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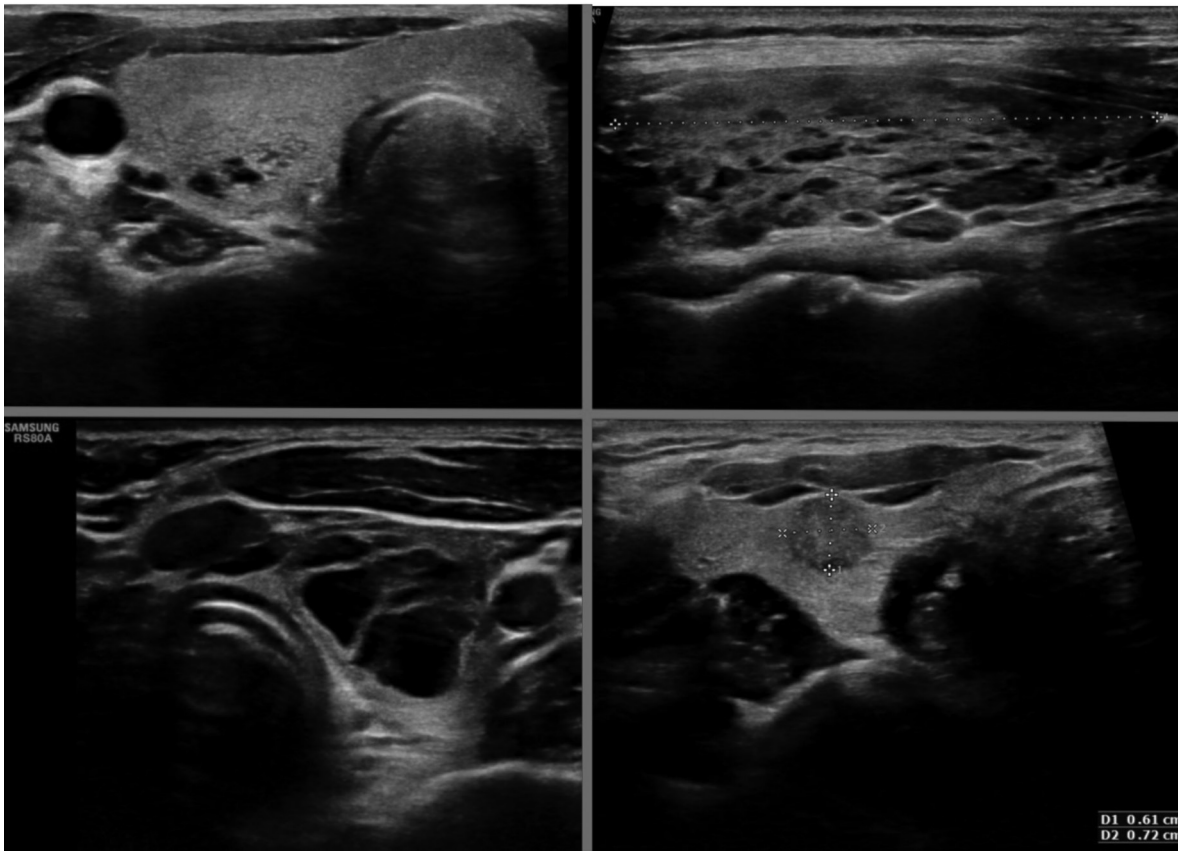

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Review

Percutaneous Closure of a Patent Ductus Arteriosus in Preterm Infants

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ABSTRACT

Spontaneous closure rate of ductus decreases as gestational age and birth weight decrease. Therefore, patent ductus arteriosus (PDA) is a very common finding in extremely preterm infants. Most popular questions discussed between neonatologists and pediatric cardiologists are: Whether the ductus is open or not, should we close it or not, when should we close it, and if we have decided to close: should we do it medical, transcatheter or by surgery? In this review we try to clarify patient selection for PDA closure, the main steps of percutaneous PDA closure, device selection, complications, transport, anesthesiology and main trick points in extremely low birth weight infants in the light of our clinical experience and the literature.

Keywords: PDA, percutaneous, preterm, invasive closure

INTRODUCTION

Patent ductus arteriosus (PDA) is an important problem in extremely preterm infants.[1,2] Most popular questions discussed between neonatologists and pediatric cardiologists are whether the ductus is open or not, should we close it or not, when should we close it, and if we close should we do it medical, transcatheter or by surgery? In this review, we tried to clarify, which PDAs should be closed, what are the main points of percutaneous PDA closure and the main trick points in preterm considering our clinical experience and the literature.

Patient Selection and Timing

There is a controversy about the topic how to manage symptomatic PDA especially extremely low birth weight preterm. This patient group needs special care, namely very sensitive hemodynamic status even affected by slight changes. Therefore; extreme caution is required in the manipulation of these babies.

1. Patient selection: PDA closure is a team approach: all patient data should be discussed in a multi-disciplinary team including a pediatric cardiologist, neonatologist, cardiac surgeon and anesthesiologist. Every member of the team should provide their opinion in the patient selection, way of closure, possible complications that they may face. Therefore, main precautions are taken before the procedure and a strategy is decided for every possible nightmare scenario.

The patients who have hemodynamic significant PDAs should be indisputably treated. The term hemodynamic significant PDA is defined as the following:

a) Clinical: PDA is associated with severe bronchopulmonary dysplasia, necrotizing enterocolitis, respiratory distress syndrome, high duration with assisted ventilation, intraventricular hemorrhage, pulmonary hemorrhage periventricular leukomalacia, and renal impairment etc.[3]

b) Echocardiography: Left heart enlargement, increased pulmonary blood flow with a velocity of more than 42 cm/s[4], the flow pattern in the mid-cerebral, mesenteric arteries can be reversed or vanished. Narrowest ductal artery diameter more than 2 mm. LA/Ao >1.4[5].

2. Timing is a controversial issue. Each patient should be evaluated on the basis of own. However; there are reports suggesting closure

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within the first 4-6 weeks. In addition to this, most extremely low birth weight (ELBW) infants with a large PDA were reported that they develop pulmonary hypertension by 8 weeks.

Procedure

The femoral vein or umbilical is accessed with 4F sheath. Arterial injury is a major problem in preterm infants;[6,7] we recommend PDA closure by only venous access. In our previous studies, we described that the major disadvantage of this method is difficulty in visualization with angiography before the release of the device. Nevertheless, good transthoracic echocardiography by experienced staff is very helpful in such circumstances. Also, aortogram can be done through PDA, which can lead to the visualization of the aorta. 50 U/kg heparin was used for heparinisation. Sathanandam et al.[8] reported that heparinized saline flushes can be sufficient to maintain activated clotting time. Therefore, they suggested not using a heparin injection.

Hemodynamic evaluation is not sine qua non-for preterm babies. The most important goal is to complete the procedure as quickly as possible without disturbing the haemodynamic status of the patient. Therefore; we did not perform hemodynamic measurements routinely.

1. Device selection: All the devices used for this age group were off-label. According to our previous experience, we usually prefer only Amplatzer Ductal Occluder II-Additional Size for preterm infants <1 kg. The ones that we have used <2 kg were detachable coils for small ducts (1.5-3 mm) and Amplatzer Ductal Occluder (ADO I, ADO II, ADO II AS) (St Jude Medical, St. Paul, Minnesota) were used for moderate-sized ducts (3-5 mm).

The main factors that help us choose the device are are the size and shape of the ductus and the structures adjacent to the ductus. As we mentioned in our previous reports, we selected the size of the Amplatzer Ductal Occluder after 1-1.5 mm adding to the narrowest diameter of ductus.

In our center from the date July 1997 up till now 609 percutaneous PDA closures were performed. 53 of them were less than 2 kg and 16 of them <1 kg. Coils (Cook Medical, Bloomington, IN) were used in 2 patients, Amplatzer Ductal Occluder was used in 53 patients (2 with ADO I, 8 with ADO II, 43 patients with ADO II AS). We preferred ADO II AS especially for ELBW infants because their retention disks are small and more flexible, which enables delivery from both arterial and venous sides and decreases protrusion risk.

Sathanandam et al.[6], had closed PDA of 55 infants percutaneously. Besides ADO II-AS; they used microvascular plug (MVP; Medtronic), and Amplatzer vascular plug II (AVP II, Abbott). Most common device they used was the MVP (44/55). They preferred MVP while the risk of protrusion of the device to the left pulmonary artery (LPA) and aorta is small and the delivery cable is flexible that makes it easy to manipulate.

The other device they used was AVP-II (3 of 55 patients). However, the authors also state that this device is unideal for preterm infants. Because sheath exchange is required, delivery cable is relatively stiff and cannot be used for 5 mm device.

Sathanandam et al.[8] also reported that the size of the patient is not always a disadvantage. Because: (a) as the patients get smaller length of the PDA gets longer that makes easier to implant the device, (b) the rate of having pulmonary vascular disease in younger patients is low procedure is better tolerated.

2. Time and radiation of the procedure: Mean fluoroscopy time and radiation dose is another popular topic in PDA closure of preterm infants. Since the procedure is a bit more complicated than the standard PDA closure; procedure time is expected to be increased so are the fluoroscopy time and radiation dose. However, as we have shown in our previous studies;[9,10] the mean dosage of radiation given for the ones <2 kg was 128.9 (98.5-285.7) cGy/cm^2; in PDA closure <1 kg: was 223±153.8 cGy/cm^2. Mean time of procedure and fluoroscopy were for <2 kg were 44.5±13.1, 13.8±5.6 min, respectively and for PDA<1 kg was median fluoroscopy time: 8.6 min median procedure time 37 min These values are unideal for a “standard PDA closure” in older children; this would be acceptable in the view of the fact that difficult and complicated procedure.

Complications

In our case series no major complication was faced. Minor complications like LPA stenosis and arterial access injuries were seen in a few patients. The peripheral pulmonary artery stenosis (LPA) of 2 patients who spontaneously resolved.

Transport

Transport of these preterm babies should be done carefully because these patients’ hemodynamic status is unstable, they are “fragile”. They are usually intubated and frequently have inotropic support. In our institution, these babies were followed by the neonatal intensive care unit which locates one floor under catheterization lab. Therefore, with only taking elevator for one floor patient can be welcomed to the catheter lab. However, 'operating room is located in a different building, which takes at least 30 minute to reach with a transport vehicle.

