procedures were carried out in patients with visible retinal breaks. PPV was performed in patients with obscure ocular media, PVR, giant tears, undetected or multiple retinal breaks, and complicated retinal detachment. Anatomical success was defined as a retinal attachment for at least six months after primary surgery (without tamponade), and final anatomical success was defined as the complete retinal reattachment (without tamponade) at the end of the follow-up period.

Statistical Analysis

Statistical analysis was performed using SPSS software (version 22, SPSS Inc., Chicago, IL). Descriptive statistics were used to evaluate epidemiologic data, type of surgery, number of operations, and final anatomic success. Data were analysed using Wilcoxon signed-rank, Kruskal-Wallis and Dunn tests. Logistic regression was used to assess anatomic outcomes with etiology, age, initial procedure, macular involvement and PVR> grade C status. A p-value <0.05 was considered statistically significant.

Results

Seventy-nine eyes of 79 patients were enrolled with a mean age of 11.63±4.36 years (range: 2-17) in the study. There were 59 (74.7%) males and 20 (25.3%) females in the study group. The laterality of eyes was 33 (41.3%) for right, and 47 (58.8%) for left eyes. The mean follow-up period was 18.65±6.04 months. Trauma was the leading etiological factor in the study group (45%). Other factors contributing to RRD were recorded as myopia in 33 (42%) eyes, congenital and developmental anomalies in 7 (9%) eyes, and previous ocular surgery in 3 (4%) eyes. The demographic and clinical features in the four etiologic groups are presented in Table I. Previous surgical procedures and congenital and developmental disorders are listed in Table II.

At presentation, VA was recorded in 60 (76%) eyes. The mean VA before initial surgery was 1.72±1.01 logMAR, and the macula was detached in 56 (70%) eyes. At the end of follow-up, the mean VA was available for 69 (87%) patients, with a mean of 1.58±0.87 logMAR. VAwas significantly improved after surgical interventions in the overall study group (p=0.042). In 30 (38.0%) eyes, the grade of PVR was recorded as ≥ grade C. The details of surgical interventions, visual and outcomes in the four main groups are presented in Table III. The mean number of surgeries required for favourable anatomic success was 1.63±0.87, with silicone oil removal procedures included. As primary surgery, 48 (60.7%) eyes had undergone PPV, 11 (13.9%) eyes had SB, and 20 (25.3%) eyes had PPV combined with scleral buckling. Air was used in 2 (3%) eyes as endotamponade. In 8 (12.9%) eyes, perfluoropropane (C3F8) and in 6 (6.4%) eyes, sulphuehexafluoride (SF6) gases were used for tamponade. The most commonly used vitreous substitute was silicone oil in those patients undergoing PPV. Eight (12.9%) eyes had 1,000 centistoke (cst) silicone oil, and 38 (61.2%) eyes had 5,000 cst silicone oil for tamponade effect.

After primary surgery, the myopic group had the highest anatomic success rate (66.7%). The retina was attached in 22 eyes in the myopia group, 2 (66.6%) patients in the previous ocular surgery group, 22 (61.1%) eyes in the trauma group, and 4 (57.1%) eyes in the congenital/developmental anomaly group. At the end of the follow-ups, the overall

Table I. Ocular characteristics of the four main study groups

	All	Trauma	Myopia	Congenital/developmental disorder	Previous ocular surgery
Eyes (n)	79	36 (45.0)	33 (42.0)	7 (9.0)	3 (4.0)
Mean age, years (SD)	11.63 (4.36)	11.2 (4.45)	13.6	6.8	7.8
Male gender [n; (%)]	59 (74.7)	27 (75.0)	24 (72.7)	5 (71.4)	3 (100)
Laterality, left eyes [n; (%)]	47 (59.4)	21 (58.3)	21 (63.7)	3 (42.9)	2 (66.7)
Macula off [n; (%)]	56 (70.8)	26 (72.2)	23 (69.7)	5 (71.4)	3 (100)
Presence of PVR > grade C [n; (%)]	30 (38.0)	13 (39.3)	11 (33.3)	4 (57.1)	2 (66.7)
Mean follow-up, months (SD)	18.2 (6.40)	18.4 (7.03)	18.8 (8.50)	15.8 (5.98)	16.7 (4.04)

SD: Standard deviation, PVR: Proliferative vitreoretinopathy

Table II. Predisposing congenital/developmental ocular disorders and previous opthalmic surgeries

Predisposing factor	No of eyes
Congenital/developmental disorder (n=7)	
Coats' disease	1
Von hippel lindau	1
Optic pit	1
Stargardt disease	1
Coloboma	1
Familial exudative vitreoretinopathy	1
Morning glory	1
Previous ocular surgery (n=3)	
Cataract surgery	1
Glaucoma surgery	1
Scleral fixation of intraocular lens	1

Table III. Summary of surgical approach and outcomes according to predisposing factors

	All n=79	Trauma n=36	Myopia n=33	Congenital/developmental disorder n=7	Previous ocular surgery n=3
Initial surgery [n; (%)]					
Scleral buckle	11 (14)	3 (8.3)	8 (24.2)	-	-
Pars plana vitrectomy	48 (61)	23 (63.8)	17 (51.5)	5	3
Combined	20 (25)	10 (27.8)	8 (24.2)	2	-
Anatomic success [n; (%)]	50 (63.2)	22 (61)	22 (67)	4 (57.1)	2 (66.6)
Mean no operations (SD)	2.21 (0.87)	2.22 (0.86)	1.90 (0.91)	2.00 (0.82)	2.66 (1.15)
Final anatomic success [n; (%)]	59 (74.6)	27 (75.0)	25 (78.7)	5 (71.4)	2 (66.6)

SD: Standard deviation

final anatomic success rate was 74.6%. Final VA was available for 69 patients with a mean 1.58±0.87 logMAR. The congenital/developmental disorder and previous ocular surgery groups were combined as a miscellaneous group for further statistical analysis. The anatomic outcome after initial surgery showed no significant differences among the trauma, myopia and miscellaneous groups (p=0.873). However, a significant difference was observed with regard to final anatomic success among the three groups (p=0.035). A post hoc test revealed significant difference in final anatomic success between the myopia and both the trauma and miscellaneous groups (p=0.031, p=0.021 respectively). A logistic regression model revealed that poor final anatomic outcome predictors were etiologies other than trauma and myopia (p=0.001), young age (p=0.010) and macular involvement (p<0.001). The anatomic outcomes were also evaluated based on initial surgical operation and no significant difference was observed in primary and final anatomic outcomes in the trauma and myopia groups with regard to initial surgery type (p=0.374, p=0.425).

Discussion

In the current study, we described the etiological factors and surgical outcomes of RRD in the paediatric age group referred to our tertiary centre. Trauma is the leading etiological factor, followed by myopia in the study group. The children in the congenital or developmental anomalies and previous ocular surgery groups were younger than those in the myopia and trauma groups. We observed successful anatomic outcomes both with SB and PPV surgeries, particularly in the myopic group.

In this study, we found that the mean age was 11.63±4.36 years in children with RRD. Similar to our findings, previous studies reported a mean age ranging from 9.6 to 12.0 years (10,12-14). Among the study groups, children with RRD were older in the myopic group and younger in the congenital/developmental anomaly group. It is plausible that cases in the developmental anomaly group presented at an earlier age than the traumatic and myopia group due to comorbidities. In accordance with previous studies on paediatric RRD, the male gender was also the dominant gender in this study (5,12,14). This preponderance is likely to be associated with the different and adventurous play habits of boys compared to girls (4). Trauma and myopia are the most commonly identified predisposing factors in this study group. Many studies have reported trauma as the leading cause of paediatric RRD, while others reported that myopia was the most common predisposing factor (10,12,14,15). The high rate of trauma in the current study may be related to the proficiency of our clinic as a tertiary referral centre. Furthermore, no specific threshold value was determined to define pathological myopia in children. In accordance with previous studies, we identified myopia as the causative factor when the refractive error was more than -4 diopters. Among etiologic factors studied, trauma is a preventable risk factor for RRD. Sports and game-related accidents are common in the paediatric age group, which may also lead to open globe injuries and consequent severe vision loss (16). Based on these results, we speculated that there might be a need to raise awareness in families and identify factors that may cause eye injury.

At initial presentation, the mean VA was better in the myopic group compared to the other groups with lower rates of PVR and macular involvement. The lack of subjective complaints and the difficulties in the examination of children may lead to a delay in the diagnosis of retinal detachment in the paediatric age group. Macular involvement, PVR development, and chronicity findings are common in paediatric RRD due to late diagnosis (7-9). In this study, myopic patients, whose average patient age is older, might have noticed their visual impairment in the early stages of the disease and were treated earlier compared to others. In contrast to our findings, Gurler et al. (17) evaluated the clinical characteristics of paediatric RRDs and observed no significant difference between trauma and myopia groups with regard to macular involvement and PVR rates. However, their sample size was smaller compared to our study.

SB may be a good option for the initial approach in the management of paediatric RRD. Prior to routine vitrectomy, the success rates of SB is around 70-80% (13,18,19). In the current study, SB was the most preferred procedure in the myopia group for initial surgery. Myopic cases are a good candidate for primary SB applications compared to traumatic paediatric RRDs. PPV is commonly employed for cases with undetected or multiple retinal tears, and PVR (20). In contrast to adult RRD patients, the posterior vitreous is not detached in paediatric patients. During vitrectomy, complete dissection of the hyaloid from the retina is a complicated process. In such cases, combining scleral band with PPV surgery may be an appropriate option (18). In the trauma group, which has a higher PVR rate compared to the myopia group, PPV was the most preferred surgical technique in the study. The commonly used vitreous substitute for the tamponade effect was silicone oil. Since it is difficult to keep children in a prone position after vitrectomy, silicon oil is commonly used for tamponade in

paediatric patients undergoing PPV. In addition, silicone oil is associated with lower PVR rates in RRD treatment.

After the initial surgery, higher success rates were observed in both the myopic and previous history ocular surgery groups compared to the other two groups. However, it should be considered that there are only three patients in the latter group. In previous studies, the success rate of single surgery for RRD was reported to be between 52 and 88% in the paediatric population (11,21-23). After consecutive surgeries to obtain retinal attachment, anatomic success was achieved in both the myopia and trauma groups with 78.7% and 75.0%, respectively. The number of operations required to demonstrate these results were lower in the myopia group. In the myopia group, SB procedure provided favourable anatomic outcomes and also required fewer operations. Since SB surgery usually does not require tamponade use, there was no need to perform a consecutive surgery for silicone removal. Final anatomic success was significantly better in the myopic group compared to non-myopic cases. Similarly, Barth et al. (14) found the reattachment rate was highest in the myopic and lowest in the ocular abnormalities group .They suggested that surgery in children with ocular abnormalities may be more challenging due to strong retinal adhesions and unusual vitreous liquefaction. In the current study, congenital and developmental disorders and a history of a previous surgery were also found to be a predictive factors for poor final anatomic outcomes. In addition to the afore mentioned anatomic alterations in eyes with ocular abnormalities, the presence of coexisting systemic abnormalities may delay and hamper the evaluation, diagnosis and treatment procedures of these patients. Other factors found relating to poor final anatomic outcomes were young age and macular involvement. Smith et al. (7) noted that younger patients are more likely to demonstrate RRD involving the macula, but no significant difference was found in successful reattachment between age groups. In accordance with our findings, Chang et al. (24) showed that a younger age and macular detachment were associated with poor anatomic outcomes. Moreover, they also found vitrectomy is associated with poor anatomic outcomes when performed as initial procedure. In another study, Wadhwa et al. (12) showed that primary vitreoretinal surgery was associated with poor visual outcomes compared to scleral buckling. Contrary to these findings, we observed that the type of initial surgery was not associated with poor anatomic outcomes in regression analysis. The discrepancy between studies may be due to different sample cohorts, settings and surgical approaches. Although anatomic success was obtained in most of the RD cases, the mean VA was only slightly improved after surgical interventions. Rejdak et al. (25) reported unsatisfactory visual outcomes after vitrectomy in paediatric retinal detachment with PVR. Previous studies regarded PVR as a predictive factor for poor visual outcomes (11,12,14). Trauma was the leading etiological factor and PVR was not uncommon (38%) among the overall study group. In addition to etiology, other factors such as coexisting ocular anomalies, amblyopia treatment, intraoperative and postoperative complications may also affect visual improvement in paediatric RRD.

Study Limitations

The current study is limited by its retrospective nature and relatively small study cohort. Since our clinic is a tertiary referral centre, this study population may also not represent the general paediatric population for RRD. The lack of data regarding the perioperative and postoperative VA hampered further comparison analyses based on visual outcomes among groups.

Conclusion

RRD in children is a significant problem that causes permanent visual impairment. This condition is likely to have a negative effect on the child's family and social life, as well as their future occupation and income. Although associated with poor visual outcomes, careful ophthalmologic assessment and surgical management can maintain sight and impact these young patients' lives positively. Favourable outcomes may be achieved with appropriate surgical intervention after considering the ocular characteristics and clinical findings of the patient.

Ethics

Ethics Committee Approval: The study was approved by the Hamidiye Ethics Committee of the University of Health Sciences and conducted in adherence to the tenets of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.A., Data Collection or Processing: G.G., A.T., Analysis or Interpretation: G.D., Writing: Ş.Ö.

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Original Article

Demographic, Epidemiologic and Clinical Analyses of Paediatric Patients Hospitalized with Henoch-Schonlein Purpura: A Retrospective Study

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ABSTRACT

Aim: Henoch-Schönlein purpura (HSP) is the most common systemic vasculitis in children. The purpose of this study was to assess the clinical, epidemiological, and laboratory features of 117 children diagnosed with HSP.

Materials and Methods: This study was conducted to evaluate the data of 117 children with HSP, retrospectively. The presence of the cardinal clinical findings such as purpura, abdominal pain, and arthralgia; and the presence of increased erythrocyte sedimentation rate, decreased serum C3 levels, leukocytosis, blood in the stool, haematuria, and proteinuria were assessed in children with HSP.

Results: Of the 117 patients enrolled in the study, 68 were males (58.1%) and 49 were females (41.9%). The median age was 85 (49) months. Purpuric skin lesions were detected in ninety-eight (97.9%) patients, arthritis/arthralgia in 71 (60.6%), gastrointestinal involvement in 52 (44.4%), and renal involvement in 27 (23%) patients. The median duration of hospitalization day was 6 (10) days. Non-palpable purpuric skin lesions mostly located on ankles were the most common involvement in the patients.

Conclusion: Non-palpable purpuric skin lesions were the most common presentations followed by arthritis/arthralgia, and gastrointestinal involvement in our patients. Seasonal distributions, gender, and ages of the patients were concluded to be noncontradictory compared with the literature. Although variable clinical findings in the patients were found, the cardinal features of HSP were determined in almost all subjects in this study.

Keywords: Henoch-Schöenlein purpura, children, vasculitis, systemic manifestation

Introduction

Henoch-Schönlein purpura (HSP), also known as immunoglobulin A (IgA) vasculitis which mediates a type III hypersensitivity reaction, is the most common vasculitis that affects the small vessels of the skin, joints, gastrointestinal tract, and kidneys in paediatric patients. HSP was primarily identified by Heberden in 1801 and described as having a relation with arthritis by Schonlein in 1837. The incidence of HSP is reported to be 10 cases per 100,000 yearly and it is generally seen during childhood between the ages of 5 to 15 years (1,2).

This vasculitis is described by the triad of palpable purpura, abdominal pain, and arthritis. Purpuric skin lesions are the most common clinical findings in HSP followed by joint, gastrointestinal tract, and kidney involvement.

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Palpable cutaneous purpura is the major clinical diagnostic lesion mostly located on the lower extremities and buttocks. The second common involvement is arthritis which occurs in around 75% of patients. This arthritis generally affects the knees and ankles. Gastrointestinal involvement including colicky abdominal pain, vomiting, and gastrointestinal bleeding occurs in 50-75% of patients. Renal manifestation is usually seen as microscopic haematuria and nephritic-nephrotic syndrome. Henoch-Schonlein purpura-associated involvements of neurological systems, cardiac systems, and the lung have also been reported during the disease in some studies (2).

Although the etiology of HSP cannot be clearly identified, the evidence of immunopathological mechanisms and possible trigger factors (upper respiratory system infections, drugs, vaccines, and other environmental exposures, etc.) have been reported in the literature (3). Leukocytoclastic vasculitis, which could be seen in other types of vasculitis, is characteristically demonstrated via skin biopsy. Renal and skin biopsies have displayed several abnormalities in IgA and IgA immune complexes (3,4). HSP is usually a benign and self-limiting disease. Despite the fact that the disease is self-limiting clinically, due to the severity of some systemic involvements, and in rare cases mortality, physicians have sought to investigate it.

Various studies have focused on the function of regional and other environmental impacts in the etiology of HSP for many years. This study aimed to analyse the clinical features of those paediatric patients hospitalized with HSP, and evaluate the epidemiologic characteristics, demographic characteristics, and possible etiologic factors of HSP.

Materials and Methods

The medical records of 117 children with HSP were assessed retrospectively. The children were admitted to Ege University School of Medicine, Department of Paediatrics, General Paediatrics Unit, Izmir, Turkey between January 2013 and December 2019. The diagnosis of HSP was made in accordance with the Paediatric Rheumatology International Trials Organisation (PRINTO) 2005 criteria (5). This study was a continuation of a retrospective clinical study of HSP published in 2014 (DOI number 10.4274/jpr.40085). The Ethics Committee of the Ege University Hospital approved the study (20-1.1T/43).

Detailed demographic characteristics were obtained from the parents with a structured questionnaire. The medical records of these patients were evaluated by physicians and the clinical and laboratory data were extracted from patients' medical files. Studied variables including previous infections, vaccinations, and insect bites were recorded as precipitating factors.

As for the clinical characteristics, they were as follows: Microscopic haematuria was defined when the urine test result was >5 erythrocytes/mm^3; gross haematuria was defined when blood in the urine could be seen with the naked eye; rash location was determined as where purpura particularly accumulated on the parts of the body. Joint involvement was described as the presence of joint swelling and/or limitation of joint movement. Gastrointestinal involvement was identified as one of the following: abdominal pain, vomiting, hematemesis, melena, or positive stool test for occult blood. Recurrence was defined as a case of HSP which had been in remission for at least 1 month presenting with new lesions on the skin or with other systemic manifestations.

The laboratory data were analysed and the sedimentation rate was defined as elevated when it was >20mm/hour, and the presence of C3 levels <900 mg/L were accepted as low. IgA level, C-reactive protein (CRP) level, anti-nuclear antibodies, albumin, and serum sodium levels were also obtained from all patients.

Statistical Analysis

Statistical analyses were performed using SPSS version 21.0 for personal computers (Chicago, IL, USA). Descriptive statistics were used to summarise the demographics and clinical features of the patients. Chi-square test and Fisher Exact test were used to assess associations between two or more qualitative variables. Continuous values were expressed as frequency (percentage) and mean ± standard deviation or median and interquartile range (IQR); and when appropriate, categorical variables were determined by percentages.

Results

Epidemiological Characteristics

Table I shows the demographic and epidemiological data of the subjects. The study group included 68 males (58.1%) and 49 females (41.9%). Their ages ranged from 12 months to 16 years (median age 6 years). It was found that 42 (35.8%) cases had been admitted to the ward during autumn (Figure 1). Prior to HSP onset, 50.6% of the patients had been recorded as being infected with an agent in their history, mostly upper respiratory tract infections. In regard to other trigger factors for HSP, 7 patients had enteritis, 3 had urinary tract infection, 1 patient was diagnosed with pneumonia. A predisposition factor was not found in 50.4% of the cases.

Clinical Characteristics

The clinical characteristics of the 117 patients with HSP are shown in Table II. The typical rash with purpuric lesions concentrated mainly on the buttocks and the lower extremities was observed in all the patients, except for 2 patients who had presented with gastrointestinal symptoms before the rash appeared. Almost all the patients (97.9%) had the initial symptom, skin purpura, while it was accompanied by joint involvement in 71 (46.6%) patients. The duration of the illness was 6 days as a median value in all the cases.

Table I. Demographic and epidemiological data of 117 children with HSP

Age, month, median (IQR)	85 (49)
Gender	
Boys, n (%)	68 (58.1)
Girls, n (%)	49 (41.9)
Seasonal pattern, n (%)	
Autumn	43 (36.7)
Winter	32 (27.3)
Spring	25 (21.3)
Summer	17 (14.5)
Etiologic factors, n (%)	
URTI	46 (39.3)
Enteritis	7 (6)
Pneumonia	1 (0.9)
Urinary system infection	3 (2.6)
Unknown	59 (50.4)
Duration of hospitalization, day, median (IQR)	**6 (10)**
City, n (%)	
İzmir	71 (60.6)
Manisa	9 (7.6)
Balıkesir	8 (6.8)
Muğla	5 (4.2)
Uşak	5 (4.2)
Aydın	3 (2.5)
Other cities	16 (13.6)

URTI: Upper respiratory tract infection, SD: Standard deviation, IQR: Interquartile range, HSP: Henoch-Schönlein purpura

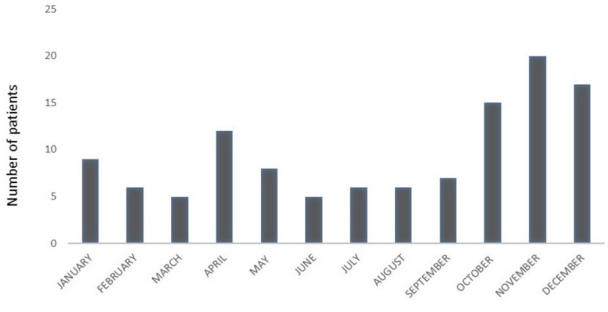

Figure 1. The seasonal pattern of patients

Table II. Main clinical features of the 117 children with HSP

Symptom	Cases (n)	Percentage (%)
First symptom		
Skin purpura alone	30	25.6
Purpura plus joint pains	46	39.3
Purpura plus sole abdominal pains	25	21.5
Purpura plus, abdominal pains and microscopic hematuria	15	12.9
Without purpura	1	0.8
Rash location		
Only LE	37	31.6
LE plus buttocks	44	37.6
LE plus buttocks plus UE	12	10.3
LE plus UE	8	6.8
LE plus buttocks plus trunk	7	6
LE plus buttocks plus trunk plus face	5	4.2
LE plus buttocks plus trunk plus face plus UE	3	2.5
Without purpura	1	0.8
Joint symptom (n=71)		
Sole ankle involvement	34	47.8
Sole knee involvement	8	11.2
Knee plus ankle involvement	12	16.9
Multiple joint involvements	17	23.6
Digestive tract symptom (n=52)		
Abdominal pains	52	100
Vomiting	30	57.6
Occult blood in the stool	25	21.3
Blood in the stool	3	5.7
Kidney symptom (n=27)		
Microscopic hematuria	15	55.5
Macroscopic hematuria plus proteinuria	10	37.1
Gross hematuria	2	7.4

LE: Lower extremities, UE: Upper extremities, HSP: Henoch-Schönlein purpura

A skin biopsy was obtained from 75 (64.1%) patients. Thirty-five of the biopsy results showed classical leukocytoclastic vasculitis, and the others had non-specific features. Thirty-seven of 117 patients had localized edema usually appearing on the feet, scalp, hand, and scrotum. Joint involvement was the most common manifestation accompanying skin rashes. The joint regions are summarized in Table II. Twenty-seven (23%) patients had renal involvement, these 27 cases can be further classified as follows: microscopic haematuria in 15 (55.5%), gross haematuria in 2 (7.4%), and haematuria plus proteinuria in 10 children (37%). Renal biopsy was performed on 8 cases, one patient had focal mesangial proliferation with crescent lesions <50%, and the others had mesangial proliferation. Gastrointestinal involvement was detected in 52 (44.4%) patients and the most common symptom was abdominal pain. The number of vomiting presentations of these patients was 30 (57.6%) and 25 of the 52 patients with gastrointestinal involvement had positive occult blood in the stool. Two patients had been hospitalized with bloody stool. As an uncommon feature; orchitis was observed in 2 patients.

Those patients manifesting with arthritis were treated with 45 mg/kg/day ibuprofen and bed rest. Thirty-one of 117 HSP patients (93.3%) were cured. Due to the fact that 32 patients had system involvements (renal or gastrointestinal), they were treated with low dose glucocorticoid medication. A pulse steroid treatment was started for two patients due to being unresponsive to low dose glucocorticoid treatment.

Laboratory Findings (Table III)

The mean serum IgA concentration was 217.8±93.7 mg/dL and C-reactive protein levels ranged between 0-2 mg/dL in 70 (70.7%) patients. The erythrocyte sedimentation rate was found to be high in 20 children (26.5%). Anti-nuclear antibody positivity was present in only 15 (12.8%) patients without any other autoimmune disease features.

Table III. Laboratory findings of study group

Parameters	**Results**
IgA (mean ± SD) mg/dL	217.8±93.7
CRP [median (IQR)] mg/dL	0.9 (2.3)
ESR mm/1 hour, n (%) (>20)	20 (26.5)
Albumin (mean ± SD) mg/dL	3.7±0.5
C3 [median (IQR)] mg/dL	134.5 (36.5)
C4 [median (IQR)] mg/dL	25.5 (14)
Positive ANA, n (%)	15 (12.8)
Histopathology (n=75)	
Leukocytoclastic vasculitis, n (%)	35 (45.4)

IgA: Immunoglobulin A, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, ANA: Anti-nuclear antibody, SD: Standard deviation, IQR: Interquartile range

Discussion

HSP described as a triad: palpable purpura, abdominal pain, and arthritis, is the most common vasculitis in childhood. Although several pathogeneses of HSP have been reported, the exact etiopathogenesis is still a mystery. One of the most widely accepted pathogeneses is its association with the accumulation of "immune complexes containing IgA" and "complement components" in the walls of small vessels (1,6). In this multisystemic disease, clinical features are usually self-limiting. However, the renal manifestations could result in chronic kidney disease in HSP patients (1).