Therefore, we follow-up patient in the neonatal intensive care unit at least 1 day before catheterization and perform the closure procedure at the catheter lab. After bleeding control is done in the femoral veins, the patient is transferred back to the neonatal intensive care unit (NICU) with a neonatologist. If the patients are the ones that have been referred from other neonatal centers, they are sent back to their centers after being monitorized for one night in our NICU following closure. There are special considerations during transport that may change the hemodynamic clinical status of the patient, body temperature, ventilation, infusions (inotrops, or fluids). All the staff included in the transport should be experienced, informed about these issues and receive special care and know how to manage any case of trouble. As our institutional policy, we accept patients from all over our country, but if the patients are from different cities, they are

hospitalized one day before in our NICU and after stabilization of their clinical status catheterization is performed. Recently a paper is published by Willis et al.[11] about the transport of ELBW neonates for PDA closure in the catheterization lab. They reported that special attention is required about the body temperature, fluid balance, and hemodynamic status. Briefly, multi-disciplinary team approach is mandatory for the safety of the transport procedure.

Bedside procedures are another popular topic. In many centers surgery is performed successfully at the bedside, which is really comfortable for such extremely risky patients. For percutaneous closure, it is challenging. The procedure can be performed with the guidance of transthoracic echocardiography; In case of any complications, such as embolization, fluoroscopy, a special catheter, or an equipment is required. In such instances, interventionalists feel themselves safe in catheter lab cause accessibility to whatever they need in a limited of time. In our institution since NICU and catheter labs are very close to each other, transport has never been a problem so we were not in need of bedside percutaneous closure.

Anesthesia

The anesthesia of these patients should be different from that of other patients. The metabolism of these ELBW infants is different so their response and tolerance to certain drugs may change such as the neurological consequences of ketamine are questionable, premature babies can react excessively to propofol and sevoflurane, severe hypotension may occur.[12-15] Only deep sedation is enough if the patients are not intubated. If the patients are intubated, only the dosage of their sedative drugs is regulated.

Lönnqvist[16] reported a good review of the anesthesia for extreme premature infants. The authors suggested that getting repeated either arterial or venous blood gas analyses during the case is better than end-tidal carbon dioxide traces to estimate arterial pCO_2 because of the high respiratory rate. Also using balanced intravenous fluid that contains adequate sodium and glucose concentrations, to avoid hypoglycemia, appears more logical than using total parenteral nutrition. Serum calcium levels can be reduced by both sepsis and transfusion of blood product. Thus, small-incremental doses of intravenous calcium can be used to support cardiac output and blood pressure, guided by plasma analyses.[17] Also, all the staff physicians and anesthesia technicians involved in the procedure should be the ones who have experience in extremely low birth weight preterm.

Follow-up

In the follow-up; patients are checked with regular control visits. During each visit, physical examination and transthoracic echocardiography and electrocardiogram are performed. The first visit is planned on the next day, then 1, 3, 6 months after implantation. After 1 year, if there is no additional problem, visits are done annually. In each visit, patients are checked for the position of the device, protrusion to great arteries, residual shunt presence. Previously, we have faced with several adverse effects after ADO implantation. The median follow-up interval of our study was 35 (6.5-20) months.

CONCLUSION

Preterm infants especially less than 1 kg, are extremely fragile, their hemodynamic status can be easily affected by small changes. Therefore, percutaneous PDA closure in this patient group is a completely different issue from the other patients. Actually our center has 22 years' experience in percutaneous PDA closure and we started to perform percutaneous closure in ELBW infants in the last 5 years. Long-term results of percutaneous preterm PDA closure are still unknown, but more data are gathered from the reports published by other experienced centers worldwide. In this review we shared our institutional experience. Not only the procedure itself, but also the transport, anesthesia are really important issues and these patients should be evaluated with a multidisciplinary approach. Moreover, follow-up is also very critical; physician should be aware of complications and check for them in each control visit of the patient.

Briefly, compatible with the literature we believe in that transcatheter closure of PDA in preterm is a safe and also an effective effective method but only in experienced centers with a multidisciplinary approach.

Ethics

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.P., N.N., Design: N.N., Data Collection or Processing: Ö.P., Analysis or Interpretation: Ö.P., Literature Search: Ö.P., N.N., Writing: Ö.P.

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Original Article

Assessment of Serum 25-hydroxyvitamin D Levels at the First Manifestation of Multiple Sclerosis in Children and Adolescents

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ABSTRACT

Objective: To evaluate serum 25-hydroxyvitamin D levels, demographic features, and anthropometric measurements at the first manifestation of disease in children and adolescents with multiple sclerosis (MS).

Methods: This retrospective study included patients with MS and healthy children and adolescents. Children and adolescents whose clinical and radiological findings were compatible with the McDonald 2017 criteria and who had vitamin D results during the first relapse were included. Having an acute or chronic disease was an exclusion criterion for healthy controls. Taking a supplementation including vitamin D is an exclusion criterion for both the MS and control groups. Age, gender, anthropometric measurements, and serum levels of 25-hydroxyvitamin D were extracted from the database.

Results: A total of 23 patients (female: 17, 73.9%) and 24 (female: 12, 50.0%) healthy children and adolescents were included. The median ages of the patient group and the control group were 16.33 (2.00), and 15.36 (2.29), respectively. There were no significant differences between the groups in terms of age, gender, weight-standard deviation score (SDS), height-SDS, and body mass index-SDS. Precisely, 87.0% of the patients had a vitamin D deficiency. The mean vitamin D values of the patients and the healthy controls were 12.76±5.52, and 18.75±5.86, respectively. Patients with MS had significantly lower levels of 25-hydroxyvitamin D than healthy controls ($p<0.0001$).

Conclusion: The current study showed that most (87.0%) of the children and adolescents had vitamin D deficiency at the first manifestation of MS. Moreover, the levels of 25-hydroxyvitamin D levels were significantly lower in patients with MS than in the healthy controls.

Keywords: Multiple sclerosis, vitamin D, 25-hydroxyvitamin D, children, adolescents, the first manifestation, height

INTRODUCTION

Vitamin D is a lipid-soluble vitamin. Calcitriol is the active form of vitamin D and has a chemical resemblance to steroidal hormones. Exposure to sunlight, diet, and taking supplements including vitamin D are the main resources.[1,2] The richest source is exposure to sunlight, especially during the summer months. However, there may be a reduction in the synthesis of vitamin D in people who have dark skin, with an older age, and people who use sunscreen. Moreover, environmental factors including the winter, high latitude, pollution, cloudy weather, and ozone levels have also have negative effects on the synthesis of vitamin D.[3]

The relationship between bone health and vitamin D deficiency has been known since the early 1900s. However, studies have shown that low levels of vitamin D have been related to various diseases such as cancers, cardiovascular diseases, type 2 diabetes mellitus, Chron's disease, and multiple sclerosis (MS).[4] In the 1970s, it was suggested that vitamin D played a role in the development and progression of MS. MS is the most prevalent-demyelinating

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disease that affects myelin that covers the nerve cells in the brain and spinal cord.[5] The disease has negative impacts on physical, mental, and psychiatric well-being. It can be considered a relapsing-remitting form when new symptoms occur during the attacks and a progressive form when new symptoms build-up without an attack.[6] Relapsing-remitting is more common in children and adolescents. Though the exact pathophysiological mechanism is not well understood, both genetic and environmental factors have roles in pathogenesis. Obesity, Ebstein-Barr virus infection, vitamin D deficiency, and smoking are proposed as environmental risk factors.[7-10] Sufficient levels of vitamin D are one of the protective factors for MS, which could have roles at different times between conception and the disease manifestation. Some epidemiological research showed that the prevalence of MS is higher in regions with lower exposure to sunlight. However, some genetic errors in the vitamin D metabolism indicate an association with MS and it was suggested that ultraviolet B (UVB) had not a beneficial role in the immunity.[11] The Endocrine Society suggests that a lower level of 25-hydroxyvitamin [25(OH)D] than 20 ng/mL is a deficiency, a level between ≥20 ng/mL and <30 ng/mL is insufficiency, and a level higher than 30 ng/mL is sufficiency.[12] There are also studies suggesting that in the presence of adequate levels of vitamin D, the risk and activity of the disease decrease.[13,14] Furthermore, it was proposed that lower levels of vitamin D in the first part of life are related to a major risk of MS.[15]

Here, we investigated the demographic features, anthropometric measurements, levels of 25(OH)D, and the ratio of insufficiency and deficiency of vitamin D in children and adolescents with MS at the first manifestation of the disease.

MATERIALS AND METHODS

The approval of the ethics committee has been obtained from Aydın Adnan Menderes University Non-Invasive Clinical Research Ethics Committee in line with the principles outlined in the Second Declaration of Helsinki (approval number: 2022/90). Informed consent was not required because of the retrospective design. This retrospective case-control study was conducted from January 2006 to April 2022 at Aydın Adnan Menderes University Faculty of Medicine, Department of Pediatric Neurology. The inclusion criteria were as follows; i) children and adolescents whose clinical and radiological findings were compatible with McDonald 2017 criteria, ii) patients with MS who had vitamin D results during the first relapse. The control group consisted of healthy children who were admitted to the General Pediatrics Outpatient Clinic for examination and had vitamin D results during the admission. Having an acute or chronic disease was an exclusion criterion for the control group. Additionally, taking a supplement including vitamin D was an exclusion criterion for both the patient and control groups. The diagnosis of MS was made by two pediatric neurologists. Demographic features including age, gender, weight-standard deviation score (SDS), height-SDS, body mass index (BMI)-SDS, and the levels 25(OH)D were extracted from the electronic database.

Statistical Analysis

Statistical analyses were performed using the SPSS-22 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). The Shapiro Wilk test was applied to specify the normal distribution of numerical variables. Categorical data were presented as n and %. Normally distributed numerical data were presented with mean ± SD, and non-normally distributed data presented with median (interquartile range). Student t-test was applied for the comparison of normally distributed data, and the Mann-Whitney U test was used for the comparison of non-normally distributed data. The chi-square test was used for the comparison of categorical data. A p-value <0.05 was set as statistically significant.