In this study, we analysed the demographics, epidemiologic and clinical features of 117 children who were hospitalized with their first attack of HSP in Ege University Children's Hospital, General Paediatrics Unit. Similar to other epidemiologic studies for HSP, our study showed that the most common admission season was autumn. Several case series and longitudinal population-based surveys have reported that HSP in childhood is generally seen during both the autumn and winter seasons consistent with the literature (7,8). Our reports showed that 50.6% of patients experienced infectious diseases, of which, the most common one was upper respiratory tract infection. Gastroenteritis and urinary system infections have also been proposed as a trigger factor for HSP. Several studies have reported other trigger events such as vaccinations, drugs, insect bites etc. (1,9). Chen et al. (1) stated that 60.8% of their patients had an infection history before the onset of the clinical features of HSP as a possible predisposition factor. They also stated that food allergy or parasite infection may be a potential trigger factor for HSP (1). In our study, there were no relevant factors for HSP onset in 59 patients. Although there are a lot of suspected factors, the etiology of HSP has not been clearly determined yet.

HSP generally presents in children aged 5 to 15 years, predominantly in boys (10). In accordance with other studies, the demographic features of our study group showed that the median age was 85 months and more than half of the patients were male (58.1%). Almost all of the patients with HSP were between the ages of 5-10 years. Anil et al. (11) reported a retrospective analysis of 430 HSP children in which they found that the mean age was 7.9 years The disease has generally been associated with a male dominance, however; some studies defined this feature as a reverse condition (12).

Skin purpura alone was found as the first manifestation for HSP in 25.6 % of the patients. All our patients showed the characteristic rashes on the lower extremities but some also on other trunk regions such as the arms or face. Four out of 117 patients had skin manifestations associated with bullous lesion concentrated on the lower extremities. The dominant initial symptom in this present study was skin rash and ankle involvement that required hospitalization for bed rest. Due to the fact that all our patients had not only skin manifestation but also joint involvement, our most frequent initial symptom was the coexistence of skin and joint involvement. The average time of the skin eruption was 14 days, ranging from 7 to 40 days in our patients. Chen et al. (1) determined that a majority of their HSP patients (69.1%) displayed skin purpura alone as the first symptom, purpura with abdominal pain was described in 11.7% and purpura with joint pain in 9.2% of their patients. Dolezalova et al. (13) also determined palpable purpura as the main symptom at onset of HSP in their study population.

Gastrointestinal system (GIS) involvement may occur in 50%-80% of patients with mild-moderate symptoms such as vomiting, nausea, abdominal pain, and transient paralytic ileus (14). Gastrointestinal haemorrhage, bowel ischemia/necrosis, intussusception, bowel perforation have also been reported in HSP. Detection of severe gastrointestinal bleeding is an important evaluation as it might engender a life-threatening event in 15 to 35% of patients, especially precedence of the typical rash (15,16). Before any skin manifestation is seen, bloody stool with abdominal pain may be initially treated as acute gastroenteritis (17). Intussusception is extremely rare, but it is the most common surgical indication for gastrointestinal involvement of HSP (18). Two cases in our study group had gastrointestinal bleeding which was not massive before skin manifestation. Cull et al. (19) investigated the clinical findings of 183 patients with HSP of whom 95 presented with GIS bleeding, and about 40% of their patients had bleeding before the typical lesions. Except for the bloody stool before purpura in two patients, our subjects did not show any rare presentations during the disease.

Renal involvement occurs in 40-50% of patients generally as microscopic haematuria and/or proteinuria. The manifestation of nephrotic syndrome or renal failure associated with renal involvement in HSP may manifest in a small percentage of patients. There is a risk of long-term renal sequelae in these patients and this risk increases with age. Renal histology generally shows a glomerular IgA deposition, endocapillary proliferation, epithelial crescents, subendothelial/subepithelial IgA deposits, and fibrin deposits. Trapani et al. (10) presented a study that evaluated 150 patients with HSP and 81 (54%) children had had urinary abnormalities such as a mild nephropathy detected in 71 (47%) cases: 42 patients with isolated mild proteinuria, 6 with microscopic isolated haematuria, and 23 patients with both abnormalities and normal renal function. Tabel et al. (6) reported that renal involvement was observed in 26.1% of their 107 HSP children. The authors have found that renal involvement was significantly more frequent in patients older than 10 years and that for the group with renal involvement, the frequency of scrotal involvement was significantly higher than for those in the group without renal involvement. Another study from western Turkey reported the renal involvement of HSP to be 44.7% in their cohort (11). During clinical follow-up in our study, our patients were examined for renal involvement by daily urinalysis and 15 (12.8%) of 117 patients presented with microscopic haematuria and 2 (1.7%) had macroscopic haematuria.

Although the dominant involvements of HSP are skin, joint, gastrointestinal, and kidney; infrequent and unusual system manifestations including cerebral vasculitis, scrotal or testicular haemorrhage, and interstitial pulmonary haemorrhage have been described. Neurological involvement of HSP might be present with obtundation, seizures, paresis, and posterior reversible encephalopathy syndrome, etc. There have also been reports of other interesting admission features of HSP in the literature such as orchitis, myositis, carditis, pulmonary haemorrhage, and anterior uveitis. Di Pietro et al. (20) reported a review of 23 paediatric cases with lung involvement associated with HSP. Those cases presenting with the pulmonary symptoms included cough, haemoptysis, epistaxis, dyspnea, tachypnea, chest pain, and shortness of breath through to acute respiratory failure. Therefore, atypical presentations affecting multiple systems should be considered in the outcome of HSP and the possibilities of different responses (20-22).

Study Limitations

There are some limitations to this study. The major limitation factor was the small number of patients. The first reason is that we did not include those patients treated and followed up in the outpatient policlinics and emergency services of our centre. The second limitation is that as a general rule in our outpatient policlinics, patients with HSP associated with skin manifestation alone are not hospitalized. Also, we did not focus on the identification of infectious agents that could have been associated with the triggering of HSP. It could have given clinicians an idea of

which agent might be the trigger factor. Finally, we could not obtain skin biopsy from all study groups which could have ruled out other vasculitic disorders.

Conclusion

HSP is the most common vasculitis and it may be associated with risks of various complications in childhood. The underlying mechanisms of HSP's characteristic findings have not been exactly defined yet. This index study presents a descriptive analyse of paediatric patients in Ege University Children's hospital during a 6-year-period. Further studies are needed to investigate the influence of its pathogenesis in these cases and to find new mechanism that may play a role in following up children with HSP.

Ethics

Ethics Committee Approval: The Ethics Committee of the Ege University Hospital approved the study (20-1.1T/43).

Informed Consent: Informed consents were not required because the study was conducted retrospectively.

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Authorship Contributions

Data Collection or Processing: Ş.G., B.E.D., A.A., Analysis or Interpretation: Ş.G., B.E.D., A.A.,Writing: Ş.G., B.E.D.

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Original Article

A Decline in Aminotransferase Activity Due to Lifestyle Modification in Children with NAFLD

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†: We are terribly sorry to announce that Professor Wojciech Sluzewski passed away on the date of 19 September 2020. We thank him for his contributions.

ABSTRACT

Aim: As obesity rates in children and adolescents increase, non-alcoholic fatty liver disease (NAFLD) has become the most common liver disease affecting this organ. This study aimed to evaluate the effectiveness of lifestyle modifications as a method of improving liver function indexes in children with NAFLD.

Materials and Methods: The study group consisted of 49 patients with NAFLD (35 boys and 14 girls), age range 3-16 years (mean 10.51±3.18 years). Anthropometric measurements were taken and laboratory tests were performed. Features of steatosis of the liver were evaluated by ultrasound. The mean follow-up period was 2.45±1.45 years. Aspartate aminotransferase (AST) to [Platelet (PLT) Ratio and Pediatric NAFLD Fibrosis Score (PNFS)] were calculated. The Mediterranean diet and physical exercises were recommended. End-point parameters were a decrease in the aminotransferase level and body weight.

Results: In the study group, 35 children (71.43%) were obese, and 7 (14.29%) were overweight. In 22/49 cases (44.9%) body mass index (BMI) loss was achieved, in the other patients, BMI gain was noted. Abnormal alanine aminotransferase (ALT) levels were observed in 25/49 children. In the group of children with initial increased ALT levels, significant reduction of ALT, AST and gamma-glutamyltransferase (GGT) levels were found with regard to baseline values. There was also a significant decline in mean AST to PLT Ratio index (APRI) level and PLT count. Moreover, a decrease in ALT level was negatively related to PNFS, APRI and GGT.

Conclusion: Lifestyle modification leads to a significant decrease in aminotransferase levels, even in children who fail to achieve BMI reduction.

Keywords: Fatty liver, obesity, children, aminotransferases

Introduction

Non-alcoholic fatty liver disease (NAFLD) is currently the most common chronic liver illness in children (1). This term describes a broad spectrum of liver disorders, ranging from simple steatosis to non-alcoholic steatohepatitis. Its estimated prevalence ranges from 3% to 12% in the general pediatric population and up to 70% in obese children (2). Suspicion of liver steatosis is usually based on imaging studies - a characteristic, hyperechogenic picture of the liver in abdominal ultrasound is the most commonly used mode of assessment. Diagnosis is established by excluding other causes of liver damage (drug poisoning, viral hepatitis, autoimmune liver disease, inborn errors of metabolism, alcoholism) (3,4).

With regard to the increase in the incidence of NAFLD, also in the pediatric population, and the possible consequences caused by its complications, the search for treatment methods has become the subject of many scientific studies.

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According to the guidelines created recently by two medical societies, namely the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition and the American Association for the Study of Liver Diseases (AASLD), lifestyle modification remains the primary method of treatment. Currently, there are no clear guidelines which present precise recommendations on lifestyle changes, such as diet type or specific weight loss. Recommendations are extrapolated from studies on the adult population. In everyday clinical practice, the first step in both the diagnosis and assessment of disease progression is to determine aminotransferases and abdominal ultrasound.

Liver fibrosis is an independent factor increasing the risk of liver-related complications and mortality (5). Liver biopsy remains a golden although imperfect standard when steatohepatitis or liver fibrosis is suspected. Furthermore, the procedure should be performed in the case of uncertain diagnosis, possible overlap syndromes or additional risk factors such as type 2 diabetes. Nevertheless, since liver biopsy is an invasive procedure with its own bias, initial assessment of fibrosis and inflammation of the liver tissue is usually performed using non-invasive tools such as serum markers or panels of markers (6). Non-invasive evaluation of fibrosis has been the subject of research of scientists for several years. Panels based on basic laboratory tests and anthropometric measurements [e.g. Aspartate aminotransferase (AST) to [Platelet (PLT) Ratio index (APRI)], Pediatric NAFLD Fibrosis score (PNFS)] are used as well as and more extensive ones, requiring more specific tests (e.g. cytokeratin 18, enhanced liver fibrosis). Serum markers enable the repetitive assessment and therefore, are used as a tool for the monitoring of the treatment (7,8).

The aim of this study was to evaluate aminotransferase level and liver damage indexes with regard to the decline in body weight as a result of lifestyle modifications in children with NAFLD.

Materials and Methods

The group in our prospective, consecutive study consisted of 35 boys and 14 girls, with a diagnosis of NAFLD, age range 3-16 years (mean 10.51±3.18 years), who visited the Hepatology Outpatient Clinic at the Department of Infectious Diseases and Child Neurology. The sample size was determined using "Sample Size Calculator" (https://clincalc.com/stats/samplesize.aspx).

The diagnosis of NAFLD was based on medical history, physical examination and additional tests-increased aminotransferases level and hepatic steatosis in abdominal ultrasound. The characteristics for NAFLD abnormalities in the liver ultrasound (hyperechogenicity, poor visualization of the diaphragm, intrahepatic vessels and posterior part of the right lobe using Samsung HS40 machine) were the inclusion criteria of this study (9). In 3 cases, according to clinical indications (uncertain diagnosis, suspected significant liver injury based on laboratory tests), a liver biopsy was performed using the Menghini technique. In differential diagnosis, viral hepatitis (type B, C, Epstein-Barr virus and cytomegalovirus infection), autoimmune hepatitis, deficiency of alfa-1-antitrypsin, hemochromatosis, celiac disease, Wilson disease, cystic fibrosis, thyroid disease, drug intake and alcohol intake were excluded. Furthermore, in children younger than 5 years, the presence of inborn errors of metabolism such as fatty acid oxidation disorders, galactosemia and tyrosinemia were excluded (1,10). Children with the diagnosed conditions mentioned above were excluded from the study group. None of the described patients had diabetes. The baseline characteristics of the research group are included in Table I.

The weight of the patients was assessed on an electronic digital scale (Radwag WPT 60/150 O; 150 kg capacity and 10 g accuracy), height was measured with a 2 m vertical wall stadiometer graduated in millimeters (Charder HM200PW). We performed measurements following recommended procedures. Patients were classified in the obese group based on body mass index (BMI) depending on age [BMI=weight/(height)^2 (kg/m^2)] greater than 2 standard deviations (SD) above the World Health Organization (WHO) Growth Reference median and in the overweight group when BMI-for-age was more significant than 1 SD above the WHO Growth Reference median (11).

Complete blood count, alanine aminotransferase (ALT), AST, gamma-glutamyltransferase (GGT) and serum lipids were assessed on standard laboratory analyzers. Normal upper values for liver enzymes were as follows: ALT <12 yo: boys <40 IU/L, girls <35 IU/L; >12 yo: boys <26 IU/L, girls <22 IU/L, AST <12 yo: <45 IU/L, >12 yo: boys <29 IU/L, girls <25 IU/L, GGT 4-24 IU/L.

The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was calculated according to the following formula:

HOMA-IR=(insulin (mU/mL)* glucose (mmol/L)/22.5. The result should not exceed 1

Non-invasive Hepatic Fibrosis Scores

APRI and PNFS were calculated based on established formulas (8,12).

APRI = AST/ULN (upper limit of normal)/PLTs (G/L)*100. APRI >1.0 has a sensitivity of 76% and specificity of 72% for predicting cirrhosis. APRI >0.7 has a sensitivity of 77% and specificity of 72% for predicting significant hepatic fibrosis. The lower the APRI score (<0.5), the greater the negative predictive value and the ability to rule in cirrhosis.

PNFS (probability distribution) = $\left[\frac{e^z}{1+e^z}\right]$*100; z=1.1+(0.34*√ALT) + (0.002*ALP) - [1.1*log(PLT G/L)]-(0.02*GGT)

Intervention and Control Visits

Before enrollment to the study, ALT and AST levels were evaluated at least 3 times with an interval of 3 to 6 months. Enrolled patients were recommended to modify their lifestyle: moderate aerobic physical exercise (at least 60 minutes 5 times a week), for example, brisk walking, cycling, swimming and additionally the Mediterranean diet - 5 portions of vegetables and fruits per day, olive oil, higher fish intake (at least 2-3 portions per week), cereals or grains and dairy products (milk, yoghurt) for breakfast, nuts (at least 2-3 portions per week), pulses (at least 1 portion per week), pasta or rice almost daily, and also a reduction in red meat, simple sugars and saturated fat. It was recommended to avoid sugar and sugar-containing beverages. It was also recommended to use computers/other screen equipment or watch TV for less than 2 hours a day. Weight reduction was not recommended in children with BMI within reference values. However, lifestyle modification was introduced in this group of children to reduce ultrasound abnormalities in the liver. Compliance to all parts of lifestyle intervention was carefully evaluated during every visit based on medical history, interviews with the children and their caregivers as well as the analysis of the weekly menu diary. All children were followed every three months during the first year of the follow-up and every 6 months afterwards during outpatient visits. The result as a note "adheres to/does not comply with lifestyle modification principles" in the medical records was prepared. Body mass and height measurements were made, and blood samples were taken during every visit according to clinical indications. During the check-up visits, their weekly menu was analyzed, if it met the minimum criteria described above, "adheres to lifestyle modification principles" was marked. The restriction modifications were semi-quantified: red meat less than twice a week, elimination of fast-food and sweets, drinking water instead of sweet drinks. The physical level was assessed according to the principles described above. The mean follow-up period was 2.45±1.45 years.

Table I. Baseline group characteristics

Parameter	Number	Percentage	Mean ± SD	Median	Range
Age (years)	-	-	10.51±3.18	11	3-16
Sex: male/female	35/14	71.4/28.6	-	-	-
Weight (kg)	-	-	68.23±25.1	62.5	24.5-122.5
Height (cm)	-	-	153.42±18.27	153	114.5-190
BMI	-	-	28.08±5.84	27.51	15.43-42.13
BMI > +2 SD	35	71.43	-	-	-
+1 SD < BMI ≤ +2 SD	7	14.29	-	-	-
BMI ≤ +1 SD	7	14.29	-	-	-
WHR	-	-	0.94±0.07	0.93	0.82-1.06
ALT (IU/L)	-		61.35±57.54	42.5	12-304
AST (IU/L)	-	-	46.21±28.65	35.5	19-149
GGT (IU/L)	-	-	26.83±17.96	21	9-75
Total cholesterol (mg/dL)	-	-	166.39±40.29	162	56-249
LDL (mg/dL)	-	-	99.07±32.72	101.5	18-151
HDL (mg/dL)	-	-	46.56±21.99	41	25-148
TG (mg/dL)	-	-	137.85±62.05	126.5	23-265
HOMA-IR	-	-	4.82±4.64	3.65	1.4-23.1

SD: Standard deviation, BMI: Body mass index, WHR: Waist to hip ratio, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyltransferase, LDL: Low density lipoprotein, HDL: High density lipoprotein, TG: Triglycerides, HOMA-IR: Homeostatic model assessment-insulin resistance

Statistical Analysis

Statistical analysis was made with STATISTICA (version 13, TIBCO Software Inc., Palo Alto, USA). Data were presented as the mean ± SD. Mann-Whitney U or Student t-tests were used to compare continuous variables, where appropriate. Pearson chi-square test was applied to categorical variables. Kruskal-Wallis test was used for testing whether samples originate from the same distribution. Wilcoxon-Signed rank test was used to evaluate dependent parameters. We used Fisher's Exact test in the analysis of contingency tables. Correlations were performed using the Spearman rank correlation test. $P<0.05$ was considered statistically significant.

The study design was approved by the Bioethics Committee of the Poznan University of Medical Sciences (no: 1074/17 of 9th November 2017). Informed consent was obtained from each patient included in the study. The study protocol follows the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

Results

Boys comprised the majority of the study group (35/49, 71.43%). In the whole study group, 35 children (71.43%) were obese, 7 (14.29%) were overweight, and 7 (14.29%) had normal weight. All patients were advised to modify their lifestyle according to described suggestions. In 22/49 cases (44.9%) BMI reduction was achieved (at least 10% from the baseline), in the remaining ones (27/49, 55.1%) BMI increased compared to initial values. In the study group, patients who followed lifestyle modification advice were compared to the group who did not follow the regimen. The latter group was considered as a comparative group. Among patients with a decrease in BMI, 100% complied with the recommendations for lifestyle changes. In the group with an increase in BMI, all of these patients were described as "does not comply with the lifestyle modification principles". This group included patients who did not meet at least 2 dietary and/or physical level criteria.

The comparison of children with and without observed BMI reduction does not include those children with normal initial body weight. In the group of patients with BMI reduction, significantly lower levels of ALT, GGT and APRI at the endpoint were found. In spite of the lack of weight reduction, a decline in ALT level was also observed in the latter group. A comparison of both groups is provided in Table II.

Abnormal ALT level was observed in 25/49 children. In the group of children with increased ALT level, significant reduction of ALT, AST and GGT level was found with regard to baseline values (Table III). There was also a significant decline in mean APRI level and PLT count.

A statistically significant decrease in ALT and GGT level was found in the group with a reduction in BMI (respectively $p=0.0028$ and $p=0.044$, Figure 1). Furthermore, in the group with increased initial ALT, higher initial APRI values (0.52±0.28 vs. 0.29±0.20; $p=0.002$) were observed (Table III).

The decline in ALT level was negatively related to PNFS ($r=-0.61$; $p<0.05$; Figure 2a), APRI ($r=-0.45$; $p<0.05$; Figure 2b) and GGT level ($r=-0.41$; $p<0.05$; Figure 2c).

Table II. Comparison of clinical parameters in patients with and without BMI reduction

	Patients with BMI reduction n=22			**Patients without BMI reduction n=20**		
Parameter	**Baseline**	**End-point**	**p**	**Baseline**	**End-point**	**p**
Gender M/F	15/7			13/7		0.827
Weight (kg)	74.07±25.92	76.83±19.85	0.313	68.58±22.83	82.78±26.86	**0.0006***
Height (cm)	151.42±17.5	163.07±14.2	**0.00005***	155.03±19.67	163.64±19.39	**0.006***
BMI (kg/m²)	31.31±4.81	28.48±4.43	**0.0007***	27.69±3.73	30.06±4.08	**0.00004***
ALT (IU/L)	65.47±60.39	38.71±45.12	**0.0282***	53.44±39.85	42.81±21.21	0.227
AST (IU/L)	46.65±30.86	35.0±34.59	0.092	41.5±20.96	33.75±13.39	0.126
GGT (IU/L)	34.92±25.36	25.85±16.35	**0.044***	21.71±9.2	21.64±6.72	0.97
PLT (G/L)	282.24±67.99	272.76±85.25	0.397	299.5±66.0	278.56±59.31	0.079
APRI	0.42±0.27	0.31±0.17	**0.037***	0.36±0.18	0.31±0.11	0.217

BMI: Body mass index, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyltransferase, APRI: AST to Platelet Ratio index, PLT: Platelet

Discussion

According to the well-known regularity, NAFLD affects the vast majority of children with excessive body mass (13). In the described study group, all children were Caucasians. Most of them were boys, which aligns with previously published works (14). Suspicion of NAFLD in children is usually based on increased level of aminotransferases, especially ALT. According to studies, in obese and overweight children, elevated liver function tests have a sensitivity of 88% and specificity of 26% (15). In the study population, just over half of the children (51%) had slightly elevated liver function tests at baseline.

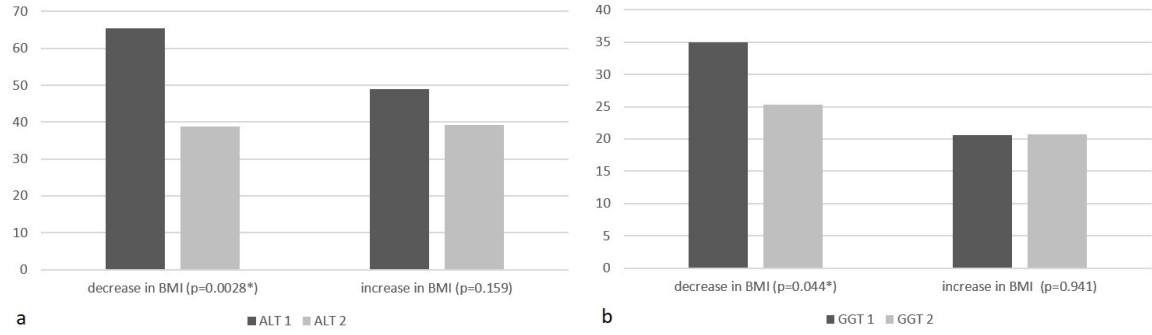

Figure 1. Comparison of ALT (a) and GGT (b) level in the group with and without a decrease in BMI at the beginning and the end of the observation period

ALT: Alanine aminotransferase, GGT: Gamma-glutamyltransferase, BMI: Body mass index

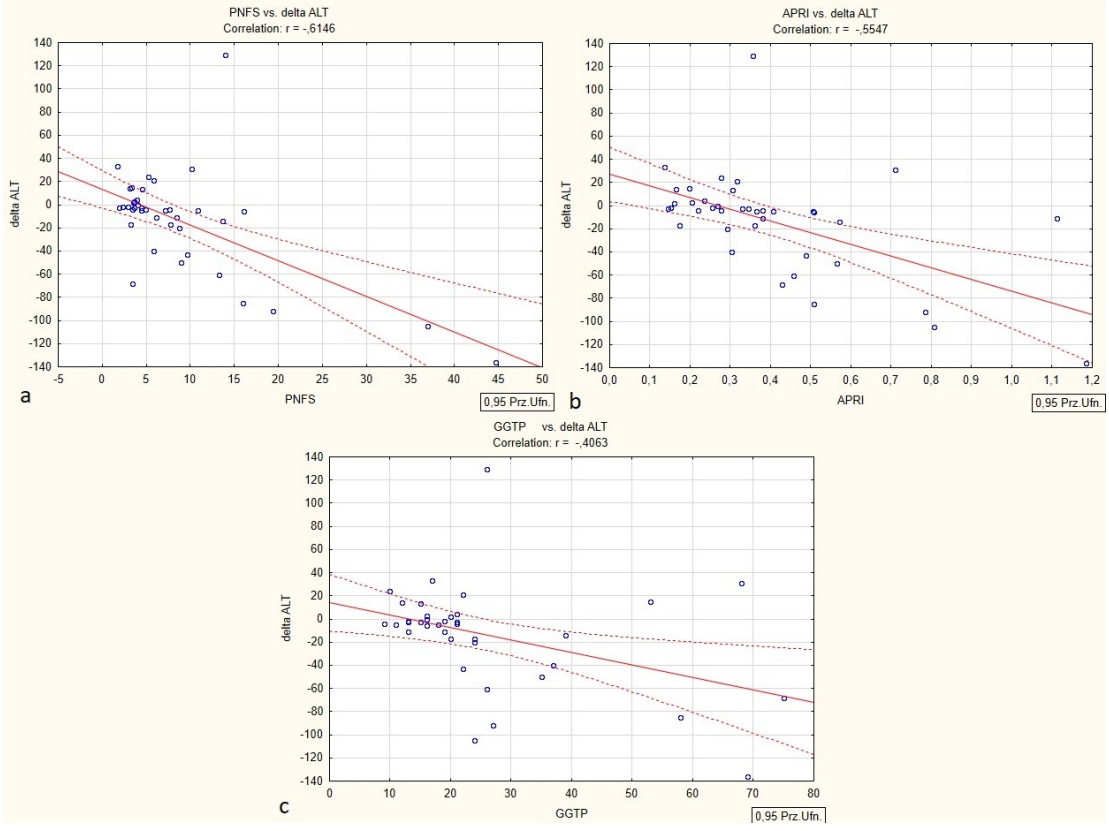

Figure 2. Correlation between the decrease in ALT level and PNFS (a), APRI (b), and GGT level (c)

ALT: Alanine aminotransferase, PNFS: Pediatric NAFLD fibrosis score, APRI: Aspartate aminotransferase to platelet ratio index, GGT: Gamma-glutamyltransferase

Table III. Comparison of clinical parameters in children regarding ALT level at baseline and at the end of the follow-up period

	Patients with increased ALT activity at baseline n=25			**Patients with normal ALT activity at baseline n=24**		
Parameter	**Baseline**	**End-point**	**p**	**Baseline**	**End-point**	**p**
Gender M/F	19/6			16/8		0.153
Weight (kg)	71.67±22.64	78.26±23.99	**0.008***	64.48±27.74	71.65±25.28	**0.003***
Height (cm)	156.52±16.47	164.86±16.43	**0.0009***	150.30±20.28	158.38±17.26	**0.0001***
BMI (kg/m^2)	28.69±5.55	28.17±5.46	0.619	27.31±6.25	27.72±5.24	0.476
ALT (IU/L)	86.96±45.66	59.79±52.86	**0.027***	24.09±6.99	26.57±12.57	0.768
AST (IU/L)	58.00±25.85	42.00±32.67	**0.0023***	29.43±10.80	27.57±5.76	0.387
GGT (IU/L)	36.33±19.54	28.28±12.80	**0.008***	14.75±3.51	17.13±4.65	0.059
PLT (G/L)	297.44±71.43	286.04±78.91	**0.022***	281.70±74.25	264.09±63.46	**0.029***
APRI	0.52±0.28	0.36±0.18	**0.004***	0.29±0.20	0.27±0.08	0.903

BMI: Body mass index, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyltransferase, APRI: AST to Platelet Ratio index, PLT: Platelet

Lifestyle modification plays a crucial role in the treatment of patients with NAFLD. Weight reduction of around 10% of the initial values is usually associated with an improvement in the markers of liver injury (16,17). The value of ALT decline as a marker of histological improvement, and thus, the effectiveness of NAFLD treatment has been confirmed in the past (18). In our research group, due to the ongoing growth of our patients, weight reduction was not observed. However, patients with a decrease in BMI at the end of the observation showed significantly lower ALT levels. Furthermore, even partial compliance to lifestyle modification without weight reduction resulted in a decline in ALT level.

The Mediterranean diet is usually considered as a recommended nutritional intervention in children and adults (19-22). In our study, this type of diet was recommended, resulting in a reduction of BMI and an improvement in biochemical parameters in a significant proportion of described patients (19). Compliance with dietary recommendations and lifestyle changes were assessed by the parents as being quite challenging to implement in their children's lives. Due to the inconvenience and fear of poor cooperation, the complete quantitative assessment of diet compliance (e.g. weighing portions) was abandoned. The medical history and the general analysis of the menu were considered a reliable source of information.

Given the observed association of ALT level with a decrease in BMI in the research group, the AASLD recommendations for biannual screening with serum ALT in obese children and BMI in the 85th-94th percentile and other risk factors seem to be appropriate (3,23).

Elevated BMI is an independent factor that increases the risk of liver fibrosis. According to the studies of Iacobellis et al. (24), the significant upper limit of BMI above which the risk of fibrosis increases is 26.3 [odds ratio: 5.85, 95% confidence interval (CI): 1.6-21]. In the analysis of the presented research group, a decrease in ALT level was negatively related to PNFS and APRI. The PNFS index has an area under the receiver operating characteristic (AUROC) value of 0.74 for advanced fibrosis, the highest among non-invasive fibrosis indicators tested in children so far. Therefore, its relation to improving the health of patients who underwent lifestyle modification was emphasized.

Out of AST/ALT ratio, APRI, PNFS, and FIB-4 fibrosis scores as markers of hepatic fibrosis in children with NAFLD, APRI was characterized by high efficacy in the diagnosis without distinguishing the advancement of the process (25). In the results of our research, the negative correlation between the decrease in ALT level and the APRI value was statistically significant. Higher initial values of parameters indicating liver injury are not a factor reducing the effectiveness of lifestyle modifications in improving the clinical status of children with NAFLD. Interestingly, lower PLT count at the end of the observation period was observed in the group of patients with ALT decline. The reason for the higher initial PLT count may be chronic inflammation and oxidative stress resulting from obesity or iron deficiency in this group of patients (26).

A negative correlation between the decrease in ALT level and GGT was found in our study. According to previous reports, advanced fibrosis can be correlated with high GGT level. The level of this enzyme >45 IU/L had AUROC 0.65

(95% CI 0.5-0.8) (27). A statistically significant reduction in GGT in the ALT and BMI decrease groups may confirm the clinical utility of this parameter. The correlation between high GGT level and insulin resistance (IR) was also described. Additionally, the relation between IR and advanced fibrosis was observed only in patients with elevated GGT (28).

Study Limitations

The limitations of this study include the lack of a control group of overweight children without NAFLD undergoing lifestyle modification. It was also challenging to assess patient involvement in diet and exercise recommendations. The analysis did not include the histopathological assessment of liver tissue due to the small number of patients who underwent liver biopsy.

Conclusions

Lifestyle modification has a significant effect on the decrease in aminotransferase levels, even in those children who fail to achieve weight loss.

Changes in diet and physical exercise have a positive effect on improving the parameters of liver function regardless of their pre-lifestyle modification values.

Ethics

Ethics Committee Approval: The study design was approved by the Bioethics Committee of the Poznan University of Medical Sciences (no: 1074/17 of 9th November 2017).

Informed Consent: Informed consent was obtained from each patient included in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: P.M., A.M., K.M.M., W.S., M.F., Design: P.M., A.M., Data Collection or Processing: P.M., Analysis or Interpretation: P.M., A.M., M.F., Literature Search: P.M., W.S., Writing: P.M., M.F.

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Original Article

Diagnostic Evaluation of Foreign Body Aspiration in Children

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ABSTRACT

Aim: The aim of this study was to evaluate the place of clinical symptoms and findings, and radiological imaging in the diagnosis of foreign body aspiration (FBA) in children, and to investigate the validity of existing diagnostic algorithms.

Materials and Methods: The medical records of 120 children with a diagnosis of FBA who underwent rigid bronchoscopy were examined. The sensitivity and specificity of the parameters used in the diagnosis of FBA and their predictive values were calculated.

Results: 78.9% of the patients were younger than 3 years and 63.8% were male. The peak incidence was 18 months. The rate of negative bronchoscopy was 30.8% and 87.3% of these patients were younger than 3 years. It was observed that the value with the highest diagnostical sensitivity and diagnostic accuracy (DA) rate (sensitivity; 92.54% and DA; 85.7%) had positivity for any of the radiological findings, and among these, there was the detection of one-sided excessive ventilation on chest X-ray (sensitivity; 70.0% and DA; 70.01%). Patients with positivity of any of the radiological findings who additionally had wheezing together with cyanosis or dyspnea had 100% specificity.

Conclusion: Particularly male children under the age of 3 years have an increased risk of FBA. Neither clinical symptoms nor radiological findings alone are sufficiently specific and sensitive in the diagnosis of FBA. The most important factor in the decision to perform bronchoscopy is the evaluation of radiological findings together with physical examination and history.

Keywords: Foreign body aspiration, children, algorithms

Introduction

Foreign body aspiration (FBA) is the most common cause of death due to home accidents in children under 6 years of age, and is one of the major causes of mortality and morbidity in childhood (1-3). The clinical features of FBA can be life-threatening airway obstruction or lighter manifestations such as recurrent pulmonary infection, wheezing, and cough (4). Therefore, it is important to diagnose immediately and provide appropriate treatment in order to reduce the mortality and morbidity rates. Foreign bodies can be removed by rigid or flexible bronchoscopy, but the prerequisite for this is the suspicion of foreign body presence (5).

In this study, we aimed to evaluate the place of clinical symptoms, findings and radiological imaging in the diagnosis of FBA in children, and to investigate the validity of existing diagnostic algorithms.

Materials and Methods

Before starting the study, (approval no: 2018/1416) was obtained from the non-interventional clinical research ethics committee of Adnan Menderes University. In this

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study, 120 patients who underwent rigid bronchoscopy for suspected FBA in Adnan Menderes University Faculty of Medicine, Department of Pediatric Surgery between 2000-2019, were evaluated retrospectively. All patients were evaluated in terms of age, gender, time of admission, cough or symptoms of cyanosis (choking) in the patient history, wheezing in physical examination, some symptoms of dyspnea; nasal flaring, the presence of intercostal and suprasternal retractions, and the presence of excessive ventilation and pneumonic infiltration on chest X-ray. The relationship between all findings and foreign body detection in bronchoscopy was evaluated statistically.

Statistical Analysis

Statistical analysis were carried out with SPSS v12.0 statistical software (SPSS, Chicago, IL). The specific parameters of diagnostic accuracy (DA), specificity and sensitivity were analyzed statistically. $P<0.05$ was considered significant.

Results

A total of 120 patients underwent rigid bronchoscopy for suspected FBA between January 2000 and March 2019 at Adnan Menderes University Faculty of Medicine, Department of Pediatric Surgery. Foreign bodies in the tracheobronchial tree were detected in 71 (59.2%), and were not detected in 49 (40.8%) patients. The mean age of all patients at admission was 2 years (5 months-14 years of age).

Fifty-four (76.0%) patients with foreign bodies and 40 (90.9%) patients without foreign bodies were under 3 years of age. Seventy-six (63.3%) patients who underwent bronchoscopy were male and 44 patients (36.6%) were female. Twenty-six (36.6%) patients with foreign bodies were female and 45 (63.4%) were male; 19 (38.8%) patients without foreign bodies were female and 30 (61.2%) were male. There was no significant difference between gender distribution and the presence of foreign bodies in the tracheobronchial tree ($p>0.05$). The mean admission time was 4 days (minimum; 1 day - maximum; 180 days).

Forty-five (63.4%) patients with foreign bodies detected via bronchoscopy had cough, 23 (32.4%) had cyanosis (choking), and 18 (25%) had both cough and cyanosis (choking).

A positive history of cough in 21 (46.7%), cyanosis (choking) in 18 (40.9%), cough and cyanosis (choking) in 16 (36.4%) patients without foreign bodies was observed.

The presence of cough in history sensitivity was 64.29%, whereas the presence of cyanosis (choking) sensitivity was 32.86%. When positive predictive values (PV^+) were examined, it was found that both values were high, although the cough value (68.18%) (PV^+) was higher than the cyanosis value (56.10%). There were no significant relations between the presence of foreign bodies and cough or cyanosis (choking) in the patient history ($p>0.05$).

Thirty-eight (53.5%) patients with foreign bodies detected in bronchoscopy had dyspnea, 21 (29.6%) had wheezing, and 18 (25%) had dyspnea and wheezing.

Eighteen (40.9%) patients without foreign bodies had dyspnea, 6 (13.6%) had wheezing, and 4 (9.1%) had dyspnea and wheezing. While the sensitivity and specificity of dyspnea were 54.29% and 63.27% respectively, the sensitivity and specificity of wheezing were 30.0% and 87.76% respectively. When evaluated statistically, there was no significant relationship between wheezing and the detection of foreign bodies ($p>0.05$), but there was a significant relationship between dyspnea and the detection of foreign bodies ($p<0.05$).

When the preoperative PA chest X-ray was evaluated, it was observed that 5 (7.01%) of the patients with foreign body had normal radiological findings, 24 (33.80%) had pneumonic infiltration, and 49 (69.01%) had excessive ventilation.

In the preoperative radiological evaluation of the patients without foreign bodies, it was observed that 9 (20.5%) patients had normal findings, 12 (27.3%) had excessive ventilation, and 9 (20.45%) had infiltration on PA chest X-ray. Foreign bodies were detected in 24 (33.80%) patients with infiltration on preoperative chest X-ray, and when evaluated statistically, there was a significant relationship between the detection of foreign bodies in the tracheobronchial tree and the presence of infiltration on chest X-ray ($p<0.05$). However, only 9 (20.45%) patients without foreign bodies had infiltration on preoperative chest X-ray. In other words, on the preoperative chest X-ray of those patients who underwent bronchoscopy and had no foreign bodies, the rate of absence of infiltration was high (90.9%).

When the preoperative chest X-ray was evaluated in terms of excessive ventilation, 49 (69.0%) patients with foreign bodies and 12 (27.01%) patients without foreign bodies had excessive infiltration and a statistically significant relationship was found ($p<0.05$) (Figure 1).

Statistical analyses are shown in Table I. Cough, cyanosis, wheezing and dyspnea were used as diagnostic parameters. Pneumonic infiltration, excessive ventilation, and the presence of any radiological findings were used as

radiological tests. It was observed that the value with the highest diagnostical sensitivity and DA rate (sensitivity; 92.54% and DA; 85.7%) had positivity of any of the radiological findings, and among these, there was detection of one-sided excessive ventilation on the chest X-ray (sensitivity; 70.0% and DA; 70.01%). When the specificities of these findings were examined, it was observed that the specificity of wheezing was 87.76%, and the highest specificity values other than wheezing were found to be infiltration on the chest X-ray at 81.63% and the detection of one-sided excessive ventilation at 80.33%.

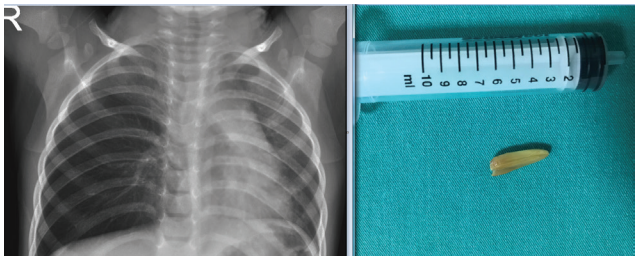

Figure 1. Chest X-ray with non-radiopaque foreign bodies and removed object

Table II shows coexisting rates of two or three of the parameters evaluated in the patient history, physical examination and radiological findings, and their statistical values. In cases of cough with dyspnea or cough with wheezing, the specificity values were 81.25% and 92.31%, respectively. Likewise, sensitivity values were found to be high in cases of presence of cough with excessive ventilation, which is one of the radiological findings, and these values were 83.33%. Among these, the highest DA was found to be the presence of dyspnea with cough

Table I. Statistical values of history, physical examination and radiological findings individually

	Cough		Cyanosis		Wheezing		*Dyspnea		*Infiltration		*EV		Radiology	
	+	-	+	-	+	-	+	-	+	-	+	-	+	-
FBA+	45	25	23	47	21	49	38	32	24	46	49	21	62	5
FBA-	21	28	18	31	6	43	18	31	9	40	12	37	40	9
DA%	55.5		35.4		22.7		47.1		34.3		70.0		85.7	
Sensitivity %	64.29		32.86		30.00		54.29		34.29		70.00		92.54	
Specificity %	57.14		63.27		87.76		63.27		81.63		75.51		18.37	
PV$^+$	68.18		56.10		77.78		67.86		72.73		80.33		60.78	
PV$^-$	52.83		39.74		46.74		49.21		46.51		63.79		64.29	

*p<0.05, EV: Presence of excessive ventilation on chest X-ray, PV$^+$: Positive predictive value, PV$^-$: Negative predictive value, DA: Diagnostic accuracy, FBA: Foreign body aspiration

Table II. Coexisting rates of two or three of the parameters evaluated in history, physical examination and radiological findings, and their statistical values

	CI		CEV		CyI		CyEV		WI		WEV		DI		DEV		CW		CD		CyW		CyD	
	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-
FBA+	17	18	30	6	9	32	16	14	9	34	16	16	12	20	29	12	18	22	24	11	5	31	18	27
FBA-	2	21	6	22	2	24	4	23	2	36	4	35	3	25	3	22	2	24	3	13	1	26	9	22
DA %	60 (46-72)		56 (43-68)		61 (48-72)		52 (34-71)		53 (41-64)		45 (33-57)		53 (40-66)		62 (49-73)		60 (47-72)		68 (54-80)		57 (44-69)		59 (47-70)	
Sensitivity %	48.57		83.33		21.95		53.33		20.93		50.00		37.50		70.73		45.00		68.57		13.89		40.00	
Specificity %	91.30		78.57		92.31		85.19		94.74		89.74		89.29		88.00		92.31		81.25		96.30		70.97	
PV$^+$ %	89.47		83.33		81.82		80.00		81.82		80.00		80.00		90.62		90.00		88.89		83.33		66.67	
PV$^-$ %	53.85		78.57		42.86		62.16		51.43		68.63		55.56		64.71		52.17		54.17		45.61		44.90	

PV+: Positive predictive value, PV-: Negative predictive value, DA: Diagnostic accuracy, FBA: Foreign body aspiration

(68%), followed by the presence of infiltration with cough (60%). Specificity of infiltration together with the presence of cough, cyanosis, wheezing or dyspnea was found to be 90% or more. The presence of wheezing with cyanosis specificity was calculated to be 96.30%. When patients with radiologically pneumonic infiltration or excessive ventilation were evaluated with these data, if the radiological findings of patients with cyanosis and wheezing and patients with wheezing and dyspnea were positive, their specificity were 100% (Table III).

Patients with cyanosis (choking) and/or cough history, wheezing and/or dyspnea on physical examination, were bronchoscopically evaluated for the presence of foreign bodies, even if they had suspicious history and excessive ventilation on chest X-ray. A total of 120 patients underwent bronchoscopy and foreign bodies were detected in 71. Foreign bodies were detected in the right main bronchus in 34 (47.88%) patients with foreign bodies, in the trachea in 13 (18.30%) and in the left main bronchus in 24 (33.80%) (Table IV). When evaluated statistically, detecting foreign bodies in the right main bronchus was significantly high ($p<0.05$). In 49 patients, no foreign bodies were detected in bronchoscopy, but 12 of these 49 patients had mucus plugs in the bronchi, and washing with saline was performed. The other 37 patients (30.8%) were considered as negative bronchoscopy. In patients with mucus plugs, clinical and radiological findings significantly improved after bronchoscopic washing and they were discharged without any further problems.

Discussion

Foreign bodies were detected in 71 (59.2%) patients, and no foreign bodies were detected in 49 (40.8%) patients. The mean age was 2 years (7 months - 14 years), the majority (n=94, 78.3%) were under the age of 3 years and it was found that more males had foreign bodies. All these data were consistent with the literature (1,6,7). According to all these data, we can say that children under 3 years of age have the highest risk for FBA.

As the distal airways are narrower, aspirated foreign bodies are most commonly located in the proximal airways and are directed to the right main bronchus as it has more vertical course and larger diameter than the left (5,7-9). In our patients, the most common site was the right main bronchus (47.88%), the second most common was the left main bronchus (33.80%) and the third was the trachea (18.30%). It was observed that the right main bronchus rate was significantly higher ($p<0.05$).

Table III. Coexisting rates of two or three of the parameters evaluated in history, physical examination and radiological findings, and their statistical values

	RC		RCy		RW		RD		RCCy		RCW		RCD		RCyW		RCyD		RWD	
	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-
FBA+	40	3	22	7	19	6	35	5	4	4	11	0	12	1	7	4	7	2	7	4
FBA-	13	1	14	5	6	9	15	6	10	1	4	1	14	0	0	21	8	4	0	21
DA %	75 (62-85)		60 (45-74)		62 (47-77)		65 (52-77)		42 (20-66)		68 (41-88)		48 (28-68)		34 (18-53)		42 (21-65)		34 (18-53)	
Sensitivity %	93.02		75.86		76.00		87.50		50.00		100.00		92.13		63.64		77.78		63.64	
Specificity %	7.14		26.32		60.00		28.57		9.09		20.00		0.00		100.00		33.33		100.00	
PV$^+$ %	75.47		61.11		76.00		70.00		42.11		73.53		46.15		100.00		46.67		100.00	
PV$^-$ %	25.00		41.67		60.00		54.55		28.57		100.00		0.00		84.00		66.67		84.00	

PV+: Positive predictive value, PV-: Negative predictive value, DA: Diagnostic accuracy, FBA: Foreign body aspiration

Table IV. Patients whose foreign bodies were removed by bronchoscopy and the locations of foreign bodies

Location of foreign body	Number of patients	%
***Right main bronchus**	34	47.88
Trachea	13	18.30
Left main bronchus	24	33.80
Total	71	100

*p<0.05

In a review of Metrangelo et al. (7), in which they presented their 8-year experience in FBA in children, they reported that the foreign bodies were most frequently encountered in the right main bronchus, but found that the encountering rate in the left main bronchus was very close to the rate of the right. They explained this as bronchial anatomy alone was not effective on the location of foreign bodies, these foreign bodies can be displaced by cough or ventilatory effort. In our patients, the foreign bodies encountering rate in the left main bronchus was second, and this can be explained by the fact that foreign bodies can be displaced by cough or ventilatory efforts, and this in line with the results of Metrangelo et al. (7).

Black et al. (4) retrospectively evaluated 548 patients who underwent bronchoscopy with suspected FBA and reported that choking, cough and wheezing were present in 95% of these patients, and bronchoscopy was required. In another study, it was reported that especially in patients with choking history, this was the most valuable data for diagnosis, and cough and wheezing were present in 95% of the patients (7). When we evaluated our patients in terms of cough, cyanosis (choking), wheezing and dyspnea presence; cough was the parameter with the highest sensitivity and DA (64.29%), followed by dyspnea at a sensitivity rate of 54.29%. When examined for their specificities, the highest value was found to be wheezing at 87.76%, followed by cyanosis (choking) and dyspnea at 63.27%. However, in the statistical evaluation of all these data, only dyspnea was found to be significantly high in patients with foreign bodies ($p<0.05$). We also attributed the fact that such a small number of patients, in discordance with literature, had cyanosis (choking) history because aspiration occurred at a time when the family was not with the child or the family's attention was distracted. These results suggest that the presence of dyspnea among the clinical findings supports suspected FBA.

In 49 (40.8%) patients who underwent rigid bronchoscopy due to FBA, no foreign bodies were found. According to the literature, the detection range of foreign bodies in children with suspected FBA is very wide (25%-90%). In Even et al.'s (10) study, foreign bodies were found in 57% of 98 children, and it was indicated that this ratio, which is close to the ratio in our study, is in accordance with the literature (11). Similarly, Oncel et al. (12) reported in their study that no foreign bodies were found during rigid bronchoscopy at the rate of 25.7%. We think that the negative bronchoscopy rate is similar due to the vital risks that may occur usually in emergency conditions if bronchoscopy, a procedure that must be decided upon quickly, is not performed. It has been reported in the literature that computed tomography can also be a good alternative in the suspicion of foreign body diagnosis, and even can be used with a DA rate of 94.5%. Therefore, in our retrospective series, the FBA detection rate in bronchoscopy is in accordance with the literature. It can be said that the negative bronchoscopy rate may be increased due to vital risks that occur in emergency conditions if bronchoscopy, a procedure that must be decided upon quickly, is not performed. It has been stated in the literature that computed tomography can be a good alternative and even be used at a DA rate of 94.5% (13). No computed tomography was used diagnostically in our patient series. Considering radiation exposure in the pediatric age group, we think that using computed tomography routinely in the diagnosis of FBA is arguable.

However, considering the risks of anesthesia and the procedure during bronchoscopy, the place of computed tomography in the diagnostic algorithm should be reassessed with prospective studies.

If cyanosis (choking) history is positive, bronchoscopy is recommended in the diagnostic approach to patients with suspected FBA, even if physical examination and radiographic findings are negative (2,14,15). When we evaluated our patients in the light of this information, there were two patients who underwent bronchoscopy who had negative physical examination and radiological findings, and positive cyanosis (choking) history, and they had no foreign bodies. Again, it was observed that the sensitivity value of history positivity, which is the most valuable diagnostic criterion when compared to the literature information, was 25% lower in our cases. In parallel with this information, in discordance with the literature, we thought that positive history alone would not be sufficient, and we evaluated the relationship between history together with any physical examination or radiological findings and the presence of a foreign bodies. In our patients, if there was wheezing as a physical examination finding with cyanosis (choking) history, or a history of wheezing and positivity of any radiological findings, the specificity was found to be 100%. In this case, according to our data, we think that history alone may not be sufficient for the indication of bronchoscopy, and bronchoscopy should be performed if any radiological findings (pneumonic infiltration or excessive ventilation) are positive.

Metallic foreign bodies can be diagnosed directly by X-ray. However, since foreign bodies are non-opaque, the diagnosis is based on secondary findings (16) (Figure 2).

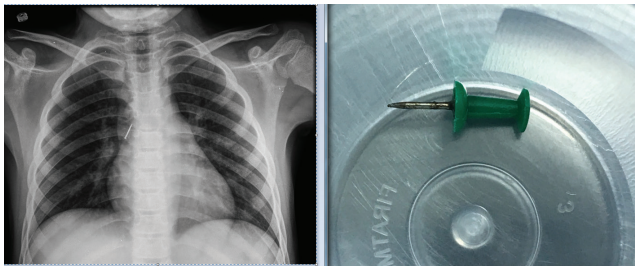

Figure 2. Chest X-ray with radiopaque foreign bodies and removed object

In addition, the DA rate (85.70%) was found to be high in patients with any radiological findings detected in chest X-ray. The detection sensitivity (92.50%) of the radiological findings was also found to be high. However, no foreign bodies were observed in 40 (39%) patients with pathological findings. With these findings, radiological finding detection alone is not sufficient to indicate bronchoscopy. However, it is seen that there is a 100% specificity value with history and physical examination findings.