Table 1. Comparison of the demographical features and levels of 25-hydroxyvitamin D between patients with multiple sclerosis and healthy controls

	Multiple sclerosis (n=23)	Control (n=24)	p-value
Age**	16.33 (2.00)	15.36 (2.29)	0.124
Gender			
• Female	17 (73.9%)	12 (50.0%)	0.092
• Male	6 (26.1%)	12 (50.0%)	
Weight-SDS**	0.82 (2.98)	0.03 (3.01)	0.160
Height-SDS**	0.39 (1.69)	0.040 (1.38)	0.758
BMI-SDS*	0.56 ± 1.56	-0.24±1.81	0.109
Levels of 25-hydroxyvitamin D categorization**			
- Sufficiency (≥30 ng/mL)	0 (0%)	0 (0%)	**0.028**
- Vitamin D insufficiency (between ≤20 ng/mL and <30 ng/mL)	3 (13.0)	10 (41.7%)	
- Vitamin D deficiency (<20 ng/mL)	20 (87.0%)	14 (58.3%)	
Levels of 25-hydroxyvitamin D* (ng/mL)	12.76±5.52	18.75±5.86	**<0.0001**

*Non-normally distributed data were given as median (IQR).

**Normally distributed data were given as mean (± SD).

IQR: Interquartile range, SD: Standard deviation, SDS: Standard deviation score, BMI: Body mass index

RESULTS

The study group consisted of 23 patients (17 female, 6 male) and 24 healthy children and adolescents (12 female, 12 male). All the patients had a relapsing-remitting form of MS. The median age of the patient group and the control group were 16.33 (2.00), and 15.36 (2.29), respectively. There were no significant differences between the groups in terms of age, gender, weight-SDS, height-SDS, and BMI-SDS. Of the patients, 87.0% had a vitamin D deficiency. Neither the patients nor the healthy controls had a sufficient vitamin D level. The mean vitamin D values of the patient group and the control group were 12.76±5.52 ng/mL, and 18.75±5.86 ng/mL, respectively. The serum levels of 25(OH)D were significantly lower in the patient group than in those healthy controls during the first relapse ($p<0.0001$) (Table 1).

DISCUSSION

The major findings of the current study were as follows; i) most of the patients (87.0%) had a vitamin D deficiency, and ii) serum 25(OH)D levels during the first attack were significantly lower in patients with MS than in those healthy controls.

The frequency of MS decreases around the equator and increases around the North and South latitudes.[16] Moreover, immigration from North and South latitudes to the equator during the first two decades may decrease the prevalence.[17] Also, a longer duration of time spent outdoors decreases the risk of MS in later life.[18] In a meta-analysis of 52 studies by Sloka et al.[19], it was found that MS prevalence was 20 times higher in the countries where the annual amount of UVB is the lowest. This study was conducted at Aydın Adnan Menderes University, located in Aydın province, in the Aegean Region of Turkey (latitude: 37° 50' 42.04'' N, longitude: 27° 50' 22.67'' E). Since the hospital is a 3rd-level center we had the opportunity to examine and follow children and adolescents from the province, and neighboring provinces. Although the climate of the Aegean Region is scalding in the summer, none of the children and adolescents had a sufficient serum level of 25(OH)D in the current study. Also, most of the patients (87.0%) with MS had a vitamin D deficiency at the first manifestation of the disease. Similarly, a high rate of insufficient levels of vitamin D was found in children and adolescents, in a study, which was conducted in the Aegean Region.[20] In another study, it was found that 74.9% of 209 adults had lower levels of 25(OH)D than 20 ng/mL.[21] Thus, despite the hot climate, especially in the summer, vitamin D deficiency may be a common problem in Agean Region. The cause of the results may be related to decreased exposure to sunlight, such as using sunscreen, wearing clothes that restrict exposure to sunlight, and/or an increased tendency to spend time indoors.

Lower levels of vitamin D than 20 ng/mL have been found in some studies before the first manifestation of MS.[22-24] However, since the disease is multifactorial, sufficient levels may be seen in patients. Behrens et al.[22] conducted a study to assessed serum levels of 25(OH)D in 76 adult patients with MS at the first manifestation of the disease and 76 healthy controls. It was found that patients with MS have significantly lower levels of 25(OH)D than the healthy controls. Martinelli et al.[23] demonstrated that low baseline levels of 25(OH)D were a risk factor for MS in patients with the clinically isolated syndrome. Moreover, the odds ratios were 3.34 [confidence interval (CI) 95%: 1.32-8.75], and 2.04 (0.9-4.36) for lower levels than the 10th percentile, and 25th percentile, respectively.[23] Munger et al.[24] performed a study among USA soldiers whose blood samples were stored. The levels of 25(OH) D, which were stored before the initial symptoms of the disease, were analyzed and compared with the age-matched healthy controls. Among whites, levels of 25(OH)D were significantly lower in patients with MS (n=148) than in the healthy controls (n=296). However, an association could not be found between the levels of 25(OH)D and MS risk among blacks and Hispanics (n=109 patients, n=218).[24] Additionally, a lower MS risk was found in people who were born in fall than in those who were born in spring. It was proposed that the results may be associated with the levels of 25(OH)D during the pregnancy since lower levels, and higher levels exist in babies who were born in spring, and autumn, respectively.[25] In this study, serum levels of 25(OH)D were significantly lower in patients with MS than in those healthy controls.

The relationship between vitamin D and MS has been explained by the immunomodulatory role of vitamin D.[26] There is research showing multiple immunological favorable effects obtained after vitamin D supplementation in patients with MS. The beneficial effects consisted of stimulation of Tregs, attenuation of B-cell autoimmune reactivity, and favorable changes in cytokines.[27,28] In addition to the immunomodulatory effects, vitamin D has neuroprotective, neurotrophic, and remyelinating effects by entering the cells in the central nervous system.[29] There are studies demonstrating the association between MS risk and various genetic abnormalities of the histocompatibility complex of the human leukocyte antigens, and gene variants concerning the metabolism of vitamin D. Also, a linkage between genetically low vitamin D levels and MS risk has been found recently.[9]

Several studies exist regarding the relationship between obesity and MS. In a study by Munger et al.[30] which was conducted on women, BMI ≥30 kg/m^2 at the age of 18 is a risk factor for developing MS after adjusting for the other risk factors (odds ratio: 2.25, 95% CI: 1.50-3.37). In a study from Norway and Italy, it has also been demonstrated the risk of MS 2-fold increases in the presence of obesity.[31] Also, in two studies, it has been suggested that obesity is a risk factor for MS or clinically isolated syndrome in pediatric patients.[32,33] In a prospective study among 302043 children between the ages 7-13, it was proposed that having a higher BMI in childhood was a risk factor for developing MS.[32] This causal relationship has been explained recently. It was suggested that some gene variants for obesity result in MS susceptibility. Additionally, it was proposed that socioeconomic status had similar impacts on both MS and obesity.[34,35] There is research regarding the relationship between obesity, final height, and vitamin D status. There was a negative correlation between obesity and vitamin D levels. It was suggested that α-1hydroxylase

has a negative impact on adipogenesis.[36] Also, it was shown that obese people have relatively lower levels of vitamin D than the non-obese controls even after the supplementation with vitamin D.[37,38] The probable cause was explained by the fact that in the presence of increased body fat, vitamin D was trapped in the fat tissue and resulted in low levels of circulating vitamin D.[39] In this study, there were no significant differences between patients with MS and healthy controls in terms of weight-SDS, height-SDS, and BMI-SDS. The absence of an association may be due to the smaller sample size in this study.

Study Limitations

There were some limitations to the current study. First, the retrospective design may lead to the risk of bias. Second, the study was performed in a single center with a small sample size. However, the current study is one of the few studies assessing the levels of serum 25(OH)D at the first disease manifestation in children and adolescents with MS. Also, being a 3rd-level center in the region allowed us to follow patients in Aydın province and from neighboring provinces. Research is needed with a larger sample size of patients with MS and healthy children and adolescents assessing serial analysis of serum 25(OH)D levels and anthropometric measurements.

CONCLUSION

In conclusion, our study shows that the levels of 25(OH)D are significantly lower in patients with MS than in the healthy controls at the first attack of the disease. Additionally, despite the hot climate, vitamin D deficiency may be a common disorder in the region, even in the healthy controls.

Ethics

Ethics Committee Approval: The approval of the ethics committee has been obtained from Aydın Adnan Menderes University Non-Invasive Clinical Research Ethics Committee in line with the principles outlined in the Second Declaration of Helsinki (approval number: 2022/90).

Informed Consent: Informed consent was not required because of the retrospective design.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Concept: M.A., A.T., Design: M.A., A.T., Data Collection or Processing: M.A., A.T., Analysis or Interpretation: M.A., Literature Search: M.A., Writing: M.A.

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Original Article

Evaluation of Bedside Echocardiography in Children with Septic Shock in the Pediatric Intensive Care Unit

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ABSTRACT

Objective: We analyzed the echocardiographic findings of children with septic shock who have a high mortality rate in pediatric intensive care units (PICU).

Methods: The study was conducted in the 3rd step PICU as a prospective observational study. Children aged 1 month-18 years, who were followed up with septic shock and started vasoactive medication, were included in the study. Echocardiography was performed within the first hour at the latest in patients diagnosed with septic shock. Echocardiographic findings were compared in non-surviving and surviving patients.

Results: There were 39 (38% female) children diagnosed with septic shock in this study. The median age of the patients was 20 months. The vasoactive medication was started in all patients. There was no statistically significant difference between the patients who non-surviving and those who survived in terms of echocardiographic findings. The ejection fraction (EF) of the patients who died was median 71.5% [minimum (min.) 40, maximum (max.) 79], and the EF of the surviving patients was 72.5 (min. 53, max. 81; p>0.05). The shortening fraction of non-surviving patients was 39.5 (min. 18, max. 46), and 40 (min. 26, max. 48) in surviving patients (p>0.05).

Conclusion: The reason why there is no difference between the echocardiographic findings of the patients who non-surviving and survived septic shock, may be due to the functioning of the compensation mechanisms in septic shock or the immediate initiation of vasoactive drug therapy. Prospective, multi-center, more comprehensive studies with a larger number of patients are needed to obtain clearer information on this subject.