Conclusion

If those patients with suspicious history, which is the most important parameter for diagnosis in FBAs, also have dyspnea and pneumonic infiltration on chest X-ray, the possibility of FBA presence should definitely be considered, even if the first thing which comes to mind in diagnosis is pneumonia. We believe that these patients with suspicious history should be evaluated bronchoscopically if they have a suspicious history together with wheezing and/or pneumonic infiltration on chest X-ray and/or excessive ventilation.

Ethics

Ethics Committee Approval: Ethics approval was obtained from the Non-interventional Clinical Research Ethics Committee of Adnan Menderes University (approval no: 2018/1416).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.O.E., B.E., M.Y., S.K.Ö., Concept: A.O.E., B.E., M.Y., S.K.Ö., Design: A.O.E., B.E., M.Y., S.K.Ö., Data Collection or Processing: A.O.E., B.E., S.K.Ö., Analysis or Interpretation: A.O.E., B.E., M.Y., S.K.Ö., Literature Search: A.O.E., B.E., M.Y., S.K.Ö., Writing: A.O.E., B.E., M.Y., S.K.Ö.

Conflict of Interest: None of the authors had conflict of interest.

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Original Article

Relationship Among Obesity Awareness, Emotional Eating, and Obesity in Middle School Children

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ABSTRACT

Aim: This study was carried out as a cross-sectional study to evaluate the relationships between obesity awareness, emotional eating, and obesity in middle school children.

Materials and Methods: The sample of the study comprised a total of 421 children who were 10-14 years of age and attended the fifth, sixth, seventh, or eighth grades. The data were collected using a socio-demographic data collection form, the Obesity Awareness scale, and the Emotional Eating scale. The heights and weights of the children were measured by the researchers and their body mass index (BMI) percentiles were calculated. The data were analyzed using Pearson's correlation analyses.

Results: Of the children, 14.7% were obese, and 13.8% were overweight according to the BMI percentile. There was no relationship between obesity, obesity awareness, and emotional eating ($p>0.05$).

Conclusion: The study found that emotional eating and obesity awareness did not affect middle school children's obesity.

Keywords: Children, middle-school, obesity, awareness, emotional eating

Introduction

Eating is a biological and behavioral process that begins in the first year of life and serves as a foundation for growth and development (1). The eating behavior that emerges as a response to an emotional state is referred to as emotional eating. This eating behavior is not based on the feeling of hunger and may lead to obesity (2,3).

The ratio of childhood obesity has doubled in the last 30 years (4). The ratio of obese children and adolescents in the US was 16.9% (5). According to the investigation report on monitoring the growth of school children (6-10-year-old age group) project in Turkey by the General Directorate of Basic Health Services of the Turkish Ministry of Health (6) 8.5% of children were obese and the ratios of overweight children in cities and rural areas were 16.3% and 11.9%, respectively. There is a global increase in the prevalence of obesity and being overweight in children and adolescents.

Researchers have the important task to investigate the causes of obesity such as sedentarism, emotional eating, parents, and children's awareness about obesity. Demir and Bektas (7) reported that eating behaviors and parental feeding styles affect the occurrence of obesity in childhood. Parents may influence their children's eating behaviors and result in high levels of disinhibited emotional eating in early adolescents (8). There are only a small number of studies that investigate the relationship between emotional eating and obesity in children (9,10).

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Emotional eating in children can be associated with deficits in emotion regulation. It may therefore represent a risk factor for becoming overweight or obese children/adolescents (11). In adults, emotional eating has been found to correlate positively with weight status (12). We think that emotional eating may be associated with obesity in children. Increased awareness about obesity among children will help to reduce the risk of obesity and also chronic diseases (13). Although the child is obese or overweight, the awareness of obesity may be low and the child may be obese or overweight due to emotional eating. With this study, this deficiency in the literature can be closed. Some instruments such as emotional eating or obesity awareness can evaluate the vulnerability and risk factors for early adolescents (13,14). It can be a way to control obesity in children. This study aimed to determine the relationships between obesity awareness, emotional eating, and obesity in middle school children.

Materials and Methods

Study Design and Participants

This cross-sectional study evaluated the relationships between obesity awareness, emotional eating, and obesity in middle school children.

The population of the study was made up of 680 students who were 10-14 years of age and attending the fifth, sixth, seventh, or eighth grades of a middle school in Izmir affiliated with the Provincial Directorate for National Education, a metropolitan region located in the western part of Turkey. This school was selected as no studies about obesity had been conducted there previously and the majority of children were from middle-income families.

The criteria for inclusion in the sample group were: a) being a middle school student, b) being 10-14 years of age, c) voluntarily participating in the study with written consent forms from the participants and their parents, d) not having deceased parents and e) having access to the parents' height and weight data. It was aimed to reach the whole population (n=680). No sample selection method was used, and 421 students who volunteered to participate in the study, met the inclusion criteria, and filled out the forms were included in the study sample. The participation rate was 61% in this study.

Data Collection

The data were collected by the researcher in a classroom environment during a visit to the school between February 2017 and June 2017. A socio-demographic data collection form, the Obesity Awareness scale (OAS), and the Emotional Eating scale (EES-C) were used for data collection. The researcher informed the children about the purpose of the study. Informed written consent from parents was received through the children. Verbal consent from the children was also received. The heights and weights of the children were measured by the researcher between 9:30-12:00 a.m. before the meal. All of the children were wearing clothes (only shirt and skirt/pants), the children's shoes were removed before the measurement. Bodyweight and height were measured by a digital weighing scale and a stadiometer and recorded on the demographic data collection form. The digital weighing scale was calibrated before the study. Body mass index (BMI) and BMI percentile were calculated for each child using the auxology program according to Turkish children's BMI references (15). In the auxology program, BMI and BMI percentile were calculated by entering the children's date of birth, weight, and height. Underweight is defined as $<5^{th}$ percentile, normal-weight is defined as 5^{th} to $<85^{th}$ percentile, overweight is defined as between the 85^{th} to $<95^{th}$ percentile, and obese is defined as $\geq 95^{th}$ percentile.

The data collection forms were handed to the children who were asked to disclose demographic data and answer the scale items. In addition to the written consent form, the parents were also asked to answer some questions about themselves on the data collection form. The BMIs of the parents were calculated using the height and weight values they gave. The BMIs of the parents were categorized as follows; underweight is defined as <18.5, normal weight is defined as 18.5-24.9, overweight is defined as 25.0-29.9, and obese is defined as >30.0.

Socio-demographic Data Collection Form: This form includes questions for children about their grade, age, gender, time spent with computers, phones or television, frequency of having breakfast, frequency of eating junk food, frequency of eating fast food, and contentment with the appearance of their bodies. It also includes questions for their parents about their own heights and weights (8-10).

The Obesity Awareness Scale (OAS): This scale was developed by Allen (16). It has 23 items in 3 subdimensions that evaluate: a) obesity awareness (8 items) and knowledge about risk factors (such as whether childhood obesity is increasing in school, society, and country), b) nutrition (7 items), dietary habits of the individual and the effects of nutrients on health (such as whether overeating at each meal causes obesity) and c) physical

activity (8 items), the effect of physical activity on health and weight (such as whether exercising for at least 60 minutes per day is necessary to be healthy). The scale is a four-point Likert scale from negative to positive. Its internal consistency coefficient was reported to be 0.80. The validity and reliability study for the Turkish scale was performed by Kafkas and Özen (17), and its Cronbach's alpha value was good at 0.87. Confirmatory factor analysis showed that the scale had an appropriate structure and that the Turkish OAS is a valid and reliable measurement tool (17). The Cronbach's alpha value was 0.90 for this study. Scale permission was received from the authors via mail.

Emotional Eating Scale (EES-C): This scale evaluates the emotional eating status of children between 8-17 years old. The original adult-based scale was adapted by Tanofsky-Kraff et al. (18) into a children's and adolescents' EES-C. The scale is composed of 25 items and three subdimensions concerning the reason for eating an excess amount of food; anxiety, anger, and frustration (EES-C-AAF), depressive symptoms (EES-C-DEP), and feeling unsettled (EES-C-UNS). The total variance of these three subdimensions was 67.2%, factor loads were between 0.61-0.79 for EES-C-AAF; 0.57-0.84 for EES-C-DEP; and 0.52-0.72 for EES-C-UNS. The Cronbach's alpha values were 0.95, 0.92, and 0.83 for the three subdimensions, respectively. In this five-point Likert scale, the answers varied between 1 (I never want to eat) to 5 (I want to eat a lot). As scores on this scale increase, so does eating as a response to emotional states. This scale was translated into Spanish and found to be a valid and reliable scale for the Spanish population (14). The validity and reliability study for the Turkish population was performed by Bektas et al. (19), and the Cronbach's alpha values for this scale and its subdimensions were 0.90, 0.86, 0.76, and 0.71, respectively. The total correlation of the items ranged from 0.57 to 0.99. The EES-C is a valid and reliable scale for determining the emotional eating of Turkish children and adolescents (19). The Cronbach's alpha value was 0.87 for this study. Scale permission was received from the authors via mail.

Ethical Approval

Before the research was conducted, permits were obtained from the owners of the scales used in the research via email. The written consent of Dokuz Eylül University Non-invasive Research Ethics Board was obtained in a decision numbered (3019-GOA, 2016/29-25). Permission was also obtained from the İzmir Provincial Directorate for National Education to conduct the study (12018877-604.01.01.-E.13824002).

Statistical Analysis

The data were analyzed using SPSS (22.0) software. The compliance of the parameters to normal distribution was evaluated through the Shapiro-Wilk test. Percentages and means were used to evaluate the socio-demographic characteristics. Their BMI percentile was categorized. The characteristics of the children were analyzed using the x^2 test and t-test. One-Way ANOVA analysis was used to compare the students' emotional eating and obesity awareness scores according to BMI percentile. The relationships between the OAS, the EES-C, and their subdimensions and obesity (obese ≥95th percentile or not) were analyzed using Pearson's correlation analysis. The threshold for statistical significance was $p<0.05$.

Results

Children Characteristics

The children's age and gender according to BMI percentile are given in Table I. Of the students, 14.7% were obese (n=62), 13.8% were overweight (n=58), 62% had a normal weight (n=261), and 9.5% were underweight (n=40). Of the students, 45.4% were females (n=191). There was a statistical difference between gender and BMI percentile ($p<0.05$). The students' mean age was 12.1±1.0 years [minimum (min)=10, maximum (max)=14]. Their

Table I. Children's age and gender according to body mass index percentile

Socio-demographics	Obese (n=62)	Overweight (n=58)	Normal weight (n=261)	Underweight (n=40)	p
Age (mean years ± SD)	12.0±1.2	12.2±1.2	12.1±1.0	11.9±0.8	0.506*
Gender					
Girls (n, %)	10 (5.2)	28 (14.7)	128 (67)	25 (13.1)	0.000**
Boys (n, %)	52 (22.6)	30 (13)	133 (57.8)	15 (6.5)	

*t-test, **X^2 test, SD: Standard deviation

mean height was 154.2±10.8 cm (min=120, max=189), their mean weight was 46.1±11.8 kg (min=25, max=95) and the mean BMI percentile was 53.8±33.7 (min=1.03, max=100.0). The ratio of the students who said that they spent half an hour per day with computers was 22.8% (n=96), 24.7% said that they spent half an hour per day with phones (n=104), and 27.1% said that they watched an hour of television per day (n=114). Of the students, 75% said that they had breakfast every day (n=316), 41.3% said that they consumed junk food every 2 or 3 days (n=174), and 24.9% said that they consumed fast food once a week (n=105). The ratio of the students who were content with the appearance of their bodies was 66.3% (n=279), and 14.3% of the students said that they were discontented with the appearance of their bodies (n=60).

Family Characteristics

The mean height of the mothers was 164.5±5.6 cm (min=136, max=185). Their mean weight was 65.3±8.8 kg (min=35, max=105), and their mean BMI was 23.7±3.3 (min=8, max=37). According to the BMI values, 5% of the mothers were underweight (n=21), 73.9% had a normal weight (n=311), 14.5% were overweight (n=61), and 6.7% were obese (n=28). The mean height of the fathers was 176.8±15.9 cm (min=176, max=198). Their mean weight was 81.0±8.7 kg (min=55, max=130), and their mean BMI was 25.1±2.6 (min=17, max=40). According to the BMI values, 1% of the fathers were underweight (n=4), 28.7% had a normal weight (n=121), 65.1% were overweight (n=274), and 5.2% were obese (n=22). There was no relationship between the children's BMI percentile and their mother's BMI values (x^2=17.191, p=0.066) and their father's BMI values (x^2=10.839, p=0.287).

The Obesity Awareness and Emotional Eating Levels of Middle School Students and the Relationships Between Obesity, Obesity Awareness, and Emotional Eating

The mean total score on the EES-C of the children was 50.4±14.8. The mean total score on the OAS of the children was 56.3±9.4 (Table II).

There was no relationship between obesity, obesity awareness, and emotional eating (p>0.05). There was a high positive relationship between the EES-C and its subdimensions (p<0.001), and the OAS and its subdimensions (p<0.001) (Table III).

Discussion

Pediatric loss of eating control in children is a problematic behavior that frequently persists into adolescence and is related to emotional distress (20). Emotional eating is reported to be a learned behavior and described as eating in response to an emotional state. Emotional overeating is associated with an increased risk of obesity, while emotional undereating may prevent childhood obesity (21). Nguyen-Michel et al. (22) found that emotional eating is associated with the frequent intake of high calorie fatty and sugary foods in Latino middle school students. They stated that emotional eating may lead to overeating. Emotional overeating among adolescents can lead to obesity (23). Sánchez et al. (10) found a significant relationship between Chilean children's eating behavior scores and BMI Z-scores. Tong et al. (9) reported that there was no relationship between Asian children's emotional eating and BMI. Nogay (24) found that BMI was significantly correlated with emotional eating subscales in Turkish adolescents. In another study, there was no significant correlation between

Table II. Obesity awareness and emotional eating levels of the middle school students

	Obese (n=62)	Overweight (n=58)	Normal weight (n=261)	Underweight (n=40)	Total (n=421)	p
EES-C-AAF	24.2±8.5 (13-52)	24.6±8.0 (13-37)	24.0±8.3 (13-65)	26.1±9.0 (13-44)	24.3±8.4 (13-65)	0.521
EES-C-UNS	9.5±2.9 (5-15)	9.3±3.5 (5-18)	9.6±3.3 (5-25)	9.6±3.5 (5-19)	9.6±3.3 (5-25)	0.926
EES-C-DEP	16.2±4.8 (8-28)	15.9±5.5 (7-28)	16.6±5.1 (7-33)	16.4±5.5 (7-30)	16.4±5.1 (7-33)	0.808
EES-C total	50.0±13.6 (30-92)	50.0±15.1 (25-75)	50.4±14.8 (25-121)	52.2±16.2 (25-85)	50.4±14.8 (25-121)	0.877
Obesity awareness	24.5±4.4 (12-32)	23.4±4.9 (10-35)	24.0±3.8 (11-36)	23.9±4.4 (15-34)	24.0±4.1 (10-36)	0.560
Nutrition	18.1±3.8 (6-24)	17.4±4.0 (6-24)	17.9±3.7 (7-24)	18.3±3.5 (7-24)	17.9±3.7 (6-24)	0.625
Physical activity	14.2±2.8 (5-20)	14.4±3.3 (5-20)	14.4±3.0 (5-20)	14.7±3.5 (5-20)	14.4±3.0 (5-20)	0.883
OAS Total	56.9±9.8 (24-69)	55.2±10.8 (22-79)	56.4±8.8 (26-80)	57.1±10.2 (28-77)	50.4±14.8 (25-121)	0.747

EES-C: Emotional Eating scale, EES-C-AAF: Anxiety, anger, and frustration, EES-C-DEP: Depressive symptoms, EES-C-UNS: Feeling unsettled, OAS: Obesity Awareness scale

Table III. The relationship between obesity, obesity awareness and emotional eating scores

	1	2	3	4	5	6	7	8	9
1. Obesity	1.0	-	-	-	-	-	-	-	-
2. EES-C-AAF	-0.084	1.0	-	-	-	-	-	-	-
3. EES-C-UNS	-0.018	0.693**	1.0	-	-	-	-	-	-
4. EES-C-DEP	-0.127**	0.619**	0.513**	1.0	-	-	-	-	-
5. EES-C total	-0.095	0.932**	0.791**	0.822**	1.0	-	-	-	-
6. Obesity awareness	0.112*	-0.068	-0.001	-0.036	-0.054	1.0	-	-	-
7. Nutrition	0.004	-0.031	-0.010	-0.011	-0.022	0.506**	1.0	-	-
8. Physical activity	0.003	-0.009	-0.038	-0.018	-0.017	0.374**	0.599**	1.0	-
9. OAS total	0.067	-0.054	-0.024	-0.039	-0.049	0.812**	0.831**	0.728**	1.0

*Correlation is significant at the 0.05 level (2-tailed), **Correlation is significant at the 0.01 level (2-tailed).
EES-C: Emotional Eating scale, EES-C-AAF: Anxiety, anger, and frustration, EES-C-DEP: Depressive symptoms, EES-C-UNS: Feeling unsettled, OAS: Obesity Awareness scale

emotional eating and BMI in early adolescent girls (25). This study also found no relationship between children's obesity and emotional eating. This may be attributed to the low mean emotional eating scores of the children in the study. It has been reported that depressive symptoms predict eating disorders (26). In another study, emotional abuse was determined to be a risk factor for eating disorders and had a relationship with BMI (27). Erickson et al. (28) determined a strong relationship between depressive symptoms and BMI, especially for girls. Fox et al. (29) reported that severe obesity versus obesity was 3.5 times higher than normal for depressed adolescents. We found no relationship between depressive symptoms and obesity. Emotional eating-depressive symptoms subdimension scores were similar for obese and non-obese children.

In countries that lack school health programs, there is a need to increase awareness of prevention against becoming overweight or obesity (30). There have been studies of parents' obesity awareness. One reported that most of the parents incorrectly classified the weights of their children and could not tell if their children were overweight or obese (31). Today, obesity, as an increasing health problem, has compelled educators to carry out programs to raise children's obesity awareness (32).

O'Dea and Wilson (33) determined that there was no relationship between BMI and nutritional knowledge and also dietary control. Similarly, this study found no relationship between obesity and obesity awareness. This may be attributed to the high obesity awareness among most of the children in this study. Family-oriented health programs to control childhood obesity have been organized and are reported to be effective (34). Raising obesity awareness among all family members and not just children is necessary. This study found no relationship between obesity awareness, emotional eating, and obesity. The children included in this study received low scores on the EES-C and had a high mean score on the OAS. These scores and the low ratios of overweight and obese children led us to conclude that the school children in this study were aware of their eating habits and obesity. In another relevant study, the predictors regarding children, their families, and school context variables were found to affect children's obesity (35). Other factors which can affect children's obesity should also be identified.

Study Limitations

No randomization was used in sample selection. In this study, obese and non-obese children could be compared using a suitable sampling method.

Conclusion

This study determined that there was no relationship between obesity, emotional eating, and obesity awareness. Obesity awareness and emotional eating both failed to explain middle school children's obesity. In a sample with more obese children, this type of study can be repeated. Additional research should examine the specific roles of emotional eating in the development of obesity in adolescents. These studies can be useful for preventing obesity and emotional eating. Longitudinal studies should be conducted to determine factors causing obesity. The knowledge and awareness of children and parents should be increased through healthy eating and physical activity programs.

Ethics

Ethics Committee Approval: The written consent of Dokuz Eylül University Non-invasive Research Ethics Board

was obtained in a decision numbered (3019-GOA, 2016/29-25).

Informed Consent: Informed written consent from parents was received through the children. Verbal consent from the children was also received.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.Ö.G., M.B., Design: G.Ö.G., M.B., Data Collection or Processing: G.Ö.G., Analysis or Interpretation: G.Ö.G., M.B., Literature Search: G.Ö.G., M.B., Writing: G.Ö.G., M.B.

Conflict of Interest: None of the authors had conflict of interest.

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Original Article

Knowledge of Dental Avulsion Among Emergency Physicians: A Survey Study

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ABSTRACT

Aim: Dentoalveolar injuries are complex conditions affecting teeth and surrounding tissues and are frequently seen in children or adolescents. The purpose of this study was to investigate the levels of knowledge on dental avulsion among emergency physicians (EPs).

Materials and Methods: A questionnaire was used to investigate EPs' level of knowledge and therapeutic approaches to avulsion. One hundred EPs were included in the study. The questionnaire was mailed to participants, and the data obtained were evaluated. Descriptive statistics and chi-square tests were used for statistical analysis.

Results: Our results showed that although EPs frequently encountered dental traumas, their medical education had not included dental emergencies. The knowledge level of dental avulsion of all EPs included in the study was as follows; 24% low, 56% moderate and only 18% high.

Conclusion: EPs possessed inadequate knowledge concerning the immediate treatment of dental avulsion. The treatment of avulsion should be included in the medical curriculum. This will result in appropriate emergency treatments in dental avulsion being provided in emergency settings.

Keywords: Avulsion, dentistry, emergencies, knowledge

Introduction

Traumatic dental injuries resulting from home/school/playground accidents, sports activities, fights, or traffic accidents are a serious oral health problem. Although they can be seen during any period of life, such injuries are more common in infancy, childhood and adolescence (1). Dental avulsion, defined as the complete displacement of the tooth from its socket, is one of the most severe traumatic dentoalveolar injuries. According to the American Academy of Pediatric Dentistry, avulsion is one of the most common traumatic dental injuries seen in children (2), and is usually experienced by children aged 2-4 and 8-12 years (3). The frequency of dental avulsion varies between 0.5% and 16% in permanent dentition and between 7% and 13% in primary dentition. These injuries usually affect the incisors, especially the maxillary central incisors (4).

All traumatic dental injuries including avulsion should be considered as emergencies and treated promptly and effectively. In addition to cosmetic difficulties, phonetic, chewing and psychological problems are also encountered following the loss of these teeth (5). Immediate and appropriate replantation of an avulsed permanent tooth is therefore highly important for good long-term prognosis (5).

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When immediate replantation is not possible, appropriate storage media and extra-alveolar time before replantation are important for the success of the treatment. In such injuries, parents frequently first apply to emergency departments (6,7). It is therefore very important that the emergency physician (EP) should have adequate knowledge concerning the emergency management of dental traumas and that they administer the appropriate treatment immediately.

The aim of the present study was to evaluate knowledge on avulsion among EPs.

Materials and Methods

This study was planned and conducted in line with the ethical standards detailed in the Declaration of Helsinki and approved by the Ethical Committee of Mersin University (2018/173).

This cross-sectional study involved EPs working at university hospitals or public training and research hospitals in Turkey. The inclusion criteria for participants were as follows; working in a hospital as an EP, willingness to take part to the study, and aged 20-60 years. Participants who agreed to participate in this research with their own consent were included. The authors modified a previously used and validated questionnaire (6). All questions were close-ended (multiple-choice), and the questionnaire was divided into three sections, the first consisting of four questions about the personal characteristics of the participating physicians. The second section included 11 questions evaluating physicians' attitudes to two different hypothetical avulsion cases, and the final section consisted of two questions evaluating self-assessment. A pilot study to evaluate intelligibility was conducted before the main study, and a few modifications were applied. The 17-item questionnaire was administered to the EPs by e-mail. For reasons of privacy, no names or other personal information were recorded. Returning the questionnaire was interpreted as indicating willingness to participate in the study. A total of 90 participants was found to be sufficient (power: 0.95, effect size: 0.3 and 5% standard error). The questionnaire was e-mailed to 150 EPs to compensate for possible dropouts, and 100 EPs finally participated in the study.

Knowledge levels were assessed using a standardized scoring method modified from Abu-Dawoud et al. (8). Eleven questions from the second section of the questionnaire were used to evaluate knowledge levels. A score of 8 indicated full knowledge while a score of 0 indicated no knowledge. Other mean scores were formulated as 6-8 points indicating high knowledge, 3-5 points indicating moderate knowledge, and 0-2 points indicating low knowledge.

Statistical Analysis

Statistical Analysis was performed on IBM SPSS 22 (IBM Corp, Armonk, NY) software. Descriptive statistics were used for the evaluation of the data. Chi-square tests were used to analyze relationships between age, gender, previous education concerning dental trauma, and knowledge levels regarding the emergency management of dental trauma. Statistical significance was set at $p<0.05$ for all tests.

Results

One hundred EPs participated in the study (34% female and 66% male). Nearly half (46%) were aged 31-40 years, and the mean length of professional experience was 9.5 years. Approximately half of the participants (52%) reported that their education had not included information about the management of dental trauma. The majority of physicians (80%) also stated that they had never encountered a dental injury (Table I).

When physicians were classified according to their levels of dental trauma knowledge, 24% had a low level of knowledge, 56% had moderate knowledge and only 18% had high knowledge. The chi-square test results revealed

Table I. Demographic characteristics of the EP

	(%)
Gender	
Female	34
Male	66
Age	
18-30	32
31-40	46
>40	22
Years of experience	
<5	31
5-10	42
>10	27
Education on management of dental trauma	
Yes	48
No	52
Eye-witnessed a dental injury	
Yes	20
No	80

EP: Emergency physician

no statistically significant relationships between levels of knowledge concerning avulsed teeth and the physician's age, gender, experience, or previous education regarding dental trauma.

In the hypothetical permanent tooth avulsion case, 78% of EPs were able to accurately identify the tooth concerned. Unfortunately, however, 72% of physicians did not suggest replantation. The majority of participants (68%) stated that the avulsed tooth should be held without touching the root. The great majority (84%) agreed that the tooth should be cleaned before replantation, the most popular method being to clean it under tap water (54%). Tetanus vaccination was also described as being necessary by the great majority (80%). In cases when the avulsed tooth could not be replanted, the most popular storage media among the physicians were milk (28%), water (16%), or a handkerchief (14%). Regrettably, only 28% of the emergency specialists correctly answered the question concerning the replantation time of the avulsed tooth, a factor which is very important in prognosis (Table II).