Keywords: Septic shock, echocardiography, pediatric intensive care unit, vasoactive drug, ejection fraction, shortening fraction

INTRODUCTION

Sepsis includes a spectrum of diseases resulting from infections with microorganisms such as bacteria, viruses, fungi, or parasites or their toxic products.[1,2] In the International Pediatric Consensus Conference in 2005, definitions related to sepsis and organ failure in children were put forward. Accordingly, sepsis was defined as the presence of two or more criteria for systemic inflammatory response syndrome (SIRS) with suspected or proven infection. SIRS is a common inflammatory response of the host to infection-related or non-infection-related trauma, chemical, malignancy, autoimmune, or idiopathic conditions.

SIRS criteria are body temperature >38.5 °C or <36 °C as measured by oral, bladder, rectal or central probe, mean heart rate tachycardia > two standard deviations above normal for age or, in children younger than one year, the mean heart rate for age bradycardia <10th percentile, mean respiratory rate tachypnea > two standard deviations above normal for age, or the need for non-elective mechanical ventilation, increased or decreased leukocyte count for age, or more than 10 percent of immature

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neutrophils. To define SIRS, one of these criteria must be either an abnormal leukocyte count or abnormal body temperature, and 2 or more of the other criteria are required. Septic shock is the development of cardiovascular dysfunction in the presence of sepsis.[3] Although these definitions are up-to-date at the time of writing of this article, studies on definitions are ongoing.

The host response to infection begins with the recognition and attachment of microbial components by innate immune cells, particularly macrophages. With the balance between pro-inflammatory and anti-inflammatory mediators, the infection is localized, bacterial invasion is prevented, damaged tissues are repaired and healing occurs. If the balance is disturbed in favor of proinflammatory mediators, a generalized inflammatory response occurs and sepsis develops.[4,5]

In the last conference of the Podium (The Pediatric Organ Dysfunction Information Update Mandate) in January 2022, organ dysfunction and criteria in critically ill children were re-evaluated and the current scoring systems were developed.[6] Accordingly, cardiovascular dysfunction in critically sick children was defined by 9 elements, 4 of which were indicative of severe cardiovascular dysfunction. These were defined as cardiopulmonary arrest lasting longer than 5 min (>5 min) or the need for mechanical circulatory support or the presence of at least 2 abnormal findings of findings of tachycardia, hypotension central venous oxygen saturation, vasoactive inotropic score, troponin-I, lactate or left ventricular ejection fraction on echocardiography.[3,7-9] Inclusion of echocardiographic ejection fraction measurement among the criteria for the diagnosis of cardiovascular dysfunction seems important in terms of diagnosis, treatment and follow-up.

Mortality and morbidity of sepsis and septic shock are high worldwide.[10] In a meta-analysis by Menon et al.[11] in children, mortality was reported to be 10.9% in sepsis and 36.8% in septic shock. To reduce mortality and morbidity, sepsis surviving campaign suggested that septic shock should be recognized within 1 h and sepsis within 3 h.[8]

Sepsis causes haemodynamic instability in children due to myocardial dysfunction, capillary leak, and vasodilation. Initially, it may be only one of these findings, and other findings may be added or changed over time. The early recognition and treatment of patients with septic shock is life-saving. Early antibiotic therapy, appropriate haemodynamic correction, and control of the source of infection reduce morbidity and mortality.[3]

Clinical signs of septic shock include fever, toxic appearance, edema (due to increased vascular permeability), respiratory distress, altered consciousness, myocardial dysfunction, and inadequate tissue perfusion. While septic shock was previously categorized as warm or cold, this classification has been sidelined recently, considering that it does not accurately reflect the underlying pathophysiology of sepsis.[6] For this reason, further monitoring such as echocardiography, may be necessary for children who do not respond immediately to the initial treatment to make a correct diagnosis. In previous studies, bedside echocardiography was shown to be a valuable tool in the evaluation of the hemodynamic status of children with septic shock.[12] Echocardiography is also useful in imaging the heart, evaluating the condition of the aorta and pulmonary arteries, and diagnosing congenital and acquired heart diseases. It also allows functional evaluation of the heart.[13] Transthoracic echocardiography is invasive and should be performed early in septic shock. It is a valuable guide for physicians in the diagnosis and management of treatment, the determination of fluid resuscitation, and the evaluation of cardiac function in patients with septic shock.[14]

Echocardiographic measurements are becoming increasingly common in patients with septic shock. In this study, we investigated the role of echocardiography in the diagnosis and treatment of children with septic shock, who were followed up in a pediatric intensive care unit (PICU), by evaluating cardiac functions with echocardiography.

MATERIALS AND METHODS

Study Design and Patients

This study was conducted in a 3rd stage PICU between June 2021 and March 2022. The study was initiated with the approval of the Kahramanmaraş Sütçü İmam University, Faculty of Medicine Non-Invasive Clinical Trials local ethics committee (decision no: 05 session: 2021/08).

Patients aged 1 month to 18 years who were diagnosed with septic shock were included in this study. Consent for this study was obtained from the patients or their families.

The diagnostic sepsis was made when 2 or more of the SIRS criteria were met in the presence of a proven or suspected infection.[3]

The diagnosis of septic shock was diagnosed when sepsis was accompanied by cardiovascular dysfunction. Cardiovascular dysfunction was defined when our patients developed hypotension or the need for a vasoactive drug to maintain blood pressure, or when two of the findings of increased arterial-lactate level, metabolic acidosis, prolonged capillary refill, or oliguria developed.[3,8] Patients who were administered vasoactive drugs were included in this study.

Patients with congenital or acquired heart disease were excluded from this study.

Echocardiographic Evaluation

Echocardiography of septic shock patients admitted to the PICU were performed at the bedside with a two-dimensional, M-mode, and color Doppler echocardiography device. Echocardiographic were examined using an Affiniti 50 echocardiography machine (Philips Medical Systems, Andover, MA, USA) using 4-2 mhz and 8-3 mhz sector probes suitable for the age and weight of patients by the same experienced pediatric cardiologist. Echocardiographic measurements were assessed according to the American Echocardiography Association Pediatric Echocardiography Guideline.[15] Ejection fraction (EF) and shortening fraction (FS)

were calculated using formulations as EF (%)=[left ventricle end-diastolic diameter (LVEDD)^3-LV end-systolic diameter (LVESD)^3]/LVEDD^{3}x100 and FS=(LVEDD-LVESD)/LVEDDx100. Images and real-time heart movements were acquired in the short and long axes of the heart. Systemic arterial pressure, mean pulmonary arterial pressure, right ventricular dilatation and hypertrophy, right atrium size, presence of pericardial fluid, left atrium (LA), left ventricle (LV), interventricular septum thickness, LVEDD, LVESD, left ventricular posterior wall thickness, left ventricular mass, EF, FS, intracardiac mass, tumor, and thrombus were evaluated.

In this study, echocardiography was performed within 1 h of when sepsis and septic shock were suspected. Echocardiography was performed by a pediatric cardiologist. When cardiovascular dysfunction developed, vasoactive drug was started without waiting for echocardiography. In other words, vasoactive medication was initiated either before echocardiography or concurrently with echocardiography.

Statistical Analysis

Statistical analysis were performed using SPSS for Microsoft Windows, version 25.0 (IBM Corp., NY, USA). The data are presented as mean, standard deviation, frequency and percentage distributions as statistics. The conformity of the data to the normal distribution was evaluated with the Kolmogorov-Smirnov test. Normally distributed data are expressed as mean ± standard deviation, non-normally distributed data are expressed as median [minimum (min.)-maximum (max.)]. Student's t-test was used in the analysis of numerical data that met the parametric test assumptions, and the chi-square test was used in the analysis of categorical data. The Mann-Whitney U test was used for the analysis of non-normally distributed data. Test results were considered significant if $p<0.05$.

RESULTS

In total, there were 39 (38% female) pediatric patients who developed septic shock and were administered vasoactive drugs. The ages of the pediatric patients ranged from 1 month to 204 months, and their median age was 20 months. In this study, echocardiography was performed within 1 h of when sepsis and septic shock were suspected. Echocardiography was performed by a pediatric cardiologist at the bedside in the PICU. When cardiovascular dysfunction developed in the patients, vasoactive drug was administered without waiting for echocardiography. In other words, patients were given vasoactive drugs either before echocardiography or started simultaneously with echocardiography. The demographic and echocardiographic findings of the children are given in Table 1. There was no statistically significant difference in terms of gender, age, height and weight of the patients who died compared with the survivors. While all the patients who died were intubated and provided with mechanical ventilator support, 38% of the surviving patients were intubated. The EF values of the patients who died were 71.5% (min. 40, max. 79), and the EF values of the surviving patients were 72.5% (min. 53, max. 81) ($p>0.05$). The FS for the patients who died was 39.5% (min. 18, max. 46), and 40% (min. 26, max. 48) for the surviving patients ($p>0.05$). There was no statistical difference in terms of other echocardiographic findings (Table 2).

The laboratory findings of the patients are presented in Table 3.

DISCUSSION

In our study, we evaluated the echocardiographic findings of patients who were followed up with the diagnosis of septic shock and who took vasoactive drugs, at the time of diagnosis or within 1 h of diagnosis in our PICU.

Even in the best intensive care units, the most common cause of death is multiple organ failure syndrome.[16] One of the common causes of multi-organ failure is sepsis and septic shock.[3,6] Severe sepsis and septic shock is a serious disease group that accounts for approximately 33% of PICU hospitalizations all over the world, with a mortality rate of between 21% and 41%.[10,11,17] The death rate for male children is higher than for female children.[11] In our study, 30.7% of our patients who were followed up with the diagnosis of septic shock and who were administered vasoactive drugs died, and for our patients who died, the mortality was higher in male children than in female children, which is in line with the literature.

It is not always possible to evaluate myocardial contraction and intravascular volume by clinical examination of patients with sepsis and septic shock. Therefore, echocardiographic

Table 1. Demographic and echocardiographic findings of children diagnosed with septic shock

	Patients n=39
Sex (female)(%)	%38
Age (month)*	20 (1, 204)
Weight (kg)*	9.45 (2.4, 60)
Height (cm)*	78 (50, 155)
IVSd*	5 (3, 9)
IVSd zs*	0.55 (-1.19, 1.49)
LVEDD*	27 (18, 40)
LVEDD zs*	-0.11 (-1.82, 2.64)
LVPW*	4 (3, 7)
LVPW zs*	0.55 (-1.3, 1.97)
LVESD*	18 (11, 26)
LVESD zs*	0 (-2.2, 3.45)
EF*	72.5 (40, 81)
KF*	40 (18, 48)

*median (min.-max.)

LVEDD: Left ventricular end-diastolic diameter, LVPW: Left ventricular posterior wall thickness, LVESD: Left ventricular end-systolic diameter, EF: Ejection fraction, zs: Z-score, IVSd: Interventricular septum end-diastolic wall thickness

Table 2. Demographical and echocardiographical findings of children who died and surviving with septic shock

	Ex n=12	Surviving n=27	p
Sex (female/ male)	3/9	12/15	0.25*
Age (month)	28 (4, 123)	13 (1, 204)	0.69†
Weight (kg)	9.2 (2.4, 34)	9.45 (2.8, 60)	0.77†
Height (cm)	82 (50, 131)	75.5 (51, 155)	0.98†
IVSd	5 (4, 7)	5 (3, 9)	0.75†
IVSd zs	0.61 (-0.46, 1.49)	0.52 (-1.19, 1.31)	0.6†
LVEDD	27.5 (19, 40)	27 (18, 40)	0.9†
LVEDD zs	-0.10 (-1.82, 1.6)	-0.10 (-1.66, 2.64)	0.6†
LVPW	4.5 (4, 6)	4 (3, 7)	0.37†
LVPW zs	0.91 (-0.57, 1.77)	0.47 (-1.3, 1.97)	0.38†
LVESD	18.5 (11, 24)	16 (11, 26)	0.56†
LVESD zs	-0.23 (-2.2, 3.45)	0.035 (-1.77, 2.09)	0.87†
EF	71.5 (40, 79)	72.5 (53, 81)	0.54†
FS	39.5 (18, 46)	40 (26, 48)	0.61†

*Chi-square test, †Mann-Whitney U test, median (min.-max.)

LVEDD: Left ventricular end-diastolic diameter, LVPW: Left ventricular posterior wall thickness, LVESD: Left ventricular end-systolic diameter, EF: Ejection fraction, FS: Shortening fraction, zs: Z-score; IVSd: Interventricular septum end-diastolic wall thickness

evaluation may guide the patient's fluid needs and the initiation of other supportive treatments such as vasoactive medication. Regarding this, Ranjit et al.[18], in their study, suggested that the echocardiographic evaluation of pediatric patients with septic shock resistant to fluid and inotropic therapy provided valuable information to determine the cause of low cardiac output that could not be detected by physical examination, and they reported that the most common finding in most patients was insufficient fluid volume. Additionally, in another study conducted in a PICU in our country, it was reported that echocardiography in pediatric patients followed up with diagnoses such as acute respiratory distress syndrome, pulmonary edema, cardiogenic shock and septic shock is a guide for initiating fluid, vasoactive and inotropic agents in the management of these patients.[19]

Feng et al.[20], in a study conducted with adult sepsis patients in intensive care units, showed that echocardiography was associated with a decrease in 28 day mortality. Accordingly, they reported that more fluid, dobutamine, mechanical ventilator support, other inotropic and vasopressor drugs, and sedative drugs were given to patients who underwent echocardiography. They attributed this to the fact that echocardiography provides useful information in patient management.[20] In a study by Rato et al.[21] on pediatric intensive care patients, they mentioned the benefits of bedside echocardiography. 38% of their patients were respiratory tract infection and 21% were septic shock patients. They mentioned that their echocardiography changed the clinical follow-up and treatment plans in most patients, and they emphasized that echocardiography is valuable as a diagnostic and hemodynamic monitoring tool in the PICU[21] In a study by Baranwal et al.[22] in pediatric patients with sepsis in India, they detected myocardial dysfunction via echocardiography in 55% of the patients who experienced septic shock, and systolic dysfunction was found in half of the them and diastolic dysfunction was found in 1/8 of them. No myocardial dysfunction was detected via echocardiography in any sepsis patient who did not develop shock.[22] We present studies reporting that echocardiographic evaluation is beneficial in terms of diagnosis, treatment and follow-up in septic shock patients. In our study, in our pediatric patients with septic shock, the median value of the ejection fraction was 72.5% and the median FS value was 40%, which is within normal limits compared to the general population.[13]

Table 3. Laboratory findings of children who died and surviving with septic shock

	Ex n=12	Surviving n=27	p
WBC (10^9/L)	7.37 (0.67, 14.48)	12.99(2.61, 29.41)	0.076 †
Neutrophil (10^9/L)	5.260 (0.0030, 11.59)	7.42 (1.61, 26.11)	0.264
Lymphocyte (10^9/L)	1.230 (0.450, 5.910)	3.625 (0.320, 10.850)	0.123 †
Hb (g/dL)	10.4 (7.5, 16.4)	10.1 (8, 18.1)	0.77 †
PLT (10^9/L)	163 (5, 480)	251 (41, 683)	0.28
Prokalsitonin (µg/L)	43.1 (1.85, 325)	2.27 (0.12, 423)	0.01 †
CRP (mg/L)	81 (2, 446)	23 (1, 425)	0.032 †
Troponin-I (µg/L)	0.005 (0.005,0.37)	0.01 (0.005,0.548)	0.41
AST (IU/L)	70 (22, 795)	33 (16, 109)	0.034 †

Mann-Whitney U test, median (min.-max.)

WBC: White blood cell, PLT: Platelet, Hb: Hemoglobin, CRP: C-reactive protein, AST: Aspartate transaminase

Additionally, no difference was found in terms of the echocardiographic findings in patients who died and those who survived. Sanfilippo et al.[23] investigated the prognostic value of echocardiographic evaluation in their meta-analysis and review study on pediatric patients with sepsis. Accordingly, they reported that they could not find any relationship between the left ventricular systolic or right ventricular function measurements of echocardiographic parameters in pediatric sepsis and mortality. However, they suggested that there is a relationship between mortality and impaired left ventricular diastolic dysfunction.[23]

Patients with fluid-resistant septic shock may have low, normal, or high cardiac output. Hemodynamics may be variable and may improve with vasoactive drug support. The hemodynamic parameters of systemic vascular resistance are heterogeneous and develop over time in response to inotropic and vasopressor support.[24,25] In our study, there was no significant difference between the echocardiographic findings in any patient who developed septic shock compared to the population, and there was no difference between the echocardiographic findings of those patients who died and those who survived, which may be due to the initiation of vasoactive drug support without waiting for echocardiography. Additionally, the initial hyperdynamic cardiac response to compensate for septic shock may also cause this.

CONCLUSION

Undoubtedly, echocardiography is a useful non-invasive method in the determination of diagnosis, follow-up and treatment of sepsis and septic shock in PICUs. However, there was no difference between the echocardiographic findings of those patients who died and those who survived in our study. This may be due to the functioning of the compensatory mechanisms in septic shock or the immediate initiation of vasoactive drug therapy. To obtain clearer results on this subject, more comprehensive, multicenter, prospective studies with a larger number of patients are needed.

Ethics

Ethics Committee Approval: The study was initiated with the approval of the Kahramanmaraş Sütçü İmam University, Faculty of Medicine Non-Invasive Clinical Trials local ethics committee (decision no: 05 session: 2021/08).

Informed Consent: Consent for this study was obtained from the patients or their families.

Peer-reviewed:

Authorship Contributions

Surgical and Medical Practices: S.İ., U.U.G., Concept: U.U.G., Design: U.U.G., Data Collection or Processing: S.İ., U.U.G., Analysis or Interpretation: S.İ., Literature Search: S.İ., U.U.G., Writing: S.İ.

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Original Article

Investigation of Patients Refusing Treatment in the Pediatric Emergency Service During the COVID-19 Pandemic

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ABSTRACT

Objective: Emergency departments are becoming increasingly crowded. Analyzing patients who refuse treatment in the emergency department is crucial to improve the quality of care and reduce overcrowding. This study determined why some parents who presented to the pediatric emergency department during the coronavirus disease-2019 (COVID-19) pandemic refused treatment for their children.

Materials and Methods: The study was conducted at the Kartal Dr. Lütfi Kırdar City Hospital, Pediatric Emergency Clinic. Patients who presented to the pediatric emergency department between November 1, 2021 and December 31, 2021 and whose parents refused treatment were analyzed retrospectively via telephone interviews. Demographic characteristics, diagnosis, and reasons for refusal to treatment were analyzed.

Results: Over the 2-month period, parents of 154 (0.3%) of 51.111 patients who presented to the pediatric emergency department refused treatment. Parents refused treatment for the following reasons: 68 (44%) parents refused treatment because the patient felt well, 36 (23%) wanted to continue treatment at home, and 18 (11%) wanted to avoid hospitalization. Of the patients who refused treatment, 16 (10%) returned to the pediatric emergency department within 72 h with the same symptoms, and 5 of them were hospitalized.

Conclusion: The COVID-19 pandemic has increased patients' refusal to treatment because of the fear of infection. The inappropriate use of emergency services, which leaves physicians with insufficient time to explain medical examinations and treatments to the family members of patients in a clear and understandable language, as well as the patients' right to re-present to hospitals after refusing treatment, are the main reasons. Actions should be taken to improve working conditions, increase satisfaction of healthcare professionals, raise awareness among patients and their family members and reduce overcrowding at emergency departments. These actions can prevent treatment refusal, even during the COVID-19 pandemic.

Keywords: Emergency department, COVID-19, pediatric patients, refusal of treatment

INTRODUCTION

Patient density in emergency services is increasing daily.[1] Inappropriate applications to the emergency services increase patient density and prevent those who genuinely require emergency health care from benefiting from the service.[2] Reduction in patient density, identification of the reasons for admission, raising awareness of patients regarding unnecessary applications, use of resources efficiently, and improvements in service qualityare extremely important factors for emergency service providers and real emergency patients. Therefore, it is important to examine patients who refuse treatment in the emergency department to address these problems.

The right to refuse treatment is based on the principle of respect autonomy. However, autonomyis the ability to make decisions independently of another person or situation, and to act based on these decisions.[3,4] However, as children are not the ability to make

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decisions independently, they cannot provide informed consent or refuse treatment. Parents or legal guardians have the right to refuse medical treatment on behalf of their children.[5]

Parents of patients admitted to the pediatric emergency department may have various reasons to refuse medical treatment. The refusal of treatment may occur due to the characteristics of the health institution, the health system, the quality of health services, communication between the patient and the physician, financial problems, fears about interventions, educational status of the families, the patient feeling well, and the desire to continue treatment at home.[6,7] Physicians must inform patients and their relatives regarding the problems and consequences that may arise after exercising their right to refuse treatment.