Table II. Knowledge of EP

	(%)		(%)
Determine the tooth correctly (permanent tooth)		**Preferred storage media**	
Yes	78	Water	16
No	22	Milk	28
		Handkerchief	14
		Saline solution	12
		Saliva	8
		Do not know	22
Replant the teeth into the socket		**Replantation time**	
Yes	28	30 min	28
No	72	A few hours	52
		Not necessary	-
		Do not know	20
Holding the tooth		**Determine the tooth correctly (primary tooth)**	
Without touching the root	68		
Holding from the root	-	Yes	90
Not matter where it is hold	-	No	8
Do not know	32	Do not know	2
Cleaning tooth before replantation		**Replant the teeth into the socket**	
Yes	84	Yes	10
No	8	No	82
Do not know	8	Do not know	8
Cleaning tooth		**Considering dental trauma as an emergency**	
By brushing	6	Yes	98
Do not clean	2	No	2
Under tap water	54		
Do not know	38		
Necessity of tetanus vaccination		**Preferred storage media**	
Yes	80	Water	16
No	20	Milk	28
		Handkerchief	14
		Saline solution	12
		Saliva	8
		Do not know	22

EP: Emergency physician

In the hypothetical primary tooth avulsion case, the great majority of EPs (90%) were able to accurately identify the tooth. Most of them (82%) stated that they would not replant the primary tooth into the socket (Table II). Dental trauma was considered an emergency condition by 98% of the physicians.

In the third part of the questionnaire, 46% of physicians reported that they would not intervene in a dental trauma case concerning an avulsed tooth and would refer the patient to a dentist. Almost all (90%) EPs reported a need for more training on dental trauma and its management.

Discussion

Traumatic dental injuries can occur at any age but are particularly common in childhood (9). These injuries may range from a simple enamel fracture to an extensive maxillofacial trauma. In cases of avulsion, the most serious type of injury, families frequently present to emergency services (7). The immediate management provided by EPs greatly affects the prognosis of the tooth (5,6). However, patients may not always be treated appropriately due to a lack of information among EPs regarding dental trauma management. The level of in-time and correct treatment for dental trauma patients was stated to be only 19.29% in a study conducted by Kayıllıoğlu Zencircioğlu et al. (7) It is therefore very important for EPs to possess sufficient knowledge of dental injury management, as they may be required to perform first-aid in traumatic events. The present study was intended to determine the baseline knowledge levels of EPs regarding dental avulsion management in both primary and permanent dentition.

In previous studies, there was no significant relationship between the gender of the physician and dental trauma knowledge (6,10,11). Bahammam (6) observed a statistically significant relationship between dental trauma knowledge levels and age. In the present study, no significant relationship was found between the age of the EP and their dental trauma knowledge. We originally expected knowledge to increase with age due to increasing professional experience. Unexpectedly, there was no correlation between experience and knowledge level due to the fact that EPs are not trained on dental trauma during their medical education or throughout their working life in Turkey.

Consistent with Lin et al. (10) and Trivedy et al. (12), nearly half of the EPs reported not receiving adequate information about emergency management in dental trauma during or after training. Similarly, Iyer et al. (13) reported that 33.3% of physicians received no training regarding first aid in the area of dental avulsion. In contrast, Needleman et al. (14) reported that the majority of physicians (80.4%) had received training concerning the management of traumatic dental injuries in Massachusetts emergency departments. This high level was attributed to these physicians being certified in pediatric emergency medicine, and therefore cannot be generalized to all EPs.

Our findings showed that most EPs possessed a moderate knowledge on dental avulsion. Another previous study also reported that EPs possessed moderate knowledge and awareness of dental avulsion (15). It is important to increase EPs' awareness of traumatic dental injuries since they may be the first specialists to encounter dental injuries in emergency departments. Their education should therefore also comprise managing dental trauma. A formal protocol for managing dental injuries and avulsed teeth should also be established for emergency departments.

Only 20% of physicians had previously witnessed any dental trauma. In contrast, Raoof et al. (15) reported that 75% of medical students had witnessed dental trauma. The results of a different study also conducted in Turkey showed that 41.2% of dental injuries were first examined by EPs, 25% by physicians, and only 7.3% by a dentist (11). That study also indicated that EPs had low levels of knowledge regarding the diagnosis and treatment of dental injuries despite having experienced or witnessed such cases (11). EPs are often the first professional to provide emergency management of dental injuries (7,16). These studies demonstrate the importance of dental emergency management being included in the education curriculum.

Similar to the present study, questions also in another in another study about permanent teeth were more often answered correctly than those regarding primary dentition (13). This may be explained by EPs having difficulty in distinguishing primary and permanent teeth and by their being more familiar with permanent dentition.

Immediate replantation is important for the prognosis of avulsed teeth (6). However, nearly half of the EPs in this study (48%) reported being unaware of what to do when encountering an avulsed tooth. More than half of the participants (54%) stated that they would prefer to communicate with a dental office in cases of such injuries. Other studies also reported that most participants would prefer to contact a dentist (6,10). This may be due to participants lacking knowledge and confidence in terms of providing first aid in cases of traumatic dental injuries. Another problem to note is that dental trauma is not considered an emergency in hospital emergency departments.

The majority of participants in the present study stated that the permanent avulsed tooth should be replanted. This result was consistent with the results of the study of Iyer et al. (13), but not with the results of the study of Holan and Shmueli (1), who reported that only 4% of physicians would replant the permanent tooth under any circumstances. However, half of the participants stated that they would not replant the avulsed permanent tooth under any circumstances. This indicates the low awareness among physicians of the possibility of saving the tooth through simple replacement in the socket. In addition, only 5% of participants in another study were aware of replantation (17). The main reason for this low rate may be the participants were physicians working in medical colleges or as residents in advanced medical training programs, and were therefore less familiar with emergency situations than EPs.

The avulsed tooth should not be held by the root. Touching the root is contraindicated as this may damage the remaining periodontal tissue and increase contamination of the avulsed tooth (14). In this study, the participants' knowledge regarding holding the avulsed tooth without touching the root was highly accurate. This was also consistent with several other studies involving EPs (8,9,18). However, the participants were generally unsure whether they would be able to replant the tooth in the correct position, although they were aware that the avulsed tooth should be cleaned before replanting. Furthermore, the majority of the participants stated that they would remove any debris under tap water. Likewise, almost half the physicians in Bahammam's study recommended rinsing the tooth under running water (6). Similarly, Raoof et al. (15) reported that most of the physicians would rinse the avulsed tooth under tap water without rubbing it.

If the tooth cannot be replanted, it should be placed in a suitable medium such as saliva, milk, blood, plain water, or contact lens solution, or it can also be placed inside the mouth. Theoretically, the best storage media are HBSS, Via Span and Eagle's medium. Our participants generally possessed inadequate knowledge of transport media. The periodontal ligament (PDL) cells can maintain their viability in milk for 6 hours during the extraoral period. Only 28 physicians agreed that the tooth could be preserved in milk. Moreover just 10 participants knew that the tooth could be kept in the mouth for storage. Although the tooth can be conserved in the buccal sulcus in children, there is a risk of the avulsed tooth being swallowed. Conserving the tooth in a handkerchief in a dry environment causes the destruction of PDL cells. This is, therefore, one of the least desirable means of preserving an avulsed tooth. Conserving the tooth in a handkerchief was a less popular choice among our participants compared with a previous study (8). This may be due to the physicians in that study not working in an emergency clinic.

Another factor affecting prognosis and the success of treatment is the extraoral time. After a dry time of 60 min or more, all PDL cells become non-viable (19). It is therefore important that reimplantation be performed in the first hour. Our participants' knowledge concerning the correct intervention time for an avulsed tooth was surprising. More than half of the participants stated that an avulsed tooth can be treated within a few hours. Only 6% stated that they would intervene immediately. Our results were in contrast with those of several studies in which physicians were aware of the need for an avulsed permanent tooth to be treated immediately (6,17). In the study of Bahamman et al. (6), there was no "within a few hours" option. The available alternatives were "immediately", "the next day", "within a few days" and "when a symptom developed". Participants who thought that avulsion required intervention on the same day therefore selected the "immediately" option.

In the second hypothetical case involving avulsion of a primary tooth, the majority of physicians were aware that a three-year-old child will have primary dentition. In this situation, approximately half the participants selected informing the parents, instead of referring the patient to a dentist. Moreover, the majority of physicians stated that a primary tooth should not be replanted. The International Association of Dental Traumatology does not recommend replantation of avulsed primary teeth due to the risk of permanent tooth damage (2).

Especially in cases such as avulsion, pediatric patients should be referred to a physician for evaluation of the need for a tetanus booster if the avulsed tooth has come into contact with soil or if tetanus coverage is uncertain (18). In parallel with this information, many participants considered that tetanus vaccination is necessary for emergency intervention in dental injuries.

More than half the physicians felt capable of intervening if they were to encounter a dental trauma. This rate was significantly higher than in Subhashraj (17) study, in which only nine physicians out of 200 were satisfied with their present knowledge on the management of dental injuries. Another study evaluated the confidence levels of physicians in four common dentofacial emergencies, and reported that physicians in emergency departments had the lowest confidence levels in terms of managing dental avulsion injuries (12). Nevertheless, it seems safe to generalize that

EPs require more education about traumatic dental injuries and their treatment. Our results were in agreement with Ulusoy et al. (20) and Bahammam et al. (6), in which most of the physicians were keen to learn more about dental trauma and felt that they required further education on this subject.

In contrast, a previous study reported that participants working in emergency departments in Massachusetts had received official training regarding traumatic dental injury management and therefore possessed excellent knowledge of managing both permanent and primary tooth avulsions (14). This study shows the need for similar training in Turkey.

Study Limitations

The main limitations of this study were that it was conducted using a random sampling method and its small sample size. This limitation may have affected the generalization of the study results.

Conclusion

This study shows a lack of knowledge regarding the immediate treatment of dental avulsions among EPs. Our findings indicate that educational campaigns must be initiated to improve physicians' knowledge regarding the emergency management of traumatic dental injuries.

Local dental organizations should also endeavor to provide the list of dentists who are knowledgeable and willing to be available on a 24-hr basis to the emergency departments. Thus, physicians in emergency departments can consult with these dentists and treat traumatic dental injuries and especially avulsion cases when necessary.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Mersin University (2018/173).

Informed Consent: Participants who agreed to participate in this research with their own consent were included.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: S.Ç., E.D., Design: S.Ç., E.D., Data Collection or Processing: S.Ç., S.K., Analysis or Interpretation: S.Ç., Literature Search: S.Ç., E.D., S.K., Ö.Ö., Manuscript Writing: S.Ç., E.D., S.K.

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

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Original Article

Frequency of Nail Abnormalities in Children and Adolescents Admitted to a Dermatology Outpatient Clinic

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ABSTRACT

Aim: The incidence and spectrum of nail abnormalities in children differ from adults. The aim of this study is to investigate the frequency and spectrum of nail abnormalities in children and adolescents admitted to a dermatology outpatient clinic.

Materials and Methods: This cross-sectional study included 600 patients under the age of 18 who presented at a dermatology outpatient clinic with various dermatological complaints between March and May 2018.

Results: In this study, among 600 patients; 325 (54.16%) were female and 275 (45.84%) were male. The mean age was 9.18±5.12 years (1 month to 17 years). Nail abnormalities were present in 226 patients of whom 131 (58%) were female and 95 (42%) were male. The rate of nail abnormalities was 37.66% (226/600) among the study group. The number of nail abnormalities detected was 288 and the number of abnormality types was 23. The most common group of nail abnormalities were surface (18.16%) and colour (16.50%) changes. The most common nail abnormalities were leukonychia (16.50%), onychoschizia (6.5%), and onychophagia/onychotillomania (6.5%). Fingernail abnormalities were significantly higher in males than females. Leukonychia and onychophagia/onychotillomania were significantly higher in males than females. The rate of patients observed with ungual complaints among the patients with nail abnormalities was 10.61% (24/226).

Conclusion: Nail abnormalities are very common in childhood. Although patients do not have a primary complaint, evaluation of the nails during physical examination may prevent the occurrence of permanent damage to the nails and stop the spread of infectious diseases to other nails.

Keywords: Child, nail abnormality, nail alteration, nail disease, leukonychia, onychophagia

Introduction

Nails have several functions such as providing support for free movement of the fingers, protection against traumas and the picking up of small objects, as well as contributing to cosmetic appearance. Nail abnormalities can lead to psychosocial problems and can affect quality of life negatively.

In childhood, although nail abnormalities are basically similar to those seen in adults, some differences regarding spectrum and frequency are present. Additionally, there are some nail alterations in children which are considered to be physiological and disappear through adulthood. Other than some differences from adults, the distribution of the nail abnormalities also may vary by age in childhood.

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In children, nail abnormalities are rarely causes of consultation and difficulties in diagnosis and treatment are present (1). These abnormalities may be congenital, hereditary or may be acquired (1). In the literature, there are few studies on the prevalence and distribution of nail abnormalities in children (2,3). It is also not clear which nail abnormalities are of major concern for the child/adolescent or parent, and so create a need for expert opinion. The aim of this study is to investigate the frequency and spectrum of the nail abnormalities in children and adolescents, their possible association with skin diseases, and to assess which mostly create a need for expert opinion for the child/adolescent or parent.

Materials and Methods

Study Design and Population

This study was a cross sectional study. The fingernails and toenails of patients under 18 years of age who presented at a dermatology outpatient clinic with various dermatological complaints between March and May 2018 were examined. Other than demographic features, personal habits such as smoking or alcohol use, the presence of previously diagnosed systemic or dermatological disease, nail abnormalities (if present) with details including localization (fingernails and/or toenails), accompanying lesions on the entire skin, and the need for expert opinion were recorded. To evaluate the relation of nail abnormalities with age, patients were grouped as follows; under two years, between two and 11 years, and above 11 years (2).

Before the study, ethical approval was received from the local ethics committee of the university (18-KAEK-044) and written informed consent was obtained from the patients' parents/guardians.

Statistical Analysis

Statistical analysis were performed using Statistical Package for The Social Sciences (IBM SPSS Inc., an IBM Co., Somers, NY). Continuous variables were expressed as mean and standard deviation whereas categorical variables were given as numbers and percentages. Chi-square and Fisher Exact tests were used to compare quantitative variables among groups. A p-value <0.05 was considered as significant.

Results

During the study period, 600 patients were examined for nail abnormalities; and among these, 325 (54.16%) were female and 275 (45.84%) were male. Their mean age was 9.18±5.12 years (1 month-17 years). Two hundred eighty eight nail abnormalities were present in 226 (37.66%) patients of whom 131 (57.96%) were female and 95 (42.04%) were male, there was no significant difference regarding gender (p>0.05).

The number of nail abnormalities detected was 288 and the number of abnormality types was 23. The most frequent abnormality group was those causing nail surface (18.16%) and colour (16.50%) changes and the most common nail abnormalities were leukonychia (16.50%), onychoschizia (6.50%) and onychophagia/onychotillomania (6.50%). The rate of leukonychia was significantly higher in males [51.53% (n=52)] than females [48.47% (n=49)] (p=0.010). Similarly, onychophagia/onychotillomania was significantly higher in males [59% (n=23)] than females [41% (n=16)] (p=0.021). Typical clinical nail abnormalities detected in this study are shown in Figures 1 (a-c)-2 (a-d).

In this study, the most common nail abnormalities were onychoschizia and leukonychia, respectively, under two years of age; whereas leukonychia and onychophagia/

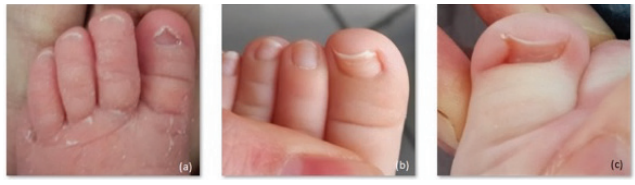

Figure 1. Incomplete development of the nail of the hallux (a); Congenital malalignment of the great toenails (b); Congenital hypertrophy of the lateral nail fold (c)

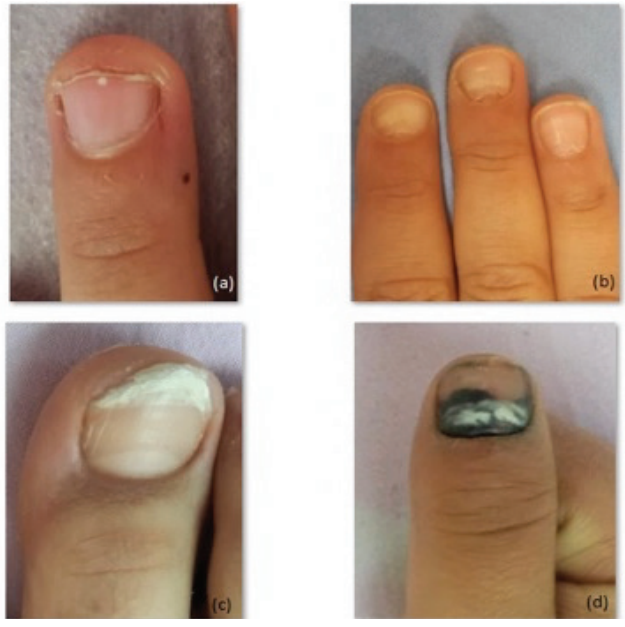

Figure 2. Onychophagia (a); Onychomadesis (b); Onychoschizia (c); Subungual hematoma (d)

onychotillomania were most commonly seen in those patients older than two years of age. The distribution of nail abnormalities by age groups is summarized in Table I.

There were nail abnormalities only on the fingernails in 127 patients (21.16%); only on the toenails in 56 patients (9.33%) and on both in 43 patients (7.16%). In the fingernails, the most common abnormalities were leukonychia [59.41% (101/170)], onychophagia [22.94% (39/170)] and longitudinal ridges [8.82% (15/170)]. In the toenails; onychoschizia [35.35% (35/99)], transverse ridges [24.24% (24/99)] and onychomycosis [11.11% (11/99)] were most commonly seen. Among those patients with nail abnormalities in fingernails; 54.12% (n=92) were female, 45.88% (n=78) were male and this difference regarding gender was statistically significant (p=0.044). The rate of nail abnormalities on the toenails was similar in both genders (p>0.05).

In this study, the nail abnormalities of seven patients (1.2%) were related to their skin diseases. The rate of patients admitted with ungual complaints among those patients with nail abnormalities was 10.61% (24/226).

Discussion

The rate of nail abnormalities among paediatric patients was found to be 37.6% with 23 different types, most of which were leukonychia, onychoschizia, and onychophagia, more commonly observed in males.

The etiology of nail abnormalities in children is various. These include congenital/hereditary causes, tumours,

Table I. The distribution of the nail abnormalities by age groups in the study

Group of nail abnormality	Abnormalities	<2 years (n)	2-11 years (n)	>11 years (n)	Total number of cases
Color changes	Leukonychia	11	48	40	99
Surface changes	Onychoschizia	13	17	9	39
	Transverse ridges	10	9	5	24
	Longitudinal ridges	0	11	9	20
	Pitting	0	10	6	16
	Trachyonychia	0	2	4	6
	Onychomadesis	0	2	0	2
	Beau's lines	1	1	0	2
Traumatic changes	Onychophagia/ onychotillomania	0	24	15	39
	Onychocryptosis	1	1	2	4
	Subungual hematoma	0	4	0	4
	Pyogenic granuloma	0	0	1	1
	Habitual tic deformity	0	1	0	1
	Onycholysis	0	0	1	1
	Onychodystrophy	0	1	0	1
Infectious diseases	Periungual warts	0	8	3	11
	Onychomycosis	2	2	6	10
	Paronychia	0	1	0	1
Contour changes	Koilonychia	1	0	0	1
	Periungual warts	0	0	1	1
Congenital and/or hereditary	IDOTNOTH	1	0	0	1
	CHOTLNF	1	0	0	1
	CMOTGT	3	0	0	3
Total		44	142	102	288

IDOTNOTH: Incomplete development of the nail of the hallux, CHOTLNF: Congenital hypertrophy of the lateral nail fold, CMOTGT: Congenital malalignment of the great toenails

infections, trauma, inflammatory events of nails and systemic diseases (4). Although the prevalence of nail abnormalities in the paediatric population is not known exactly, it has been reported to be approximately 3-11% in a few studies (2,5). In a previous study which included only infants, the rate of nail abnormalities was found to be 6.8% (3). In our study, the rate of nail abnormalities in children and adolescents was found to be 37.7%, which is quite high compared to the rates reported in the literature (2,5). This may be due to different ethnical, environmental and sociocultural factors, but more than these, it is probably because of certain differences between the designs of the studies, the abnormalities considered and the populations evaluated in the studies. Since the studies regarding prevalence or rate of nail abnormalities in children were often retrospective evaluations, nail alterations which are of little clinical significance may not have been considered or recorded (2,6). For instance, leukonychia which was the most common nail abnormality in our study, was either not recorded in any patients or was noted in very few patients in some of the other studies and this was similar for some other abnormalities such as transverse or longitudinal ridges (2,6). As our study was not a population-based study, our results cannot be generalized to the whole paediatric population. Prospective studies with larger series are needed for more definitive knowledge of the prevalence of nail abnormalities in children.

The spectrum of nail abnormalities in childhood and adolescence exhibits some differences from adults. Physiological changes, congenital and hereditary nail abnormalities, bacterial and viral diseases affecting nails are more common in this age group, while fungal infections of the nails are less common than in adults (7). In our study, the most common nail abnormality was leukonychia. Leukonychia is described as white discoloration of the nail plate and basically, it is classified as being true, apparent or pseudo-leukonychia (8). Apparent leukonychia which results from pathologies involving subungual tissue, disappears when pressure is applied. Pseudo-leukonychia is the whitening of the nail due to exogenous factors such as fungal infections (9). True leukonychia does not disappear by applying pressure to the nail plate and depending on the degree of involvement; it is classified as total, subtotal or partial leukonychia. Total and subtotal leukonychia may be related to hereditary, sporadic or systemic diseases (10). Partial leukonychia often results from direct injury to the nail matrix and is grouped according to the clinical appearance as punctate (white spots), transverse (parallel line in the nail plate) or longitudinal (vertical line in the nail plate) leukonychia (10). Among these, transverse leukonychia may be associated with Kawasaki disease, acquired immune deficiency syndrome, chronic renal failure and treatment with chemotherapeutic agents (11-13). In our study, all of the leukonychia cases were in the form of true leukonychia and its subtype punctate (point) leukonychia and it was significantly more common among boys than girls. We thought that this difference may be related to intense traumas that the hands are exposed to due to the higher physical activity of boys during their daily activities.

In our study, the second most frequently observed nail abnormality was onychoschizia which is described as splitting of the distal nail plate into layers from the free edge. It is very common especially in thumbs and great toes (14). Although the etiology is not known exactly, repeated trauma, frequent bathing or use of solvents are thought to be predisposing factors (15).

Onychophagia (nail biting) and onychotillomania (nail picking) are common nail abnormalities in childhood. The rate in children between 7-10 years of age is reported to be 28-33% (16). In our study, the highest rate of onychophagia/onychotillomania was found between the ages of 2 and 11 years. Despite reports in the literature stating similar rates for both genders; in our study, their rates were found to be significantly higher in boys than in girls (17). They should not be considered only as cosmetic problems. In a study evaluating 450 children with a history of onychophagia, it was reported that 74.6% of patients had comorbid attention deficit and hyperactivity disorder, 36% had oppositional defiant disorder and 20.6% had separation anxiety disorder (18). In addition, the temporary shortening of nails, viral or bacterial infections secondary to trauma, and microbial carriage of enterobacteriaceae are complications that may occur secondary to onychophagia. Since onycophagia is very difficult to treat and is often associated with a psychological stress factor in children, removal of the stressor is an important step (18). In our study, the rate of hospital admission of patients with onychophagia/onychotillomania directly due to this complaint was quite low, so we thought that it is important to increase the knowledge and awareness in parents for early diagnosis and treatment of this disease and its comorbid pathologies.

In our study, among the infectious diseases of the nails, the most common pathologies were nail warts and fungal infections. Nail warts were more common in the group of 2-11 years of age whereas fungal infections were more frequent in patients 11 years and older. Onychomycosis is less common in children than adults due to the structural

differences of the nail plate, less trauma, higher growth rate of the nail, less exposure to collective living areas and a lower rate of accompanying tinea pedis infection (19). However, its incidence may be rising due to the increased number of swimming pools, occlusive shoes, immunodeficiency and the presence of fungal disease in family members (18).

Onychomadesis refers to the separation of the nail plate from the nail bed and it may affect the nail entirely starting from the proximal nail fold and may result in the drop and loss of the nail. It is thought to occur as a result of arrest in the growth of the nail matrix and often occurs after systemic diseases or drugs as well as infectious diseases such as hand-foot and mouth disease as in the two cases in our study (20).

In our study, onychocryptosis (ingrown nail) was detected in four children. It is an inflammatory and painful clinical condition resulting from the penetration of the nail into the nail bed (21). Although it is more common in adolescence, it can be seen at any age, even in the neonatal period. Genetic factors, improper cutting of nails (cutting ovally towards the sides) and narrow-tipped shoes are some of the predisposing factors for onychocryptosis.

Congenital hypertrophy of the lateral nail fold was present in one patient in our study. It is a relatively common nail abnormality in children (22,23). It is characterized by hypertrophy of the periungual soft tissue of bilateral great toenails. It can exhibit spontaneous regression over time within the first year of life (24). Although it is a benign condition, it may lead to complications such as onychocryptosis, paronychia and coilonychia.

In the current study, three infants were diagnosed as having congenital malalignment of the great toenail. It is an isolated nail abnormality and described as lateral deviation of the great toenail axis relative to the axis of the distal phalanx (7). It can cause ingrown nail or onychogryphosis. Spontaneous regression occurs in half of the cases.

Another nail abnormality which was present in one infant in our study was incomplete development of the nail of the hallux. It is characterized by a triangular shape of the great toenail and is reported in approximately 50% of the term new-borns (25). It does not cause inflammation or ingrown nail and improves spontaneously in the first few years (26).