This study aimed to determine the reasons for parents refusing treatment for their children to provide better quality service, increase patient satisfaction, use existing resources efficiently, eliminate deficiencies, and solve existing problems.

MATERIALS AND METHODS

This single-center retrospective cross-sectional descriptive study was conducted in the Pediatric Emergency Clinic of Kartal Dr. Lütfi Kırdar City Hospital. Patients who applied to the pediatric emergency department between 01 November and December 31, 2021, and whose parents refused treatment were retrospectively analyzed. Age, sex, diagnosis, triage codes, average length of hospital stay, reasons for refusing treatment, re-admissions to the hospital after refusing treatment were analyzed in patients who signed the "medical treatment refusal form" using electronic data and via telephonic interviews. Pediatric patients aged 0-18 years and whose information was fully accessible were included in the study. Patients with missing information were excluded from the study. The necessary administrative permissions and ethical approvals were obtained from the relevant authorities.

SPSS ver. 18.0 for Windows (SPSS Inc.; Chicago, IL, USA) program was used for statistical analysis of data. Descriptive statistics were examined and qualitative data are presented as numbers and percentages.

RESULTS

Parents of 154 (0.3%) children among the 51,111 patients who applied to the pediatric emergency department in the two-month study period refused treatment. Of these patients, 76 (49%) were female and 78 (51%) were male. Furthermore, 8 were newborn, 8 were aged 1-3 months, 57 were aged 3-36 months, 31 were aged 3-6 years, and 50 were aged 6-18 years. The triage code of all patients included in the study was yellow. The mean length of hospital stay was 4 years.

Diagnoses of the patients who were refused treatment included lower respiratory tract infection [(LRTI); n=48], intoxication (n=20), coronavirus disease-19 [(COVID-19); n=19], seizures (n=13), acute gastroenteritis (n=11), upper respiratory tract infection (n=8), and others (aspiration, dizziness, preseptal cellulitis, and urinary tract infection, among others) (n=35). The distribution of the diagnoses is presented in Figure 1.

Treatment was refused based on the following reasons: the patient was feeling well (44%; n=68; 25% of these patients were diagnosed withintoxication), desire to continue treatment at home (23%; n=36; 69% of these patients had LRTI), desire to not be hospitalized (11%; n=18), desire to visit another hospital (11%; n=17; 2 patients due to lack of an endoscopy device and 2 patients to get a second opinion), prolonged treatment (n=6), fear of interventions (n=3), and other reasons (n=6; getting ready for hospitalization and waiting for COVID-19 test result at home, among others) (Figure 2).

Of the patients who refused treatment, 14 (9%) were re-admitted to our hospital for follow-up examination and 66 (42%) were re-admitted owingto other health problems. Although 16 (10%) patients applied to the pediatric emergency service again within 72 h with the same complaints, 5 of these patients were hospitalized. Seven of the re-admitted patients were diagnosed with LRTI and four revisited the hospital for a follow-up examination. Three patients applied to the hospital were owing to increased respiratory distress and one of them was hospitalized. One patient who refused treatment had a febrile convulsion and was re-admitted to the hospital. Of the five patients who were hospitalized after re-admission, one patient-refused treatment to wait for COVID-19 test results at home, and one patient left the hospital to prepare for hospitalization before applying later for hospitalization. Three patients were hospitalized as their conditions worsened.

DISCUSSION

Parents may have several reasons for refusing medical treatment for their children in the pediatric emergency department. This study aimed to determine the reasons for refusing treatment of pediatric patients. During the study period, parents of 154 (0.3%) pediatric patients refused treatment. Similar results were obtained in previous studies conducted in Turkey.[8-10]

In this study, none of the parents refused treatment owingto financial reasons. However, in most studies conducted in other countries, financial reasons take the first place among reasons for refusing treatment.[11,12] Previous studies conducted in Turkey show that although financial reasons have never been one of the most common reasons for refusing treatment, the rates were considerably high in the past and have been decreasing steadily.[9,13] This is attributable to the changes and innovations in the health system in Turkey and the increase in the population with health insurance.

The two most important reasons for refusing treatment in this study were patient feeling well after the examination and wanting to continue the treatment at home. The diagnosis of most of the patients who felt well after the examination was intoxication. The most common cause of intoxication in children is medications. Although most cases of drug intoxication are associated with

suicidal purposes in adults, the most common cause in children is accidental ingestion.[14] Parents often do not know whether their children have ingested the toxic substance and apply to the emergency department due to suspicions regarding the same. The fact that the observation period issued by the 114 intoxication control centers in Turkey is too long in most patients can be considered a factor for refusing treatment.

The diagnosis of those who wished to continue the treatment at home was predominantly LRTI. LRTIare a common disease of childhood worldwide. In developing or underdeveloped countries, it is among the causes of mortality in children under the age of 5.[15] Recurrent LRTI is considered more than one attack of bronchitis, bronchiolitis, or pneumonia within 6 months or 3 or more attacks within 1 year.[16] Most of the patients with a diagnosis of LRTI who refused treatment had recurrent LRTI and were experienced patients with home nebulizers.

In this study, 18 (11%) patients refused treatment because they did not want to be hospitalized. COVID-19 pandemic was a serious threat to the time of the study, and some parents stated that the reason for not wanting hospitalization was the fear of contagion. After the onset of the pandemic, there has been a decrease in the number of emergency room patients in several countries. It has been reported that the number of emergency department admissions decreased by 30-40% in China.[17] In Turkey, the number of emergency department admissions also decreased. reportedly, social isolation, thereby a decrease in the spread of infectious factors, postponing the follow-up of chronic diseases, and fear of COVID-19 contamination was effective in decreasing

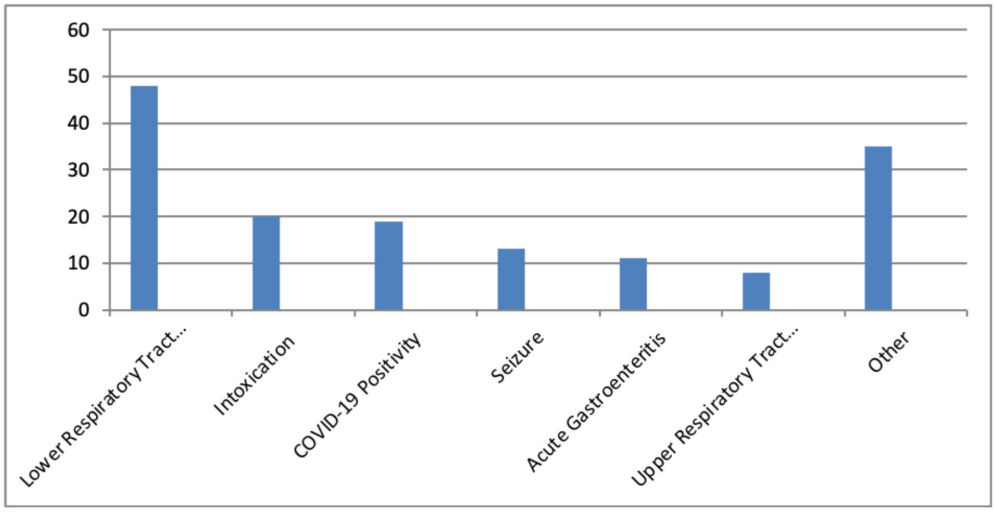

Figure 1. Distribution of diagnoses

COVID-19: Coronavirus disease-2019

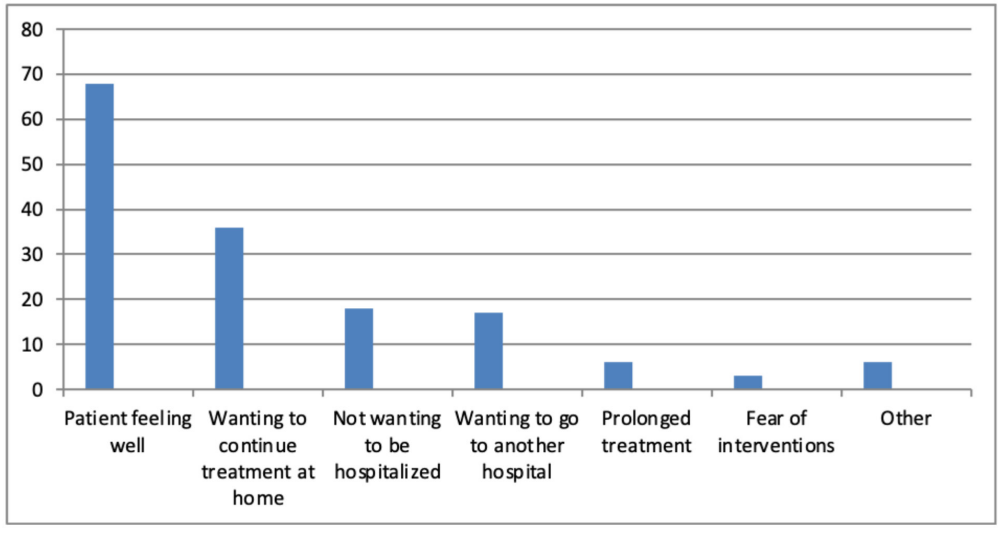

Figure 2. Reasons for parents for refusing treatment

hospital admissions.[18] COVID-19 also affected parents in terms of hospitalization.

Frequent use of emergency services by non-emergency patients creates significant problems for both patients and service providers. Inappropriate use of emergency services is defined as "the use of emergency services for health problems that develop without accident or injury, do not require special emergency services, and can be safely treated in primary healthcare institutions".[19-21] Such inappropriate use of emergency services increases patient density. However, efficient use of resources is extremely important. By reducing the patient density in the emergency services, physicians can spend more time with patient relatives and explain the examination and treatment processes in a way they can understand. Working conditions should be continuously improved and the satisfaction of healthcare workers should be increased. The refusal of treatment can be prevented by a holistic approach checking all of these boxes. This in turn prevents the waste of both labor and other resources.

Study Limitations

The limitations of the study; the demographic and socio-economic characteristics of parents who refused treatment due it being a retrospective study are unknown.

CONCLUSION

In conclusion, the physicians need to assign enough time to explaining the examination and treatment to the patient's relatives in a way they can understand to prevent treatment refusal. To achieve this, patient density in emergency services should be reduced, and the awareness of the patients and their relatives should be increased. The presence of primary healthcare services that patients can use outside working hours is also extremely important in reducing the patient density in emergency services.

Ethics

Ethics Committee Approval: Ethical approval was obtained from Kartal Dr. Lütfi Kırdar City Hospital Clinical Research Ethics Committee (date: 30.03.2022, approval no: 2022/514/222/5).

Informed Consent: Retrospective study.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

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

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Original Article

Evaluation of Thyroid Pathologies Detected During School Screening in Healthy School-Age Children

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ABSTRACT

Objective: The authors of this study took part in a screening program in schools in Aydın province (unpublished study). This study assessed the final thyroid pathologies of these children with pathology detected during ultrasonography (USG) screening obtained as part of the screening program.

Methods: A handheld wireless point-of-care USG device was used to screen the thyroid gland. Children with thyroid pathology were invited to the hospital where detailed lab study and an USG was examined. The study obtained the thyroid measurements, parenchymal features, and noted the presence of nodules in the detailed USG examination. Nodules were classified according to the Thyroid Imaging Reporting & Data System (TI-RADS™) and an USG-guided fine needle aspiration (FNA) was performed according to TI-RADS.

Results: A total of 1,553 cases from 21 schools between the ages of 6-17 were evaluated in the screening program. Thyroid pathology was detected in 176 (11.3%) cases. One hundred twenty of 176 patients' families agreed to attend our centre for further examination, where pathology was confirmed in 108 (90.0%) of the 120 cases. Among the 108 thyroid USG pathologies, 52 (48.1%) patients had a nodule and thyroiditis; 28 (25.9%) patients had only a nodule; 28 (25.9%) patients had only thyroiditis. Thyroiditis was present in 74.0% (n=80) of the cases, of those cases 56.3% (n=45) had peripheral thyroiditis, 31.3% (n=25) had diffuse thyroiditis and 12.5% (n=10) had overweight-related changes. Nodules were present in 73.4% (n=80) of the cases. A total of 9 USG-guided FNA were performed, and their pathology results were as followed; 55.6% (n=5) benign cytology, 11.1% (n=1) follicular adenoma, 11.1% (n=1) atypia of indeterminate significance, 11.1% (n=1) non-diagnostic cytology and 11.1% (n=1) papillary thyroid cancer.

Conclusion: This study showed that thyroiditis and nodules in the thyroid gland are common disorders in children. Thyroid nodules may also have a high malignancy potential and the chance of early diagnosis of thyroid cancers with screening is demonstrated.

Keywords: Children, diffuse thyroiditis, nodule, over-weight related changes, peripheral thyroiditis, point of care ultrasound, screening, thyroid, TI-RADS, ultrasound-guided fine needle aspiration

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INTRODUCTION

Whilst thyroid pathologies are common in children, they are often asymptomatic in the initial clinical stages, thereby making the early diagnosis, treatment, and the management of thyroid disease particularly important.[1] The most common thyroid pathologies during childhood include autoimmune thyroid diseases, thyroid nodules, and malignancies.[2]

Hashimato's thyroiditis (HT), an autoimmune chronic inflammatory disease, is the most common cause of acquired hypothyroidism in children and adolescents.[3] Diagnosis of HT is confirmed by high serum levels of anti-thyroid peroxidase antibodies (anti-TPO) and/or thyroglobulin antibodies (anti-TG).[4] Although USG is not usually required to diagnose diffuse thyroid disease, when typical ultrasonography (USG) findings are present, especially in conditions such as subclinical HT, the diagnosis can be made before the disease becomes obvious.[5,6]

The incidence of childhood thyroid nodules and cancers has increased considerably recently, with most cases being asymptomatic and in the absence of any risk factors.[7] The presence of solid nodules in children also presents a higher risk of malignancy compared in adults[8,9]. The Thyroid Imaging Reporting and Data System (TI-RADS) classification was developed to determine the malignancy risk of thyroid nodules in adults. Although there are various studies to have adapted this classification to a pediatric age group, its safety has not yet been clearly demonstrated.[10]

Over the past five decades, there has been an increasing incidence of diagnoses of differentiated thyroid cancer in the pediatric age group. This is largely due to the increased incidence of papillary thyroid cancer. Most pediatric patients diagnosed with differentiated thyroid cancer present with an asymptomatic thyroid nodule found incidentally on physical examination or non-thyroid-related head and neck imaging.[8] Therefore, screening comes to the fore in early diagnosis and treatment. Generally, whilst most thyroid nodules are benign, when a child or adolescent is found to have a thyroid nodule, there is a two to three-fold increased risk of malignancy compared with adults.[11]

Thyroid pathologies can be asymptomatic in children and can be detected during imaging or routine physical examination performed for another purpose.[2] Accordingly, imaging plays an important role in the evaluation of thyroid diseases in pediatric patients. USG provides detailed information about the anatomical structure and characteristics of the thyroid gland and is the first-line diagnostic test to detect thyroid abnormalities.[5,12,13]

The authors of this study conducted a screening program titled "Current Iodine Status and Thyroid Volumes in Healthy School-Age Children" in schools within Aydın province, Türkiye (unpublished study). This retrospective study assesss the final thyroid pathologies of the children with suspected thyroid pathologies detected during screening program.

MATERIALS AND METHODS

The authors were screened 1,553 children between the ages of 6-17 across 21 schools in the study entitled as "Current Iodine Status and Thyroid Volumes in Healthy School-Age Children" (unpublished study). The weight and the height of the children were recorded, and a thyroid was examined using a handheld wireless point-of-care USG device. Thyroid imaging was performed with SonoStar™ Wireless Ultrasound Scanner (Uprobe-C5PL 3 in 1 Linear/Convex /Phased Array Probe, Universal Diagnostic Solutions Inc., California, USA).

Children with suspected thyroid pathologies on physical examination and/or thyroid imaging was invited to the hospital and were investigated for thyroid diseases. Finally, the auxological, clinical, laboratory and radiographical data of the subjects were obtained from the hospital records, retrospectively. Participants were tested for serum-free thyroxine (fT4), thyrotropin stimulating hormone (TSH), anti-TPO and anti-thyroglobulin (anti-TG). In addition detailed thyroid USG was performed with the LA2-9 MHz linear high-resolution probe of the Samsung™ RS80A USG device (Gyeonggi-do, Republic of Korea) in the department of radiology by the same radiologist who was involved with the screening program. Body mass index (BMI) was calculated using the "weight (kg)/[height (m)]^2" formula and body surface area (BSA) was calculated using the Dubois and Dubois formula "0.007184 x height (cm)$^{0.725}$ x weight (kg)$^{0.425}$".[14] BMI percentiles were calculated using the website http://www.ceddcozum.com with >85 percentile considered as overweight.[14]

Thyroid-stimulating hormone (TSH) in laboratory tests: 0.6-5.5 µIU/mL; fT4: 0.8-1.9 ng/dL; anti-TPO: 0-60 IU/mL; anti-TG: 0-60 IU/mL were considered normal. Those with normal TSH and fT4 levels at the time of diagnosis were considered euthyroid, whereas fT4 was normal, those with high TSH were considered subclinical hypothyroidism, and those with low fT4 and high TSH were considered overt hypothyroidism.

In the USG evaluation, the dimensions [antero-posterior (AP), medio-lateral (ML) and longitudinal (long)] and volumes of both lobes of the thyroid glands were measured. The volume of the thyroid gland was calculated using the formula of the World Health Organization (WHO) "[AP x ML x Long]x 0.479".[15] The isthmus thickness was measured. The parenchymal features of each lobe of the thyroid gland were evaluated (parenchymal echo, parenchymal contours). Next, the presence of the nodules investigated. For this purpose, both thyroid glands were scanned craniocaudal. If nodules were detected, they were classified according to the TI-RADS-scoring system. USG-guided fine needle aspiration (FNA) was decided in line with the TI-RADS management strategy.

The patients, who had planned to be performed USG guided fine needle aspiration (FNA), were informed about the procedure. All patients's complete blood count and bleeding parameters were checked before performing the procedure. Patients were placed in the supine position with the neck hyperextension, and USG

guidance procedure was performed using a 22-gauge needle. The aspirated material was spread on a glass slide. If the incoming material was insufficient, the FNA was repeated. Finally, the materials were sent to the pathology laboratory and pathological was examined.

Diffuse parenchymal heterogeneity increased thyroid gland sizes, echogenic septations, micronodular or pseudonodular appearance were accepted as HT in the USG examination. Additionally, anti-TPO and/or anti-TG positivity was accepted as HT, regardless of the USG findings. Peripheral thyroiditis was defined as the presence of parenchymal heterogeneity changes and/or accompanying millimetric colloidal cystic changes only in the peripheral zone of the thyroid gland (Figure 1). In children with overweight and thyroiditis, findings in the thyroid parenchyma were accepted as overweight-related changes in autoantibody negativity.

Statistical Analysis

The statistics of the study were obtained using the Statistical Package for Social Science "SPSS" program (IBM Corp. Released 2019, IBM SPSS Statistics for Windows, version 26.0. Armonk, NY: IBM Corp.). The normality of the distribution was evaluated with descriptive statistics, steepness and skewness coefficients, histogram, and Shapiro-Wilk test. Categorical variables n and percent were given as mean ± standard deviation if numerical variables were normally distributed, and median (25-75 percentile) if not normally distributed. In the comparison of the three groups, the ANOVA test was used if the data were normally distributed (Tukey if the variances were homogeneously distributed in the post hoc analysis, Tamhane's T2 test if the variances were not homogeneously distributed), the Kruskal-Wallis H test (Dunn test in the post hoc analysis), and the chi-square test was used for the comparison of the categorical variables. The compatibility between the USG performed during the scan and the USG measurements performed in the hospital was evaluated using the Bland-Altman method. Type 1 error was determined as 5%, a p-value of <0.05 was considered statistically significant.

Informed consent from the parents of the patients had already been obtained before including the patients to the screening programme. This study was approved by the Aydın Adnan Menderes University Faculty of Medicine, Clinical Research Ethics Committee (no: 2022/67, date: 07.04.022).