Study Limitations

This study has some limitations. As nail abnormalities were not investigated in the general population but only in those patients who presented at a dermatology outpatient clinic, the results of this study cannot be generalized to the general population although the vast majority of the patients did not admit primarily due to ungual complaints. Also, the rate of some abnormalities which exhibit seasonal or national variations could be different due to the study population and period. However, to the best of our knowledge, this is one of the few studies regarding nail abnormalities performed on a relatively large child and adolescent population.

Conclusion

Nail abnormalities are very common in children and adolescents and although patients do not have a primary complaint, evaluation of the nails during physical examination may prevent the occurrence of permanent damage to the nails and stop the spread of the infectious diseases.

Ethics

Ethics Committee Approval: The study, ethical approval was received from the local ethics committee of the university (18-KAEK-044).

Informed Consent: Written informed consent was obtained from the patients' parents/guardians.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.A., Concept: A.A., Design: A.A., Data Collection or Processing: A.A., Z.T., H.Y.S., Analysis or Interpretation: A.A., T.K., Literature Search: A.A., T.K., Writing: A.A., T.K.

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Original Article

Review of Tuberous Sclerosis Complex: A Single Center Experience

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ABSTRACT

Aim: The aim of this study is to review the clinical features and treatment of tuberous sclerosis complex patients followed up in our hospital and to compare our findings with the literature.

Materials and Methods: The clinical-laboratory findings and treatment of 15 tuberous sclerosis patients who presented at a child neurology policlinic between 2007-2017 were retrospectively reviewed.

Results: Fifteen patients aged between 8 months and 17 years were included in the study. The female/male ratio was 47%/53%. Thirteen patients (86%) were referred with convulsions, 1 (7%) with skin hypo-pigmented macule and 1 (7%) with the detection of a renal cyst in ultrasonography. At the time of diagnosis, skin findings were present in 93% of the patients. There were infantile spasms in 23%, focal seizures in 54%, generalized tonic-clonic in 15% and atonic seizures in 8% of those patients who referred with seizures. In addition to the known antiepileptics in treatment, mTOR inhibitors were used in two patients. Forty percent were diagnosed with resistant epilepsy. Seven of the patients (46%) had various levels of mental retardation. There were cardiac findings in 33%, ocular findings in 33%, and renal involvement in 27% of the patients. The most common (87%) neuroradiologic finding was subependymal nodule.

Conclusion: It was observed that the signs and symptoms of our patients were compatible with the literature. In childhood, refractory epilepsy and mental retardation were the most important clinical findings. The age of onset of seizures in patients with resistant epilepsy was under one year of age. These patients had infantile spasms and a larger number of cortical tubers in cranial magnetic resonance imaging findings. It was observed that everolimus treatment had no marked effect on seizure frequency. However, patients with tuberous sclerosis should be closely monitored for the development of malignancies in the long term and this monitoring should be continued in adulthood.

Keywords: Childhood, tuberous sclerosis complex, clinical-laboratory findings-treatments

Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant inherited genetic disease in which multiple organ involvement is characterized by common hamartomas in many organs especially including the brain, skin, heart, eye, kidney, lung and liver. TSC is due to programmed hyperplasia of ectodermal and mesodermal cells, which is characterized by epilepsy, adenoma sebaceum and mental retardation. It has a variable age of onset and variable clinical severity. About 2/3 of these cases are formed via spontaneous mutation. Due to mutations in the *TSC1 (9q34)* and *TSC2 (16p13.3)* genes respectively, the functions of the hamartin and tuberin proteins encoded by these genes are impaired. The mammalian target of hamartin-tuberin proteins is to

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inhibit (mTOR) the signal pathway of rapamycin and thereby control cell growth and proliferation. Clinical findings occur with the impaired inhibitor function of these proteins. Its diagnostic criteria were restructured at the International Tuberous Sclerosis Consensus Conference in 2012. (Table I) (1).

The aim of this study is to review retrospectively the clinical features and treatments of TSC patients who had been referred to our hospital and to compare our findings with the literature.

Materials and Methods

Fifteen patients diagnosed with tuberous sclerosis who presented at the Pediatric Neurology Policlinic of Aydın Adnan Menderes University Faculty of Medicine between 2007 and 2017 were included in this study. The age, gender, neurological and systemic examinations, the age of onset of convulsions, seizure types, interictal electroencephalography (EEG), cranial magnetic resonance imaging (MRI), abdominal ultrasonography (USG), echocardiography (ECHO) and ocular findings of these patients were evaluated. The seizure classification was carried out according to family testimony, observed seizure activity and classification of the International League Against Epilepsy.

Statistical Analysis

The SPSS 17.0 package program was used in the statistical analyses. Descriptive statistics was utilized, categorical variables were expressed as frequency and percentage. This is a retrospective file scanning study, so informed consent forms were not obtained from the patients. This study was approved by the Aydın Adnan Menderes University Medical Faculty Ethics Committee (date: 10.05.2018, approval number: 2018/1396).

Results

Fifteen patients (8 male/53%) were included in the study, ranging in age from 8 months to 17 years. The age of the patients at diagnosis was between 2 months and 9 years, consistent with the age at which they were referred to the clinic. Six of the patients (40%) were diagnosed before one year of age, 3 patients (20%) between 1 and 5 years, and 6 patients (40%) at 5 years of age or over. The most common reason for referring to the clinic was convulsion for 13 patients (86%) as well as skin lesions for 1 patient (7%) and renal cyst for 1 patient (7%).

There were skin findings of TSC in 14 patients (93%) at the time of diagnosis. Hypopigmented skin lesions were found in all 14 of these patients, adenoma sebaceum in 5 patients (33%) and ungual fibroma in 2 patients (13%).

Infantile spasms were detected in 3 (23%) of 13 the patients with seizures. The average age of those patients with infantile spasms was 8 months. The first preferred antiepileptic was vigabatrin for those patients with infantile spasms. Seizure control with vigabatrin was achieved in only one patient. There were no seizures in 2 patients treated with ACTH, for 1 month and 7 months respectively. One of these patients was seizure-free for one year with a ketogenic diet, but later focal seizures which were controlled with vigabatrin and topiramate developed. There were 7 patients with focal seizures (54%). Three patients were treated with phenobarbital, 1 patient with vigabatrin, 1 patient with

Table I. Tuberous sclerosis diagnostic criteria (1)

Major findings	Minor findings
1. Hypomelanotic macule, "ashleaf sign" (≥3, minimum 5 mm diameter)	1. Confetti skin lesions
2. Angiofibromas (≥3) or fibrous cephalic plaques	2. Numerous cavities in the tooth enamel (≥3)
3. Ungual fibroma (≥2)	3. Intraoral fibroma (≥2)
4. Shagreen patch	4. Hypopigmentation in the retina
5. Multiple retinal hamartomas	5. Multiple renal cysts
6. Cortical dysplasia	6. Non-renal hamartoma
7. Subependymal nodules	-
8. Cardiac rhabdomyoma	-
9. Subependymal giant cell astrocytoma	*Final diagnosis: 2 major findings or 1 major + ≥2 minor finding
10. Lymphangioleiomyomatosis (LAM)	**Possible diagnosis: 1 major or ≥2 minor findings
11. Angiomyolipomas (≥2)	A combination of the 2 major features (LAM and angiomyolipomas) without features does not meet criteria for definite diagnosis

carbamazepine, 1 with levetiracetam and 1 patient with valproate as the first antiepileptic treatment. The patient who received carbamazepine treatment was followed up without medication for 1.5 years and the 13-year-old patient who received valproate treatment was followed-up without medication for 10 years. Two patients had generalized tonic-clonic seizure (15%) and one patient had atonic seizure (8%). In 7 patients, seizure control was provided with polytherapy and 5 patients were followed with drug resistant epilepsy. The best response to anti-epileptic treatment in those patients with drug resistant epilepsy was achieved with vigabatrin and clobazam dual therapy. No response to therapy was observed in the two patients with drug resistant epilepsy who received everolimus (0.1 mg/kg/day max. 10 mg/day) (Table II).

Seven of the patients (46%) had mental retardation. Obsessive compulsive disorder was detected in one patient and two patients had autism.

Rhabdomyoma was detected in 5 (33%) of the patients by ECHO. The earliest age for the diagnosis of rhabdomyoma was 2 months and latest age was 11 years.

Table II. Cranial MRI and EEG findings in tuberous sclerosis patients

No	Age at diagnosis	Number of cortical/ subcortical tubers	Subependymal nodule	Other MRI findings	First EEG	Follow-up EEG	AED
1	6 years	2	2	Radial migration line	Centro parietal	Parietotemporal	VGB, LEV
2	3 years	1	-	-	Right frontal	No epileptic activity	-
3	4 years	7	4	-	No epileptic activity	No epileptic activity	CBZ
4	8 month	11	2	-	Focal-generalized	Hypsarrhythmia left parasagittal	PB, VGB, ACTH, CBL
5	10 months	9	2	-	Right parasagittal	Generalized	VGB, LEV, CBL
6	2 months	5	2	-	No epileptic activity	Bilateral temporal	VGB, VPA, CBL
7	5 years	14	6	Cerebral atrophy, SEGA	Left temporal	Bilateral frontal-centrotemporal	VGB, LEV, CBZ, TPM, CBL, VPA, LCS, ZNS, EVL
8	9 months	9	4	-	Hypsarhythmia	Left parietal	VGB, ACTH, KETOGENIC DIET, TPM
9	6 years	5	3	-	Right frontal	No epileptic activity	-
10	5 years	7	4	-	Right parietoocpital	No epileptic activity	VPA, OXCBZ, CBL
11	2 months	9	2	-	Hypsarrhythmia	Right parieto occipital	PB, VGB, CBL
12	5 years	13	2	Venous angioma	Generalized	Right frontal	VPA, OXCBZ, LEV, CBL
13	5 months	7	3	Thin corpus callosum	Hypsarrhythmia	Left temporoparietal	VGB, ACTH, CBL
14	5 years	6	1	Cerebral atrophy	Left parietooccipital	Fokal-generalized	LEV, VPA, CBL
15	2 years	14	-	-	Right frontal	Hypsarrhythmia right frontal	LEV, VGB, VPA, CBL, TPM, CLN, RFM, EVL

MRI: Magnetic resonance imaging, EEG: Electroencephalography, SEGA: Subependymal giant cell astrocytoma, AED: antiepileptic drug, CBZ: Carbamazepine, VGB: Vigabatrin, LEV: Levetiracetam, PB: Fenobarbital, ACHT: Adrenocorticotropic hormone, CBL: Clobazam, VPA: Valproic acid, TPM: Topiramate, OXCBZ: Okskarbazepin, EVL: Everolimus, RFM: Rufinamide, CLN: Clonazepam

Findings of ocular involvement of TSC were detected in 5 of the patients (33%). Two of them (13%) had retinal hamartoma, one had retinoblastoma, astrocytoma and a hypo-pigmented area in the retina.

In the renal USG, Angiomyolipomas was determined in 4 (27%) patients and two of them were bilateral.

Cortical/subcortical tubers and/or subependymal nodules were detected in all patients. The most common finding in cranial MRI was subependymal nodules (87%). Subependymal giant cell astrocytoma (SEGA) developed in one of the cases (Table II).

Discussion

TSC, which affects many systems including the brain, skin, kidney, eye and heart, was first described by Bourneville in 1880 (2,3). Its incidence is estimated to be 1 in 5.800 (4). The most common neurological complication is convulsion, which occurs in about 90% of patients and begins in the first year of life in 1/3 of patients (5,6). Consistent with the literature, epilepsy was present in 87% of our cases and seizures started in the first year of life in 46%. Infantile spasms, which are seen in 30-60% of TSC, were the first referral cause in 23% of our cases (6-8).

Skin manifestations are common in TSC. The most common skin findings are hypopigmented macules. Usually lesions are seen from birth, while they become more apparent in the first years of life (9,10). Adenoma sebaceum is usually observed in the adolescence period (8,11,12). Hypopigmented skin lesions were present in 93% of our patients and adenoma sebaceum in 33%, skin lesions were not detected in only one 8-year-old patient.

The most common cardiac finding in TSC is rhabdomyoma, one of the tumours with a good prognosis found in 60-80% of cases (13-15). Cardiac rhabdomyomas are detected during the antenatal period or infancy and then stabilization or spontaneous regression is observed with age. The development of a new cardiac rhabdomyoma after infancy is very rare. In one study, a patient at the age of 2 years with rhabdomyoma was presented requiring a new resection after a rhabdomyoma resection as a new-born (16). Rhabdomyomas are usually asymptomatic but may cause atrial or ventricular arrhythmias, sinus node dysfunction and heart block. Even if these cases are asymptomatic, it is necessary to observe new rhabdomyomas and cardiac conduction defects that may develop in follow-up (17,18). There was rhabdomyoma in 33% (5 patients) of the patients in our study. Regression was observed in 3 patients and there was no change in size in 2 patients.

The most common renal lesions are Angiomyolipomas and renal cysts. Renal angiomyolipomas occur in about 50% of the patients (19). While the frequency of angiomyolipomas increases with age, there is no such relationship in renal cysts (20). Renal involvement was detected in 27% of our patients, lower than the rate reported in the literature. This was related to the young age of our patients.

Ocular findings of patients with TSC include retinal and non-retinal lesions. Retinal hamartomas remain stable for many years and rarely affect vision. Non-retinal lesions consist of depigmentation in the iris, choroid coloboma, and eyelid angiofibromas. Eye findings were reported at different rates in the literature. Retinal hamartoma was found in 44%,10.2% and 25% in different studies (21,12,22). In a cohort study in the United States, they were seen in approximately 50% of patients (23). There were findings of ocular involvement in 33% of our patients.

Cranial lesions in TSC are developmental anomalies such as cortical tubers, subependymal nodules, heterotopic grey and white matter abnormalities, and SEGA. It has been reported that cortical tubers are seen at a rate of 82-100%, and subependymal nodules at a rate of 50-100% (7,24). When the cranial MRI findings of our cases were examined, the incidence of the cortical tuber (93%) and subependymal nodule (86%) was consistent with the literature. Giant cell astrocytomas are seen in 10-15% of patients with TSC and frequently in the first 20 years. In one study, the mean age of diagnosis of SEGA was 13.3 years (25). Therefore, yearly MRI scans up to 21 years of age are recommended (25-27). In one of our patients, SEGA was detected at the age of 11 years.

In TSC, mental retardation is reported at a rate of about 50% (5,28). There was a significant relationship between the average number of cortical tubers of more than 7-10, the presence of these tubers in the occipital lobe, the presence of infantile spasm in the history and the learning disability (29,30). Various levels of mental retardation were detected in 46% of our patients. The cortical tuber number was between 9 and 14 in cranial MRI in our patients with infantile spasm and learning disability. These cortical tubers were mostly located in the occipital region. The cortical tuber numbers in patients without learning disabilities were between 1 and 5.

The association of autism with TSC has been reported at a rate of 25-50% (31,32). Early-onset of seizures is also associated with severe cognitive impairment and autism-like behavior (6,33). In our cases, obsessive compulsive disorder was detected in one patient and two patients had autism. The fact that it was detected less than the literature

may be associated with the low number of patients in our study.

Epilepsy is the most common neurological finding in patients with TSC (6). The most common types of seizures are infantile spasm or focal seizures, but most of them also have other types of seizures, such as tonic, clonic, tonic-clonic, myoclonic, atonic, and atypical absences (34). Infantile spasms can also turn into epileptic spasms (6,35). Focal seizures were mostly commonly observed in our patients (40%). The earliest seizure onset age was 1 month and the average age was 16 months. The presence of epileptic activity in EEG was found to be 76% (28.5% focal, 9.5% generalized, 38% hypsarrhythmia) in one study (7). Epileptic activity was detected in 80% of our patients (47% focal, 13% generalized, 20% hypsarrhythmia). The presence of early onset seizures in children with TSC increases the risk of developing resistant epilepsy and/or epileptic encephalopathy. It was shown that 42% of children who were diagnosed with TSC before the age of 2 years developed drug resistant seizures (6). In a meta-analysis, vigabatrin was found to be effective in 95% of cases with infantile spasms (36). However, visual field defects (incidence 30-40%) limits the usage of the drug (37,38). Valproate and topiramate have similar efficacy for infantile spasm. Vigabatrin can be used as a single agent in infantile spasm and add-on therapy can be applied when drug resistance develops (38,39). Benzodiazepines such as nitrazepam and clonazepam are rarely efficient as a single agent for infantile spasm and are often used as adjunctive therapy or rescue medication. Antiepileptic drugs such as topiramate, lamotrigine, levetiracetam, zonisamide, and carbamazepine were found effective in preventing seizures or reducing seizure frequency in other seizure types in TSC (40,41). Felbamate is a useful for individuals with partial-onset refractory partial seizures, especially together with vigabatrin (42). It has also been shown that clobazam is a potential beneficial agent in TSC (43). More than 20% of patients with TSC can develop drug resistance epilepsy. For these patients, ketogenic diets, vagal nerve stimulation and resective epilepsy surgery are increasingly used (44). An over 50% reduction in seizures was observed in 11 of 12 refractory epilepsy patients who received ketogenic diet (45). In a study on epilepsy surgery, 37 out of 70 patients (53%) were seizure free and a further 8 (11%) had a significant decrease in seizure frequency (46).

In our patients, the best response to anti-epileptic treatment in patients with resistant epilepsy were achieved with vigabatrin and clobazam dual therapy. At a rate of 40%, seizures resistant to treatment continue. The age of onset of seizures in patients with resistant epilepsy is under 1 year of age and prevalent for those who have a large number of cortical tubers in their cranial MRI findings. Increasing evidence suggested that mTOR inhibitors may be useful in the treatment of epilepsy in TSC. mTOR is a serine/threonine kinase belonging to the phosphotidylinositide 3-kinase (PI3K)-related protein kinase family. It plays an important role in the regulation of a number of cellular functions, including particularly cell growth, metabolism and proliferation and in the maintenance of cellular homeostasis. Glutamate, an excitatory neurotransmitter and subclinical epileptiform discharges increase mTOR activity. mTOR regulates long-term synaptic potency, depression and epileptogenesis learning and memory formation (47,48).

Many investigators have found an improvement in learning disability, seizure frequency, survival and motor development for TSC-related mice, following treatment with everolimus or rapamycin (mTOR inhibitors) (47,49). In non-TSC animal models, rapamycin inhibits epileptogenesis in post-traumatic epilepsy (50). Significant reduction in seizure frequency was observed in treatment with rapamycin in patients with TSC (51). In one study, 5 out of 7 patients with resistant epilepsy treated with rapamycin were seizure-free after 6 months of treatment (52). In a multicentre study, everolimus as an adjunctive therapy for treatment-resistant focal onset seizures was compared with a placebo. A significant decrease in seizure frequency was found (53). Another randomized controlled study showed that sirolimus treatment resulted in a 41% reduction in seizure frequency (54). In our study, two refractory epilepsy patients received everolimus but no marked change in seizure frequency was achieved.

Study Limitations

This study has small number of patients with TSC and the lack of a longer follow-up term, including into adulthood are considered to be the limitations of our study.

Conclusion

We found that the clinical features, organ involvement, and treatment resistance of our patients were not different from the literature. The onset age of seizures in patients with resistant epilepsy was under 1 year of age and they had a larger number of cortical tubers in their cranial MRI findings. Patients with tuberous sclerosis should be closely monitored for the development of malignancies due to defective tumor suppressor genes. The need for this observation should be continued in adulthood

especially in terms of giant cell astrocytoma in patients with subependymal nodules, cardiac conduction defects in patients with rhabdomyoma, and for the development of "lymphangioleiomyomatosis" in women.

Ethics

Ethics Committee Approval: This study was approved by the Aydın Adnan Menderes University Faculty of Medicine Ethics Committee (date: 10.05.2018, approval number: 2018/1396).

Informed Consent: This is a retrospective file scanning study, so informed consent forms were not obtained from the patients.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: A.T., A.A., Design: A.T., Data Collection or Processing: B.K.Y., Supervision: A.A., Writing: A.T., B.K.Y.

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

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Original Article

Pediatric Pain Management Knowledge Scale for Nursing Students: Assessment of the Psychometric Properties

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ABSTRACT

Aim: This study was designed to determine the psychometric properties of the scale developed to evaluate the pediatric pain management knowledge (PPMK) and the skills of nursing students.

Materials and Methods: This is a methodological study conducted to develop the PPMK scale for nursing students. A 29-item scale was administered to a total of 343 nursing students who were in their 3rd year taking the pediatric nursing course or in their 4th year carrying out their internship training at a state university. The scale items were selected through item-total score correlation analysis, and the sensitivity and specificity of the scale were evaluated using receiver operating characteristic analysis.

Results: The students' mean age was 21.92±1.150 years and 76.2% were female. As a result of explanatory factor analysis, the scale consisting of six subscales was found to explain 50.30% of the total variance. The fit indexes of confirmatory factor analysis were calculated to be root mean square error of approximation 0.063, goodness of fit index 0.85, comparative fit index 0.93, incremental fit index 0.93, relative fit index 0.86, normed fit index 0.88, and Tucker-Lewis index 0.92. The Cronbach alpha coefficient of the entire scale was determined to be 0.864. The correlations of the scale items with the scale total score ranged between 0.285 and 0.625.

Conclusion: In this study, it was determined that the PPMK scale was a valid and reliable tool for nursing students. It is recommended that after the students' knowledge level is determined using the current measurement tool for PPMK, the nursing curriculum should be revised and enriched, and further studies should be conducted on this topic.

Keywords: Nurse, student, pediatrics, pain, knowledge

Introduction

One of the most common symptoms in childhood, pain is an important problem affecting children's growth, healing, mental health, and life quality. In cases where pain cannot be controlled, children, their families, and the community may suffer physiologically, psychosocially, and economically (1). Successful pain management can provide an increase in children's life quality and satisfaction, early mobilization, a shortening of in hospital stay, a decrease economically in treatment costs, and an acceleration in the healing process (2-4).

It is known that children are more sensitive to pain that stems from illness, surgery, and medical procedures

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(5,6). However, it is extremely difficult to recognize, diagnose, and evaluate pain in children, which challenges the healthcare staff most. Studies in the literature show that nurses working with the pediatric group experience various difficulties and inadequacies in this regard (7-11). It is emphasized in the World Health Organization's 2012 report that pediatric pain is not sufficiently recognized or even ignored by healthcare professionals (12). Therefore, nurses have an important role in the evaluation and management of children's pain during hospitalization. Nurses' knowledge about pain, their behaviors, and self-efficacy in pain management affect nursing care (6). Nursing education is important in making correct pain assessments and follow-ups. It is vital for student nurses to take an inclusive education about pain before their professional life (13-15). In studies evaluating the knowledge and attitudes of nursing students taking pediatrics courses about pediatric pain, it has been determined that students had poor knowledge about pain assessment, and pharmacological and non-pharmacological pain management (6,9,14-17).

It is possible to improve and develop the existing curriculum and teaching methods used in nursing schools by evaluating the quality of education and monitoring the students' level of pain knowledge. Strengthening the pediatric pain management (PPM) education in this regard can lead to successful practices in professional life (6,15,18). In the literature, there are scales developed or adapted to measure nurses' and student nurses' knowledge and attitudes regarding PPM. It has been found that there are very few measurement tools for the evaluation of pediatric pain management knowledge (PPMK) and competencies of student nurses in particular. One of them is the Pediatric Nurses' Knowledge and Attitude Survey Regarding Pain (PNKAS) developed by Manworren (19), which is the modified form of the Nurses' Knowledge and Attitude Survey Regarding Pain created by McCaffery and Ferrell (1997). PNKAS has been used for nursing students in various studies after it was adapted for pediatric nurses (9,16).

Another measurement tool is "The Knowledge and Attitudes of Pain Management Questionnaire" consisting of scenarios and questions about pediatric pain, which was developed by MacLaren et al. (20) to determine the effectiveness of an education program. When both measurement tools were assessed, it was observed that the scales were not up to date, the main focus to control pain was on the use of cognitive-behavioral strategies, the pharmacological dose questions were not suitable for student nurses who had no clinical experience, and that non-pharmacological pain control methods using current technologies such as virtual reality were not addressed (19,20). Therefore, the necessity of developing a scale for all components of PPM including pain awareness, pain pathophysiology, pain management barriers, diagnosis, evaluation, and control of pain has arisen. This scale was designed under the current literature and guidelines, to fit the growth and development characteristics of children, and to cover all the bases of parents and family (12,19-23).

The tools developed for student nurses can measure the knowledge and skills of PPM and evaluate the effectiveness of the basic PPM education and the quality of pain management in practice. However, there is no valid and reliable measurement tool to evaluate the PPMK of student nurses in our country. In the light of the findings of current studies, it was determined that there was a need to develop a valid and reliable scale to evaluate the knowledge and qualifications of students and cover all types of pain and pediatric care areas in children to eliminate the educational shortcomings of nursing students in PPM.

The aim of this study was to develop a valid and reliable measurement tool to assess the knowledge and qualifications of student nurses in PPM. The research question of this study is as follows:

Is the PPM scale for nursing students a valid and reliable tool in determining the student nurses' pain management knowledge level of children?

Materials and Methods

Study Design, Sampling, and the Population

This study used a methodological, descriptive, and cross-sectional design to develop "the PPM scale for nursing students" and carry out its validity and reliability studies.

While the sampling size is determined in validity and reliability studies, three rules, namely the 5s, 10s, and 100s rules, are mentioned in the literature. It is emphasized that the researcher should recruit at least five people per item when carrying out factor analysis (24). In the literature, it has been reported that a sampling size less than 100 is considered as insufficient for developing a scale, 100-200 as medium, 200-300 as good, 300-500 as very good, and 500-1.000 as excellent (25,26). This study was conducted with 3rd year students taking a pediatric nursing course and 4th year students carrying out their internship training in the field of pediatric nursing in the spring semester of the 2017-2018 academic year at the Nursing Faculty of a state university. A total of 344 students who agreed to participate in the study voluntarily and filled in the forms were included in the study.

Socio-demographic Characteristics

The mean age of the students participating in the study was 21.92 years (±1.150, range=19-26). 76.2% of the participants were female and 76.7% of them had a medium grade point average (50-79). 59.6% of the participants had not had education in PPM prior to the study. 96.6% of those who had received PPM education stated they had received it at school as part of the curriculum. It was identified that the majority of the participants (98.8%) had graduated from a non-health high school (Table I).

Data Collection Tools

• **Demographic Data Form:** This is an 8-item form that includes the students' grade point average, age, gender, marital status, the high school which they graduated from, previous PPM training, and type of training if taken and current level of PPM.

• **Pediatric Pain Management Knowledge Scale for Nursing Students:** This 5-point Likert type scale aiming to measure the PPMK of student nurses was developed by the researchers in light of the related literature (8,23,27-37). The scale consists of 29 items that address the six dimensions of PPM. The scale consists of six subscales for assessing student nurses' knowledge levels and qualifications for pain awareness, pain physiopathology, barriers to pain management, pain diagnosis, assessment, and control of pain. The subscales, items, and answers are as follows. The first subscale addresses pain awareness and it has six items (M1, M2, M5, M6, M7, M50) such as "Babies can't perceive pain." (Correct response: I strongly disagree). The second subscale deals with pain physiopathology and it has four items (M8, M9, M44, M45) such as "Attention, emotion, and memory affect the transmission of pain." (Correct response: I strongly agree). The third subscale is "barriers to pain management" and it has eleven items (M10, M11, M12, M13, M14, M15, M16, M17, M19, M21, M22) such as "The child who maintains his/her activity has no pain." (Correct response: I strongly disagree). The fourth subscale addresses pain diagnosis and it has two items (M24, M25) such as "If the child or his/her mother/caregiver says they have pain, then they have pain." (Correct response: I strongly agree). The fifth subscale is about pain assessment and it has two items

Table I. Demographic data of the nursing students (n=344)

Demographic data	n	%	M	SD
Grade point average			2.23	0.423
50-79 80-100	264 80	76.7 23.3		
Age			21.92	1.150
19-22 23 and over	254 90	73.9 26.1		
Gender			-	0.427
Female Male	262 82	76.2 23.8		
Marital status			-	0.54
Married Single	1 343	0.3 99.7		
High school			-	0.107
Health vocational high school Other	4 340	1.2 98.8		
Previous pain education			-	0.497
Yes No	139 205	40.4 59.6		
Type of the eduation			-	1.486
Course Seminar Lesson Congress	0 3 141 2	0.0 2.1 96.6 1.3		

SD: Standard deviation

(M28, M29) such as "For patients who cannot communicate verbally, physiological and/or behavioral pain assessment scales could be used." (Correct response: I strongly agree). The sixth subscale is pain control and it has four items (M30, M33, M46, M47) such as "The treatment of pain is a patient right." (Correct response: I strongly agree). The scale items were rated using a 5-point Likert scale ranging from 1 to 5 (1: Strongly disagree; 2: Disagree; 3: Undecided; 4: Agree; 5: Strongly agree). The lowest score that can be obtained from the scale is 29, and the highest score is 145. An increase in scores indicates that the students have more information about PPM.

Ethics Approval

To conduct this research, approval of the Non-invasive Research Ethics Committee of the University from the Nursing Faculty (IRB: 3970-GOA/2018/11-18) and the nursing faculty, and the written and verbal informed consent of the participants were taken. At the beginning of the study, the aim and procedures were stated to the participants by the researcher, their approval was obtained and they were assured that their knowledge scores would not affect their school grade points. It was stated that the participation of the students in the study was on a voluntary basis and they would be allowed to leave without stating a reason at any stage of the study.

Study Procedure

All the students included in the study were attending the nursing faculty of a university. They were taking a pediatric nursing course (3rd grades) or carrying out their internship training (4th grades). After the students were informed in a classroom by the researcher at the end of the semester, they were asked to fill in the required forms. These forms which took approximately 30-40 minutes to complete were collected by the researcher.

Data Collection and Statistical Analysis

The development stages of the PPM Scale for nursing students were as follows.

• **Determination of Draft Scale Items:** A literature review was conducted to develop the PPM Scale for Nursing Students. A draft scale item pool consisting of 51 items was formed using relevant databases and the literature.

• **Obtaining Expert Opinions:** Content validity refers to the extent to which the scale as a whole and each item in the scale serve the purpose. Gözüm and Aksayan (38) stated that the draft prepared for the content validity should be submitted to the opinions of at least three experts and that these experts should come together to present their opinions after making an independent evaluation. After this process, items that fall below the minimum consistency limit should be removed from the scale or rearranged (38). In this study, the draft scale was submitted to expert opinion for content validity. The expert group consisted of 12 faculty members working in pediatric nursing departments of various universities in our country. The scale was sent to these experts via e-mail and they were asked to score each item between 1 and 5 (1: Not appropriate - 5: Fully appropriate) to assess the eligibility of the items. The consistency between the experts participating in the evaluation process was assessed by the content validity index (CVI).

• **The Pilot Test of the Draft Scale:** It is recommended that after expert opinions are obtained, the scale should be administered to a group of about 10-20 people who have similar characteristics with the subjects of the study but will not be included in the sampling of the study (24,39). The draft scale, which was revised based on expert opinion, was administered to 10 students who met the characteristics of the study sample. At the end of the pilot test, no negative feedback was received regarding the comprehensibility of the items, therefore the researchers decided to use the scale without any modification.

• **Reliability Calculations:** Pearson correlation analysis was used for the item total score analysis of the scales and subscales, and inappropriate items were removed from the scale by considering the correlation value 0.20 (24,39). 14 items including M20, M26, M31, M32, M34, M35, M36, M37, M39, M40, M41, M42, M48, and M51 were removed from the scale. Cronbach's alpha coefficient was calculated to determine the internal consistency of the scale and subscales (24,38-40).

• **Validity Calculations:** Explanatory factor analysis was used to determine the item-factor relationship, and confirmatory factor analysis was employed to see whether the items and subscales explained the original structure of the scale. The items whose factor loads were below 0.30 were removed from the scale (24,38-40). After implementing the explanatory factor analysis, 8 items including M3, M4, M18, M23, M27, M38, M43, and M49 were removed from the scale. Time-invariance was analyzed by t-test and Pearson correlation analysis in dependent groups.

Statistical Analysis

The following calculations, tests, and analyses were employed in the study: percentage and mean calculations for descriptive statistics; Shapiro-Wilk normality test for

determining if the data conform to normal distribution; CVI for consistency analysis of the expert opinions; Pearson correlation analysis for item-total score analysis of the scale and subscales; Cronbach's alpha coefficient for determining the internal consistency of the scale and subscales; explanatory factor analysis for determining item-factor relationship; confirmatory factor analysis to determine whether the items and subscales explain the original structure of the scale; t-test for known group comparison; Pearson correlation analysis for determining the relationship between the factors of the scale; and paired sample t-test and Pearson correlation analysis for evaluating test/retest. In the evaluation of the data, the error margin was taken as p=0.05.

Results

Content Validity

The CVI was determined to be between 0.99 and 1.00 on the item-based content validity index (I-CVI) and 0.99 on the scale-based content validity index (S-CVI).

Explanatory Factor Analysis (EFA)

As a result of the EFA, the Kaiser-Meyer Olkin (KMO) coefficient was found to be 0.858, the Bartlett test X^2 value as 2,715.733, and p=0.000. As a result of EFA, it was determined that the scale consisted of six subscales. The scale explained 50.30% of the total variance. The first subscale (awareness) of the scale was found to explain 23.042% of the total variance, the second subscale (physiopathology) 8.420%, the third subscale (barriers) 5.643%, the fourth subscale (diagnosis) 4.914%, the fifth subscale (assessment) 4.496%, and the sixth subscale (control) 3.785%. Table II shows the EFA results of the scale.

The factor loadings of the "awareness" subscale were between 0.402-0.516; those of the "physiopathology" subscale were between 0.363-0.535, those of the "barriers" subscale were between 0.300-0.540, those of the "diagnosis" subscale were between 0.368-0.471, those of the "assessment" subscale were between 0.557-0.622, and those of "control" subscale were between 0.552-0.687 (Table II).

Confirmatory Factor Analysis (CFA)

The calculated chi-square value of the six-factor model was found to be 844.06, the degree of freedom was 356, and p=0.000. The X^2/standard deviation section was determined to be 2.370. The fit indexes were calculated to be root mean square error of approximation (RMSEA)=0.063, goodness of fit index (GFI)=0.85, comparative fit index (CFI)=0.93, incremental fit index (IFI)=0.93, relative fit index (RFI)=0.86, normed fit index (NFI)=0.88, and TLI=0.92 (Table III).

As a result of the CFA, the factor loadings of the "awareness" subscale was found to be between 0.35-0.52, those of the "physiopathology" subscale were between 0.26-0.51, those of the "barriers" subscale were between 0.27-0.59, those of the "diagnosis" subscale were between 0.46-0.62, those of the "assessment" subscale were between 0.46-0.54, and those of the "control" subscale were between 0.58-0.70 (Figure 1).

In Table IV, the mean total score of the upper group, which accounted for 27% of the group, was 132.98+4.35, while it was 104.60+8.16 for the lower group. The difference between the mean scores of the groups was statistically significant (p=0.000).

Hotelling's T squared test was used to reveal whether there was a response bias and the values for the test were found to be 1626.983, F=53.533 and p=0.000. As a result of this test, it was determined that there was no response bias in the scale. The additivity feature of the scale was analyzed using Tukey additivity analysis and it was determined to be F=3.077 and p=0.079. Therefore, the scale was found to be summable.

Cronbach's alpha coefficient of the entire scale was 0.864. The alpha values of the subscales were 0.635 for the "awareness" subscale, 0.425 for the "physiopathology" subscale, 0.734 for the "barriers" subscale, 0.445 for the "diagnosis" subscale, 0.394 for the "assessment" subscale, and 0.766 for the "control" subscale. As a result of the split-half analysis, the Cronbach's alpha value of the first half was 0.791 and that of the second half was 0.746. The Spearman-Brown coefficient was 0.825. The Guttman-split-half coefficient was 0.822. The correlation coefficient between the two halves was found to be 0.703. There was no floor effect for the entire scale and there was a ceiling effect at the limits in the assessment and control subscales. These values are given in Table V.

The correlations of the scale items with a total score of the scale ranged between 0.285 and 0.625. The item-subscale total score correlations were between 0.450-0.632 for the "awareness" subscale, 0.557-0.622 for the "physiopathology" subscale, 0.383-0.645 for the "barriers" subscale, 0.745-0.852 for the "diagnosis" subscale, 0.708-0.858 for the "assessment" subscale, and 0.700-0.807 for the "control" subscale (Table VI).

Table II. The results of explanatory factor analysis (n=344)

Items	Factor loads of the subscales					
	Awareness	**Physiopathology**	**Barriers**	**Diagnosis**	**Assessment**	**Control**
M1	0.451					
M2	0.453					
M5	0.402					
M6	0.516					
M7	0.465					
M50	0.499					
M8		0.363				
M9		0.535				
M44		0.497				
M45		0.371				
M10			0.364			
M11			0.455			
M12			0.473			
M13			0.359			
M14			0.540			
M15			0.300			
M16			0.357			
M17			0.406			
M19			0.433			
M21			0.300			
M22			0.450			
M24				0.471		
M25				0.368		
M28					0.557	
M29					0.622	
M30						0.663
M33						0.552
M46						0.583
M47						0.687
Explained variance (%)	23.042	8.420	5.643	4.914	4.496	3.785
Overall explained variance (%)	50.30					
Eigenvalue	6.682	2.442	1.637	1.425	1.304	1.098
KMO	0.858					
Bartlett X^2 (p)	2715.733 (0.000)					

KMO: Kaiser-meyer olkin

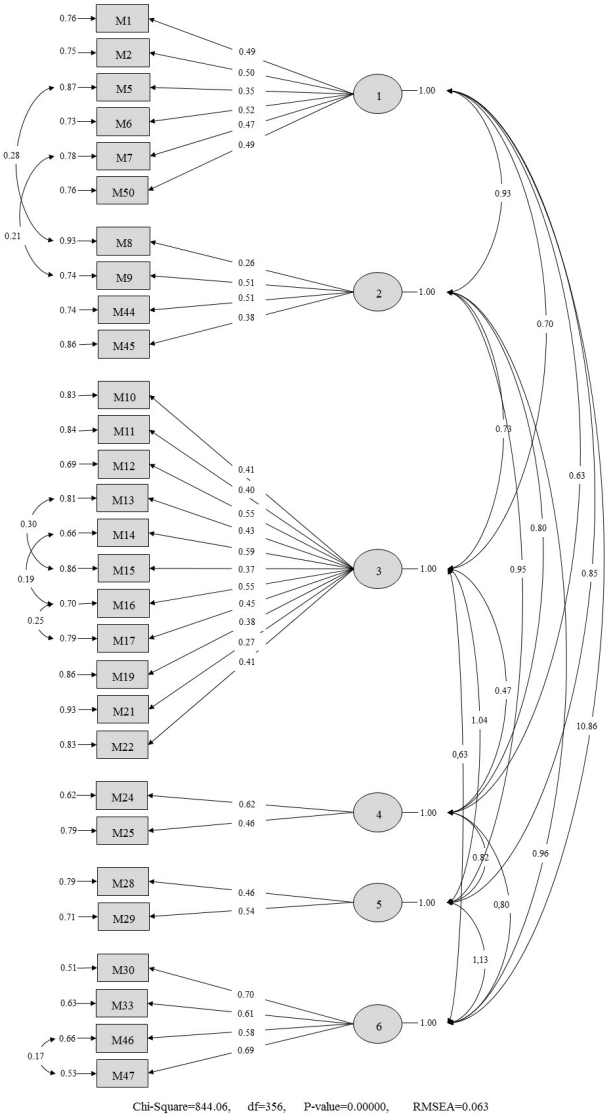

Figure 1. Confirmatory factor analysis
RMSEA: Root mean square error of approximation

Discussion

It was observed that the CVIS were over 0.80 on the I-CVI and S-CVI, there was a high level of fit among the experts, and that the items represented the desired field adequately (41,42). These results were found to support the content validity of the scale.

Construct Validity of the Scale

It was reported in the literature that to do a factor analysis, the Barlett Sphericity test value should be statistically significant and the KMO value should be at least 0.60 (41,42). In this study, the value of the Barlett Sphericity test was $p<0.05$ and the KMO value was greater than 0.60 ($p=0.000$, KMO value=0.858). These results indicated that the data of the study were adequate and appropriate for factor analysis (41-44).

In the EFA, the eigenvalue was accepted as 1 or above in determining the factor number (43). It was determined that the scale consisted of six subscales. The six subscales explained 50.30% of the total variance. The total explained variance in this study was more than 50% and this revealed that the scale was a valid measurement tool. These results also supported the construct validity of the scale. When determining under which factor the items would fall within, it is emphasized in the literature that the minimum factor load should be 0.30 or above and that those items below this value should be removed (41-44). In this study, it was determined that the factor loadings of the items in the "awareness", "assessment", and "control" subscales were greater than 0.40, those of the "physiopathology" and "diagnosis" subscales were greater than 0.36, and that the factor loadings of the items in the "barriers" subscale were greater than 0.30. In this study, the total explained variance was greater than 50% and the factor loadings were greater

Table III. Fit indexes of the model

	X^2	SD[a]	X^2/SD	RMSEA[b]	GFI[c]	CFI[d]	IFI[e]	RFI[f]	NFI[g]	TLI[h]
Six-factor model	844.06	356	2.370	0.063	0.85	0.93	0.93	0.86	0.88	0.92

SD: Standard deviation, RMSEA: Root mean square error of approximation, GFI: Goodness of fit index, CFI: Comparative fit index, IFI: Incremental fit index, RFI: Relative fit index, NFI: Normed fit index, TLI (NNFI): Trucker-lewis index

Table IV. Comparison of the upper and lower groups, each of which represented 27% (n=344)

Class	n	M	SD	t	p
27% Upper group	93	132.98	4.35	29.589	0.000
27% Lower group	93	104.60	8.16		

SD: Standard deviation

Table V. The reliability analysis results of the scale and subscales (n=344)

Subscales	Cronbach's α	First half cronbach α	Second half cronbach α	Spearman-brown	Guttman split-half	Correlation between the two halves	M	SD	Floor effect %	Ceiling effect %
Entire scale	0.864	0.791	0.746	0.825	0.822	0.703	118.90	11.84	0.0	0.6
Awareness	0.635	-	-	-	-	-	26.41	2.84	0.0	10.8
Physiopathology	0.425	-	-	-	-	-	16.04	2.20	0.3	7.0
Obstacles	0.734	-	-	-	-	-	42.50	5.69	0.0	0.9
Diagnosis	0.445	-	-	-	-	-	8.02	1.47	0.0	20.0
Assessment	0.394	-	-	-	-	-	8.31	1.33	0.6	22.4
Control	0.766	-	-	-	-	-	17.59	2.11	0.0	25.3

SD: Standard deviation

Table VI. Total score correlations for the item-scale and the item-subscales (n=344)

Subscales	Items	Item-scale total score correlations (r)*	Item-subscale score correlations (r)*
Awareness	M1	0.443	0.632
	M2	0.427	0.613
	M5	0.452	0.631
	M6	0.489	0.588
	M7	0.441	0.626
	M50	0.436	0.450
Physiopathology	M8	0.441	0.622
	M9	0.503	0.557
	M44	0.454	0.602
	M45	0.358	0.611
Barriers	M10	0.441	0.531
	M11	0.473	0.419
	M12	0.523	0.621
	M13	0.424	0.571
	M14	0.561	0.645
	M15	0.381	0.565
	M16	0.557	0.629
	M17	0.441	0.562
	M19	0.430	0.403
	M21	0.285	0.383
	M22	0.446	0.431
Diagnosis	M24	0.437	0.745
	M25	0.379	0.852
Assessment	M28	0.584	0.858
	M29	0.563	0.708
Control	M30	0.591	0.700
	M33	0.479	0.769
	M46	0.525	0.787
	M47	0.625	0.807

*Significant at p<0.001

than 0.30, which indicated that the scale had the necessary capacity to measure the pain knowledge correctly and that the scale had strong construct validity.

As a result of CFA, it was found that the factor loadings of all six subscales other than two items were greater than 0.30, whereas the factor loadings of items 8 and 15 were 0.26, 0.27, respectively (Figure 1). The explanatory factor loadings of these two items were greater than 0.30 and they had a good correlation with the item total and subscale total score, which suggested that the scale was entirely correlated. As a result, they were not removed from the scale as it indicated that the scale was adequate in measuring the pain concept. When the fit indexes of the scale were analyzed, it was determined that the fit indexes were greater than 0.85 (GFI=0.85, IFI=0.93, NFI=0.88, CFI=0.93), RMSEA value was 0.063 and X^2/df was 2.370 (Table III). According to the literature, fit indexes greater than 0.85, RMSEA values less than 0.08, and X^2/df less than 5 confirm the factor structure of a scale. The DFA results showed that the scale confirmed the six-factor structure, the subscales were correlated with the scale, and that the items in each subscale defined their own factor sufficiently (41-43).

The results of the explanatory and confirmatory factor analysis in this study supported the construct validity of the scale and proved that the scale was a valid tool.

Reliability of the Scale

Internal Consistency Analysis of the Scale and Subscales

A Cronbach's alpha coefficient value of lower than 0.60 indicates low reliability for a scale, a value between 0.60 and 0.80 indicates the scale is quite reliable, and a value between 0.80 and 1.00 shows the scale is highly reliable (45,46). In this study, the Cronbach's alpha coefficient was found to be 0.864 for the entire scale. It was determined that the Cronbach's alpha coefficient of the "awareness", "barriers", and "control" subscales were greater than 0.60 and that the coefficient was less than 0.60 for "physiopathology", "diagnosis" and "assessment" subscales. The reliability levels were found to be quite high for the entire scale and three of the subscales, whereas it was found to be lower for the other three subscales. However, when the entire scale was considered, the most important evidence that indicated items of the scale made up a whole was the Cronbach's alpha value which was calculated for the entire scale. The Cronbach's alpha value for the entire scale was 0.86 and it was a highly reliable value. Therefore, it was concluded that these subscales could be used on the scale, too. Moreover, both the explanatory and confirmatory factor analysis constituted a good correlation matrix for the entire subscales and between the subscales, which indicated that the scale and its subscales could be used. When the literature was reviewed, the Cronbach's alpha value and Kuder-Richardson-20 value were found to be 0.64 and 0.69, respectively, for the measurement tool developed in the study of Salanterä and Lauri (17), in which they studied the knowledge and views of nursing students about pediatric pain. The Cronbach's alpha value found by Manworren (19) for the scale adapted for pediatric nurses was 0.72. The Cronbach's alpha value of the Norwegian version of the same scale was 0.71 (47). The Cronbach's alpha value of another scale, which was developed to measure the pain management beliefs of nurses, was 0.83 from the pretest and 0.85 from the posttest (11). The internal consistency values obtained in this study and the values of other scales were similar. The results of this study indicated that the scale could be used reliably for nursing students. In this study, the Cronbach's alpha values found as a result of the split-half method and Spearman-Brown and Guttman-split-half coefficients were found to be greater than 0.70, indicating a strong and significant relationship between the two halves. These results were important evidence supporting the reliability of the scale. These results revealed that each item was highly correlated with the entire scale and the subscales, the items represented the areas to be measured adequately, the scale measured the PPMK level of the nursing students satisfactorily, and that the scale and the subscales had high reliability.

Item-total Score Analysis of the Scale and Subscales

It is recommended that the item-total score and the item-subscale total score correlations should be greater than 0.20 and as close to 1 as possible, and positive (24). It was determined in this study that the total scores of the items and the total scores of the subscales and their correlations were found to be mainly over 0.25 (Table VI). With these results, it was observed that each item was highly correlated with both the entire scale and the subscales, they represented the areas to be measured adequately, the scale measured the PPMK level of the nursing students satisfactorily, and that the item reliability of the scale and the subscales were high.

It is predicted that the scale developed to measure PPMK of nursing students will contribute to the literature in evaluating the qualification and efficacy of pediatric pain education in nursing students. Additionally, it is

thought that increasing the awareness of nursing students in PPM in their future lives by improving their skills will contribute to helping students gain sufficient knowledge of physiopathology, better pain diagnosis, assessment, control, and the effective management of barriers that can be encountered in pain management in practice.

Study Limitations

There are some limitations in the study despite having many strengths. The first limitation is the use of a convenience sampling method. This may affect the generalizability of the study. However, this study can provide insights about the importance of revision to the nursing curricula and improving it to improve knowledge of PPM. Further research is required to confirm the current research findings and to investigate all practice areas of nursing students for PPM.

Conclusion

As a result of this study, it was found that the scale was valid and reliable in evaluating nursing students' qualifications in PPM. With this study, the literature has gained an objective measurement tool for the assessment of the PPM knowledge level of nursing students. Using this scale, students' knowledge levels can be determined. The scale can be used for validity and reliability studies of both nurses and other health workers. It may lead to the spread of the scale to other nursing areas, the planning of further studies on these areas, and the assessment of the effectiveness of the current education.

Ethics

Ethics Committee Approval: To conduct this research, approval of the Non-invasive Research Ethics Committee of the University from the Nursing Faculty (IRB: 3970-GOA/2018/11-18).

Informed Consent: The written and verbal informed consent of the participants were taken.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.B., B.A., Design: M.B., B.A., Data Collection or Processing: M.B., B.A., Analysis or Interpretation: M.B., Writing: B.A.

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

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Case Report

Differential Diagnosis of Recurrent Hypersomnia: A Case Report of Primary Narcolepsy and Acute Transient Psychotic Attack

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ABSTRACT

Narcolepsy is a childhood and adolescence disorder, that until recently remained unidentified until adulthood, with a reported time from onset to diagnosis of around a decade. This disorder affects approximately 0.05% of the population and starts in childhood and adolescence about half of the time. The main symptom of hypersomnia is excessive daytime sleepiness or prolonged night-time sleep that has occurred for at least 3 months prior to diagnosis. Patients with narcolepsy also exhibit hallucinations and delusions, however the differential diagnosis between the disorders is often unclear. Case presented in our study is an example of atypical narcolepsy with coexistence of psychotic symptoms. In our case upon the set-off of the second attack of excessive daytime sleepiness, the differential diagnosis of recurrent hypersomnia was not considered. This is due to the fact that the first attack of narcolepsy with hallucinatory component of the patient could have been misdiagnosed as acute transient psychotic attack. Hallucinations and delusions sometimes appear in patients with narcolepsy. The differential diagnosis between the disorders is not always simple. In our study we present the case which illustrate this overlap. Child and adolescent patients, which demonstrate psychotic symptoms and excessive daytime sleepiness component, should be concidered in case of evaluation for a diagnosis of primary hypersomnia following a multidisciplinary cooperation of neurologists, paediatricians and psychiatrists.

Keywords: Narcolepsy, primary hypersomnia, excessive daytime sleepiness, psychotic symptoms

Introduction

Narcolepsy is a childhood and adolescence disorder, that until recently remained unidentified until adulthood, with a reported time from onset to diagnosis of around a decade. This disorder affects approximately 0.05% of the population and starts in childhood and adolescence about half of the time (1).

The main symptom of hypersomnia is excessive daytime sleepiness (EDS) or prolonged night-time sleep that has occurred for at least 3 months prior to diagnosis.

Hypersomnia can be primary (of central/brain origin) or secondary to a number of medical conditions. However, more than one type of hypersomnia can coexist in a single patient. The true primary hypersomnias include narcolepsy (with or without cataplexy), idiopathic hypersomnia and recurrent hypersomnias (such as Klein-Levin syndrome).

Secondary hypersomnias are numerous. Hypersomnia can be secondary to disorders such as clinical depression, multiple sclerosis, encephalitis, epilepsy or obesity. Hypersomnia can also be a symptom of other sleep

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disorders such as sleep apnea. It may occur as an adverse effect of the taking or withdrawal of certain medications, or of drug or alcohol abuse. A genetic predisposition may be a factor for the development of hypersomnia. In some cases, hypersomnia results from a physical condition, such as a tumour, head trauma or dysfunction of the autonomic or central nervous system (2).

According to the DSM-5, narcolepsy is a disorder in which the individual will experience recurrent periods of an irresistible need to sleep, or will fall asleep, or nap within the same day, regardless of whether or not the time and place are appropriate. These episodes must occur at least three times per week over the prior three months, accompanied by at least one of the following symptoms: episodes of cataplexy, or loss of muscle tonus, occurring several times a month, episodes lasting seconds to minutes of sudden full body loss of skeletal muscle tone without Loss of Consciousness (LOC) that are precipitated by an episode of strong emotion, or objective measure of hypocretin deficiency in the cerebrospinal fluid. Laboratory test results must reveal hypocretin-1 immunoreactivity equal to or less than one-third of hypocretin-1 found in healthy subjects (alternatively, equal to or less than 110 pg/mL). In addition, nocturnal sleep polysomnography (PSG) study should reveal abnormally low rapid eye movement (REM) sleep duration (<15 minutes inclusive) or a multiple sleep latency test (MSLT) showing a mean sleep latency <8 minutes, and >2 REM sleep episodes upon the onset of sleep (3).

Patients with narcolepsy also exhibit hallucinations and delusions, however the differential diagnosis between these disorders is often unclear.

A number of patients with narcolepsy have also experienced hypnagogic or hypnopompic hallucinations, which were possibly misdiagnosed as schizophrenia due to the similar symptomatology (4). However, the association between narcolepsy and schizophrenia remains inconclusive. A review article suggested that comorbidity of narcolepsy and schizophrenia is likely to be rare and sporadic (5).

We report a case of a 17-year-old boy with recurrent EDS, which was first noticed 2 years before the diagnosis, and subsequently noted again the following year in the same season. During the first episode of excessive sleepiness, the patient was experiencing psychotic symptoms such as delusions of reference and persecution, as well as visual and acoustic hallucinations. In the second episode, negative psychotic symptoms were observed.

Case Report

Y. is a 17-year-old boy. He is the first and only living child of a 31-year-old house wife mother and 37-year-old farmer father. Y.'s mother and father are first degree cousins. The birth of the patient was through a planned caesarean section, both pregnancy and delivery were unremarkable. There is nothing out of ordinary in the patient's birth and postnatal history. The patient was healthy and reached developmental milestones within normal ranges. He was raised by his mother and grandmother at home and did not attend nursery. When Y. was 2 years old, his 3-month-old sister died of febrile convulsion. When he was 3 years old, he suffered from measles. At the age of 4, he was operated on due to inguinal hernia.

No unusual behaviour or problems were noted until the patient began secondary school (at 15 years of age) and his parents observed that he became internally preoccupied and inattentive. Before the excessive sleepiness started, the patient was seen by a physician because of flu-like symptoms. The physician prescribed anti-flu medications and the patient recovered in one week. Subsequently, the patient started exhibiting social withdrawal, suspiciousness, inattentiveness, excessive sleepiness and the tendency to fall asleep in public places. At first, the patient had difficulty waking up in the morning to go to school and he became drowsy at school. His academic performance became poor and he failed to attend school because of increasing sleepiness. Approximately 2 months after the onset of excessive sleepiness, he started experiencing psychotic symptoms including delusions of reference and persecution, as well as visual and acoustic hallucinations. Both of these symptoms (EDS and psychotic symptoms) lasted for approximately 4 months, during which the average daily sleep period during the episodes was 20 hours.

Y. was referred to our psychiatry department. The main reason for this referral was the change in the boy's behaviour. This change in the patient's attitude was first noticed 4 months before the referral and he exhibited no response to a 500 mg valproic acid per day and 10 mg fluoxetine per day medication programme that was prescribed in the outpatient clinic. When the patient was referred to our clinic, excessive sleepiness was no longer observed. He had no unusual physical or neurological features. Standard laboratory tests were carried out, including diffusion magnetic resonance imaging (MRI), antinuclear antibodies, C3, Lyme and Brucella tests, all of which were reported within the normal range. The patient's awake electroencephalography (EEG) showed slow wave pattern in basic rhythm, whereas sharp wave paroxysmal

activity was detected in the frontal hemispheres. Y. was diagnosed with acute transient psychotic attack. The patient was treated as an in-patient with medication consisting of 2 mg risperidone per day. Y. showed sustained clinical and functional improvement, which was noticeable soon after the administration of risperidone. After 1 month of treatment in our psychiatry clinic, the patient was discharged and he returned to his premorbid condition. The patient underwent a Wechsler Intelligence Scale for Children test that was performed in a symptom free period yielding IQ scores indicating mild mental retardation.

Y. was free of symptoms for 22 months following discharge from the psychiatry clinic. During this symptom-free period, he was administered 1 mg risperidone per day and episodes of hypersomnolence were not noticed. A few weeks prior to the second psychiatric referral, the patient was seen by a physician due to complaints of apathy and sleepiness. The patient was prescribed anti-flu medications. This coincided with the onset of excessive sleepiness. The patient's daily average sleep in these episodes was 20 hours. Y. was again referred to our clinic and was treated as an in-patient for a range of symptoms he was suffering from: hypersomnia, long unsatisfactory naps, difficulty waking up from naps, sleep related cognitive problems (concentration problems, poor blurry memory), drowsiness and a diminished sense of well-being. The patient's symptoms restricted him from engaging in normal social activities. The patient did not have sleep paralysis, snoring was not observed, and he did not exhibit symptoms indicative of cataplexy. During the first interview, his cooperation was unsatisfactory, his mood was depressive and irritable, he displayed flat affect and he gave short answers consisting of "yes" or "no". He was not disorientated in the sense of time, direction, and recognition of people or places. He was aggressive, showing psychomotor retardation, however, he did not have suicidal thoughts nor was he experiencing positive psychotic symptoms. The patient also did not exhibit abnormal eating patterns, an increase in sexual interest/masturbation or absurd behaviour. In the Clinic Global Severity scale, he was given 5 points. During the first 2 weeks of the in-patient treatment, he was sleeping for approximately 15-20 hours per day. When the patient was awake, he was unhappy and tired. At the beginning of his in-patient treatment, he became agitated and was disinhibited. During the interview, he started swearing and was uncooperative. After that incident, 15 mg olanzapine per day and 7.5 mg lorazepam per day were added to his 3 mg risperidone per day treatment.

Standard laboratory tests were carried out, including blood count, biochemistry (liver and kidney parameters) and endocrinology parameters. Aspartate aminotransferase 84 and alanine aminotransferase 147 were reported. Due to an increase in transaminase levels, the patient was referred to the Child Gastroenterology Department. Upon physical examination and abdomen ultrasonography, hepatomegaly was observed. Since portal doppler ultrasonography was indicative of portal hypertension, the patient was transferred to the Child Gastroenterology Department for further examination. Differential diagnosis of chronic liver disease (autoimmune hepatitis/Wilson disease) was made and a liver biopsy was taken. Serologic examination for hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis E virus, cytomegalovirus, Rubella, and Brucella was negative. Control portal doppler ultrasonography did not show any pathology typical for chronic liver disease. The patient's liver biopsy was normal.

The patient was referred to Child Neurology to investigate the cause of the hypersomnia. Diffusion brain MRI was normal. His awake EEG, limbic encephalitis, quantitative urine-blood amino acid chromatography (TANDEM) and homocysteine were reported to be in the normal range. Neurologic aetiology was not detected. Our patient was referred for a screening PSG sleep study. The initial sleep study revealed increased REM sleep latency (43% of total sleep time). The result of the PSG study was abnormal and suggestive of narcolepsy. Sleep-disorder breathing was not identified. Finally, a MSLT was performed to objectively quantify the degree of sleepiness. This test consisted of 5 naps opportunities, given at 2-hours intervals. His MSLT showed an overall mean sleep latency of 1 min. His mean REM latency was 1.7 min, and sleep-onset REM was observed 3 times. Between the tests, he had no episodes of cataplexy, hence the patient was diagnosed with narcolepsy without cataplexy. We found that the mixed symptoms of narcolepsy and psychotic attack improved with anti-psychotic agent treatment. Y. showed sustained clinical and functional improvement, which was noticeable soon after the administration of risperidone. After 2 months of treatment in our psychiatry clinic, the patient was discharged with a medication programme of 1 mg risperidone per day. He returned to his premorbid condition and so far has not experienced either EDS attack or psychotic symptoms. The approval concerning publication of case's treatment and follow up period was obtained from patient's parents.

Discussion

The case presented in our study is an example of atypical narcolepsy with the coexistence of psychotic symptoms. The patient's psychotic symptoms were especially prominent

during the first attack. The EDS period was followed by psychotic symptoms including delusions of reference and persecution, as well as visual and acoustic hallucinations. However, during the second attack, negative psychotic symptoms were more prominent.

Y. was first admitted to our department with a diagnosis of a psychotic attack. After he was prescribed risperidone therapy, psychotic symptoms diminished and the patient was diagnosed with acute transient psychotic attack. As there was no excessive sleepiness when Y. was first admitted to our department, primary hypersomnia was not considered as a differential diagnosis.

In our case, upon the onset of the second attack of EDS, the differential diagnosis of recurrent hypersomnia was not considered. This is due to the fact that the first attack of narcolepsy with hallucinatory component of the patient could have been misdiagnosed as acute transient psychotic attack.

Hallucinations and delusions sometimes appear in patients with narcolepsy. The differential diagnosis between these disorders is not always simple. Here we present examples which illustrate this overlap.

Mlynczak (6) reported that 17% of psychotic patients suffered from a variant of narcolepsy. Saucerman suggested that some patients diagnosed with schizophrenia or other psychotic disorders may actually be suffering from a variant of narcolepsy with a genetic background involving dominant hypnagogic hallucinations (7). Narcolepsy in which a hallucinatory component is unusually prominent is rare, but has been previously described and may lead to the development of an illness indistinguishable from the Schizophrenic syndrome. Takeuchi et al. (8) described a case of a narcoleptic female patient whose delusions and hallucinations appeared at diagnosis of narcolepsy. Her psychotic state improved with anti-psychotic medication (8). Royant-Parola (9) found that nearly half of 11 narcolepsy patients manifested a psychiatric disorder, in which a hallucinatory component was central, leading to a misdiagnosis of schizophrenia. However, all of the above cases consider adult patients, whereas the coexistence of narcolepsy and psychotic syndromes in children or adolescents has been reported just twice in the case report study of a 13-year-old patient suffering from comorbidity of childhood-onset narcolepsy and adolescent-onset schizophrenia (9) and the case report of a 14-year-old girl who developed narcolepsy with cataplexy and a psychosis during adolescence (10).

In reviewing the previous literature, three possible differential diagnoses were found that could explain the comorbidity (11-14). First, narcolepsy may co-occur by chance with schizophrenia or other psychiatric disorders. Second, some authors support the existence of a psychotic form of narcolepsy, in which the psychotic symptoms exceed the common hypnagogic or hypnopompic hallucinations. Third, psychotic symptoms develop sequentially after treatment with central stimulants (i.e., methylphenidate and modafinil). Although they might be difficult to differentiate, psychotic symptoms differed between patients with narcolepsy and schizophrenia (4,11,12,14). Previous studies demonstrated that narcoleptic patients experience multisensory hallucinations to a significant extent, and not just the predominantly verbal-auditory hallucinations of schizophrenic patients. Delusions and associated delusional behaviour are rarely observed in patients with narcolepsy. Although the psychotic-like symptoms of narcoleptic patients (sleep-associated hallucinations) differ from the core symptoms of schizophrenia (delusions, disorganized behaviour, and negative symptoms) the differential diagnosis between the disorders is often unclear (4,15).

Our patient did not exhibit any comorbidities that would match with secondary hypersomnia. The initial sleep study did however reveal increased REM sleep latency (43% of total sleep time). The result of the PSG study was abnormal and suggestive of narcolepsy. Finally, a MSLT was performed to objectively quantify the degree of sleepiness. As a result of the above examinations, the patient was diagnosed with primary hypersomnia-narcolepsy without cataplexy. We found that the mixed symptoms of narcolepsy and psychotic attack improved with anti-psychotic agent treatment.

Child and adolescent patients who demonstrate psychotic symptoms and EDS component should be evaluated for a diagnosis of primary hypersomnia following a multidisciplinary cooperation of neurologists, paediatricians and psychiatrists. Additionally, a carefully scrutinized clinical assessment and a sleep test can help clinicians make a proper differential diagnosis.

Ethics

Informed Consent: The approval concerning publication of case's treatment and follow-up period was obtained from patient's parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: J.M.K., S.K., B.Ö., M.H.B.D., Design: J.M.K., Data Collection or Processing: J.M.K., M.H.B.D., Analysis or Interpretation: J.M.K., S.K., Literature Search: J.M.K., S.K., Writing: J.M.K.

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

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Case Report

Successful Orthotopic Heart Transplantation in Patients with Becker Muscular Dystrophy

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ABSTRACT

Cardiomyopathy is a major factor contributing to mortality and morbidity in patients with Duchenne and Becker muscular dystrophies (DMD/BMD), and is therefore among the increasingly important findings. These X-linked recessive disorders involve the deficiency or absence of dystrophin in the skeletal muscle as well as the myocardium. This defect brings about changes in the cardiac muscle in three phases: an initial hypertrophic stage, followed by an arrhythmogenic stage, and finally end-stage dilated cardiomyopathy due to increased loss of myocytes. While cardiac involvement can be observed in carriers of BMD and DMD, the incidence of dilated cardiomyopathy is reported to be higher in BMD patients than DMD patients. The only curative treatment option for medically refractory dystrophinopathic end-stage heart failure is heart transplantation. In this report, we present two patients, 14 and 15 years of age, who presented with dilated cardiomyopathy and were diagnosed with muscular dystrophy. One of the patients remains under follow-up with a left ventricular assist device as a bridge-to-transplantation, while the other underwent successful orthotopic heart transplantation.

Keywords: Becker muscular distrophy, heart tranplantation, left ventricular asist device

Introduction

Case 1

Cardiac muscle involvement is one of the most important causes of death in muscular dystrophies. Heart transplantation and ventricular assist device applications are controversial in these patients due to their neurological prognosis. In this article, 2 cases successfully treated with heart transplantation and VAD applications are presented (1). Permission was obtained from patients to share their medical informations.

Fourteen-year-old boy

Initial echocardiography performed at age 14 due to complaints of chest pain, coughing, and tiring easily following an upper respiratory tract infection revealed findings consistent with dilated cardiomyopathy (left ventricular ejection fraction [(LVEF) was 24%]. The patient was referred to our center to undergo testing for possible metabolic and genetic diseases and preparation for transplantation. On physical examination at admission, his body weight was 50 kg (50^{th}-75^{th} percentile), height was 171 cm (97^{th} percentile), body temperature was 36.7°C, heart rate was 98/minimum (min), blood pressure was 93/62 mmHg, respiratory rate was 20/min, and oxygen saturation was 100%. Systemic examination revealed rhythmic S1 and S2, grade 2-3/6 systolic murmur, weak peripheral pulses, capillary refill time of 2-3 s, jugular venous distension, normal bilateral respiratory sounds, and palpable liver 2 cm below the costal margin. Asthenic body type and

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bilateral calf muscle (gastrocnemius) hypertrophy were noted. Upper and lower extremity proximal muscle strength was 4/5 and Gowers' sign was positive. The patient had been born at term by normal spontaneous vaginal delivery (NSVD) with a birth weight of 3,700 gram (g) and had exhibited mental and motor development comparable to his peers. His parents were not consanguineous and his family history was unremarkable. Results of routine tests included white blood cell (WBC) count: 9,350/mm^3, hemoglobin (Hb) level: 13.1 g/dL, platelet count: 217,000/mm^3, creatine kinase (CK): 2,161 U/l, troponin: 142 ng/L, and pro-brain natriuretic peptide (pro-BNP): 3,005 pg/mL. Echocardiogram showed dilated cardiomyopathy, increased left ventricular end-diastolic (LVED) diameter, LVEF 20%, and first-degree mitral regurgitation. Treatment was initiated with digoxin, enalapril, aspirin, spironolactone+thiazide. Due to his elevated muscle enzymes and proximal muscle weakness observed in physical examination, the neurology, metabolism, and genetics departments were consulted regarding muscular dystrophy. Muscle biopsy and DMD gene analysis were ordered. The results of the muscle biopsy were consistent with BMD. Three months after diagnosis, the patient was admitted due to heart failure and an left ventricular assist device (LVAD) was implanted by the cardiovascular surgery team (Image 1).

After 2.5 years of follow-up in the pediatric cardiology outpatient clinic with the LVAD, a suitable donor was found and the patient underwent orthotopic heart transplantation. Post-transplantation ventricle size and functions were normal (LVEF 65%) and valve functions were normal (Image 2). Antithymocyte globulin, mycophenolate mofetil, and methylprednisolone were given at immunosuppressive doses. Tacrolimus therapy was initiated on postoperative day 3. Ganciclovir and acyclovir prophylaxis against cytomegalovirus and herpes infections, and trimethoprim-sulfamethoxazole prophylaxis against Pneumocystis carinii were added to his treatment. Cardiac biopsy was performed in post-transplantation week 1 to evaluate for acute rejection and findings were consistent with grade 1 acute cellular rejection. Explant biopsy material revealed dilated cardiomyopathy. The patient remains under follow-up in our clinic with no complications.

Case 2

Fifteen-year-old boy

The patient had been previously evaluated for muscle disorders due to history of tiring quickly and performing poorly in competitive sports compared to his peers since the age of 3 years, but had not received a definite diagnosis. At the age of 15, he was diagnosed with dilated cardiomyopathy after presenting with effort dyspnea and stomachache, and was referred to our center. On physical examination at admission, his weight was 57 kg (25th-50th percentile), height was 170 cm (75th percentile), body temperature was 36.7°C, heart rate was 106/min, blood pressure was 103/62 mmHg, respiration rate was 20/min, and oxygen saturation was 100%. Systemic examination findings included rhythmic S1 and S2, grade 2/6 systolic murmur, normal bilateral respiratory sounds, palpable liver 2 cm below the costal margin, and bilateral calf muscle hypertrophy. Gowers' sign was positive. Upper and lower limb proximal muscle strength was 3/5. The patient had been born at term by NSVD with a birth weight of 3,200 g and had mental and motor development consistent with his peers. His parents were not consanguineous and his family history was unremarkable except that his older brother had died at age 19 due to DMD. Routine tests revealed WBC: 10.250/mm^3, Hb: 14.2 g/dL, platelet count: 285,000/mm^3, CK:2.812 U/l, troponin: 234

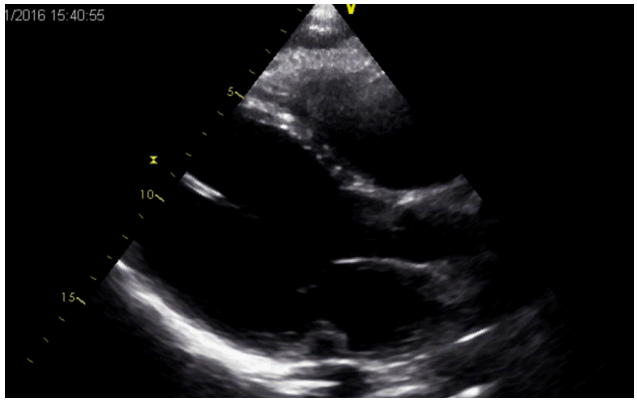

Image 1. Echocardiographic image before heart transplantation. The LVAD cannula placed in left ventricle can be seen

LVAD: Left ventricular assist device

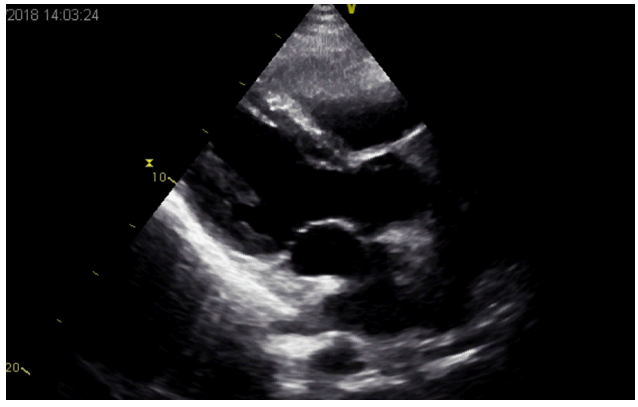

Image 2. Echocardiographic image after heart transplantation. LVED diameters are smaller

LVED: Left ventricular end-diastolic

ng/L, and pro-BNP: 10,740 pg/mL. Echocardiogram showed dilated cardiomyopathy, increased LVED diameter (6.5 cm), LVEF 24%, grade 1 MR, grade 1/2 tricuspid regurgitation (TR), TR right ventricular systolic pressure: 90 mmHg, mean pulmonary artery pressure: 35 mmHg, and tricuspid annular plane systolic excursion: 20 mm. Treatment with digoxin, enalapril, aspirin, spironolactone + thiazide therapy was initiated. Due to the patient's elevated muscle enzymes and proximal muscle weakness, the neurology and genetics departments were consulted for muscular dystrophy assessment. Muscle biopsy and DMD gene analysis were ordered. Muscle biopsy revealed sporadic absence of dystrophin consistent with BMD. Results of genetic analysis showed no deletions but duplication between exons 5 and 7 of the dystrophin gene. The patient was diagnosed with BMD based on these clinical, genetic, and pathological findings. Two months after presentation, the cardiovascular surgery team implanted an LVAD due to medically refractory heart failure. The patient has been under follow-up with the LVAD for 2 years in the pediatric cardiology outpatient clinic.

Discussion

Becker muscular dystrophy affects 1 in 18,450 males; symptoms can appear between the ages of 3 and 21, but the average age at onset is 11 years. Unlike DMD, its progression is slow (2). Mutations responsible for the disease can be deletions or duplications involving any of the 79 exons of the dystrophin gene. Areas of cardiac muscle that lack dystrophin due to these mutations develop myocardial fibrosis, while areas still expressing dystrophin develop compensatory hypertrophy, resulting in local ventricular repolarization heterogeneity and arrhythmias. The development of diffuse fibrosis leads to dilated cardiomyopathy and heart failure.

Although end-stage heart failure is common patients with muscular dystrophy, heart transplantation is not often done. This is due to donor scarcity and the belief that the benefit of transplantation will be limited due to the accompanying myopathy. Moreover, it is widely believed that respiratory muscle involvement will result in longer intubation time and more anesthesia-related complications. Therefore, literature data on transplantation outcomes and pre- and post-transplantation protocols for muscular dystrophy patients are very limited.

There are only a few studies in the literature that report heart transplantation in patients with muscular dystrophy. There are no studies from Turkey on this subject. Cripe et al. (3) reported a successful heart transplantation in a 14-year-old DMD patient 4 years after diagnosis. Rees et al. (4) published 3 cases in which successful orthotopic heart transplantation was performed after a mean follow-up of 40 months. All of these patients tolerated immunosuppression and had no postoperative complications.

BMD patients are considered better candidates for heart transplantation because they have higher rates of dilated cardiomyopathy, longer life expectancy, and better mobility. In a study of 128 children with muscular dystrophy evaluating the frequency of cardiomyopathy and long-term prognosis in BMD and DMD, it was determined that the BMD group had more severe MR and larger LVED diameter compared to the DMD group (p=0.002). The DMD group had a lower 5-year survival rate than the other groups. Heart transplantation was performed in 25% of the patients in the study during follow-up (5).

In a large-scale, multi-center study performed at 29 transplant centers between 1990 and 2005, Wu et al. (6) compared 15 BMD patients who underwent heart transplantation with 275 patients who underwent heart transplantation for other reasons and found similar 5-year survival rates. There was also no significant difference between the groups in terms of complications such as infection, rejection, and allograft vasculopathy (6). In another single-center study performed in Spain with 3 BMD patients, intraoperative and postoperative complication rates were no different from those in patients who underwent transplantation for other reasons, but the risk of cyclosporine-induced rhabdomyolysis and secondary myopathy in these patients was emphasized (7).

These studies support heart transplantation as a successful treatment option, particularly in BMD patients who have moderate muscle weakness with no respiratory involvement.

Another option that can be used as an alternative to heart transplantation or a bridge-to-transplantation is the LVAD. Amodeo and Adorisio (8) reported 7 DMD patients who used an LVAD for end-stage heart failure. Three of these patients were lost during the 45-month follow-up period due to infections and hemorrhage. Bleeding, thromboembolic events, and skin infections at the device entry site were recorded as early postoperative complications. The authors of the study reported that LVAD was a life-extending palliative method for patients with refractory end-stage heart failure.

Conclusion

Understanding the impact of cardiac involvement on mortality and morbidity in patients with muscular dystrophy is important for the development of guidelines for the

management of cardiomyopathy. Regular neuromuscular and cardiomuscular follow-up and supportive treatment will continue to be therapeutic mainstays until etiology-specific gene therapies are developed.

As BMD is asymptomatic during the first decade of life, obtaining a detailed family history and conducting biomarker analyses are especially important for early diagnosis.

The only curative treatment option for end-stage heart failure in these patients is heart transplantation. Although few cases have been published to date, long- and short-term outcomes were similar to those in patients who underwent transplantation due to idiopathic dilated cardiomyopathy. Therefore, the available literature data demonstrates that these patients also deserve the opportunity to undergo heart transplantation. In patients for whom a suitable donor cannot be found, the ventricular assist device as a bridge to transplantation is an important option.

Ethics

Informed Consent: Permission was obtained from patients to share their medical information.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Design: Z.Ü., Surgical and Medical Practices: E.D., E.L., Literature Search: D.A., Writing: D.A.

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

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