RESULTS

Thyroid pathology was detected by physical examination and/or USG across 176 participants (11.3%) from the screening program, and they were invited to the hospital (107 girls, 60.8%). One hundred twenty (68.1%) of the 176 participant families agreed to attend our hospital for further examination. Pathology was detected on USG in 108 (90.0%) of the 120 cases, the right lobe hemiagenesis of the thyroid was found in one case but was considered as a normal variant (Figure 2).

The median age of participants was 14.0 (11.0-16.0) years. Sixty point two percent (n=65) of 108 cases were girls. Median height was 160.0 cm [(146.0-166.5 cm), [-0.0±1.0 standard deviation score (SDS)], body weight 54.0 kg [(43.0-65.0 kg), (-0.3±1.4 SDS)], body surface area 1.6 (1.3-1.7) m^2, BMI 20.9 (18.1-24.2) kg/m^2, and 25.9% (n=28) were overweight. All cases were euthyroid and the median TSH was 1.7 (1.1-2.3) µIU/mL, fT4 was 1.0 (0.9-1.1) ng/dL. The right thyroid volume was 4.9 (3.2-6.5) cc, left thyroid volume was 3.2 (2.1-4.4) cc, total thyroid volume 8.0 (5.5-10.5) cc, and isthmus thickness was 2.1 (1.7-2.7) mm (Table 1).

In the Bland-Altman analysis performed in terms of the correlation of detailed USG measurements (right thyroid volume, left thyroid

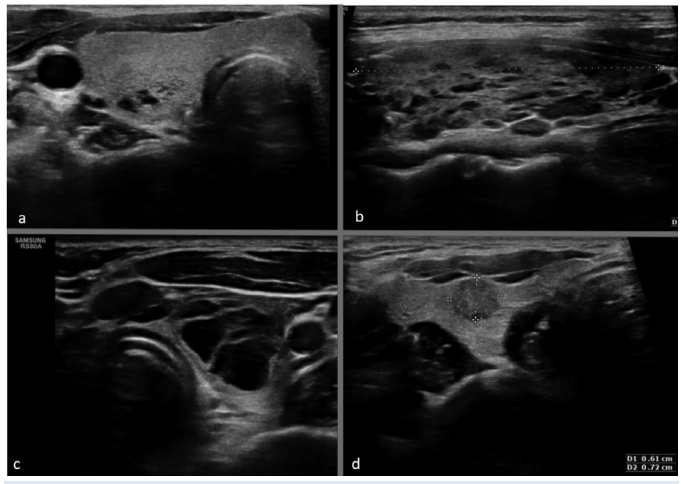

Figure 1 a-d: An axial plane image of a case with peripheral thyroiditis with isolated peripheral heterogeneity and colloidal-cystic changes (a). A longitudinal image of a case with diffuse thyroiditis with diffuse parenchymal heterogeneity and colloidal-cystic changes (b). An axial plane image of a case with a pathologically diagnosed mostly cystic benign nodule (c). An axial plane image of a case with TI-RADS 5 nodule (solid, hypoechoic, with microcalcification), pathologically diagnosed as papillary thyroid cancer (d)

TI-RADS: The Thyroid Imaging Reporting and Data System

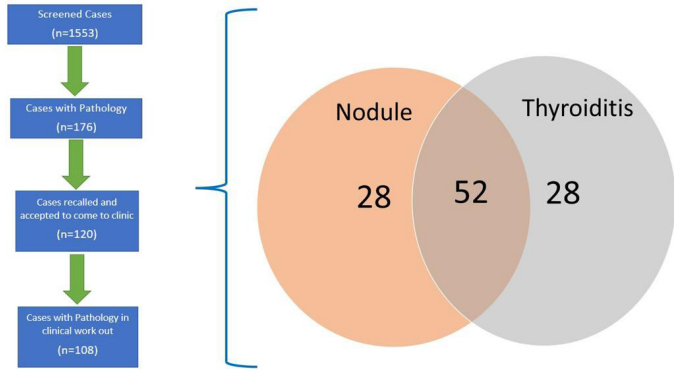

Figure 2. Flowchart of the study cohort and distribution of thyroiditis and nodule cases

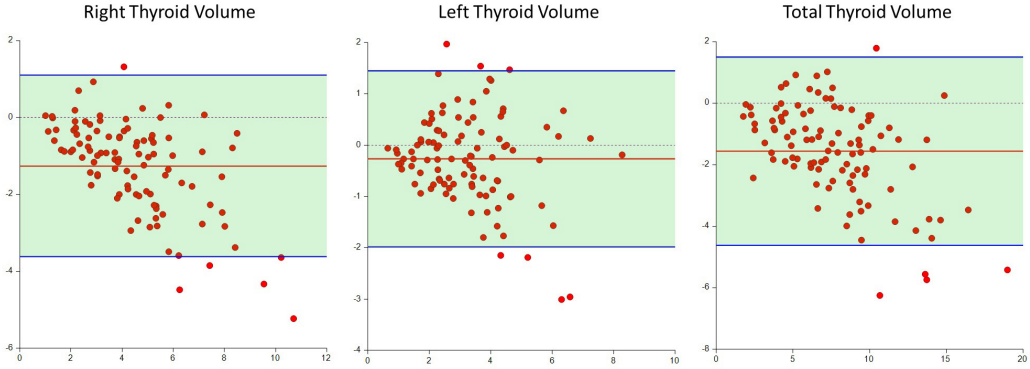

Figure 3. The Bland-Altman analysis of the USG measurements (right thyroid volume, left thyroid volume and total thyroid volume) between screening and detailed USG examination

USG: Ultrasonography

volume and total thyroid volume) that was performed in the hospital with the same age group at the screening; a strong correlation was found between the measurements (Figure 3). The difference between the screening measurements and the measurements made in the hospital is expressed as cc, and -1.3 [(-3.6)-1.1] for the right lobe volume, -0.3 [(-2.0)-1.5] for the left lobe, and -1.6 [(-4.5)-1.5] for the total thyroid volume. The most consistent results among measurements were for left thyroid measurements (Table 2).

Among 108 thyroid USG pathologies, 52 (48.1%) patients had nodule and thyroiditis; 28 (25.9%) patients had only nodule; 28 (25.9%) patients had only thyroiditis (Figure 2).

Thyroiditis was present in 74.0% (n=80) of the cases, of those cases 56.3% (n=45) had peripheral thyroiditis, 31.3% (n=25) had diffuse thyroiditis and 12.5% (n=10) had overweight-related changes. Sixty five percent (n=52) of thyroiditis cases were with nodules. Seventy-six-point nine percent (n=40) of those nodules were multinodular and 23.1% (n=12) were solitary. The median age of the subjects with thyroiditis was 14.0 (12.0-16.0) years [(62.5% (n=50) girls)]. The characteristics of the groups with only nodules, only thyroiditis, and both pathologies are presented in detail in Table 3. The subjects with different types of thyroiditis (diffuse, peripheral, and overweight-related changes) were compared and there was no significant difference between the groups (Table 4).

Nodules were present in 73.4% (n=80) of the cases. Sixty percentage (n=48) of those cases were multi-nodular, 40.0% (n=32) were solitary nodules. Sixty-five percent (n=52) of nodule cases were associated with thyroiditis. The median age of subjects with nodules was 14.0 (11.5-16.0) years [58.8% (n=47) girls]. The TI-RADS classification features of the detected thyroid nodules are given in Table 5. A total of 9 USG-guided FNA performed, and their pathology results were as followed; 55.6% (n=5) benign cytology, 11.1% (n=1) follicular adenoma, 11.1% (n=1) atypia of indeterminate significance, 11.1% (n=1) non-diagnostic cytology and 11.1% (n=1) papillary thyroid cancer (Figure 1) (Table 5).

DISCUSSION

Thyroiditis is an inflammation of the thyroid gland, which can clinically appear as euthyroid, hyperthyroid or hypothyroid. The most common form of these in a pediatric age group is Hashimoto's thyroiditis with prevalence of 1%-3%, peaking during adolescence.[16,17] It is seen more frequently in girls with a female/male ratio previously reported as 4-8:1.[18] HT is the gradual destruction of the thyroid gland by an autoimmune mechanism, with or without an enlargement of the thyroid gland (goiter). The diagnosis of HT is made by the presence of anti-thyroid antibodies (anti-TPO or anti-TG) and/or the presence of typical USG findings. At the time of diagnosis, 52.1% of the thyroid function tests of children with HT were euthyroid, 22.2% were overt, 19.2% were subclinical hypothyroid and 6.5% were overt and subclinical hyperthyroid.[19] In the study of Admoni et al.[20] 75% of the children diagnosed with HT were euthyroid and remained euthyroid. In other studies 87% HTs were asymptomatic, and 50% of them underwent spontaneous resolution.[16,17] For this reason, the literature on the subject still has not reached a consensus on screening for HT. In our study, HT findings were present in 27 (25%) of 108 cases, who were all euthyroid in their thyroid function tests. Thirteen (12.1%) of them had only diffuse parenchymal heterogeneity with serological markers without typical USG findings. Ten (9.3%) had both typical USG findings and positive serological markers, 2 (1.9%) had serological markers only and showed peripheral parenchymal heterogeneity. Autoimmune diseases such as type 1 diabetes mellitus, or chromosomal anomalies such as Turner syndrome increase the risk of HT. As such, it is recommended to routinely screen for HT in these individuals. Screening for HT with USG is not recommended for the healthy populations.

Twenty-eight (25.9%) of the 108 cases were classified as overweight. In 12 of these children's USG, decreases in parenchymal echogenicity, heterogeneity and colloidal cystic changes were detected in the periphery of the thyroid gland. A review by Szczyrski et al.[21] suggested that parenchymal heterogeneity in the thyroid peripheral zone of obese children is

Table 1. Basic demographic information, thyroid function test and USG findings of the cases		
	N/mean ± SD	%/med (25-75 P)
Gender		
Boy	43	39.8
Girl	65	60.2
Age (years)	13.1±3.2	14.0 (11.0-16.0)
Height (cm)	156.4±16.0	160.0 (146.0-166.5)
Height (SDS)	0.0±1.0	0.1 (-0.7-0.7)
Weight (kg)	54.3±19.1	54.0 (43.0-65.0)
Weight (SDS)	0.3±1.4	0.1 (-0.6-1.1)
BSA (kg/m²)	1.5±0.3	1.6 (1.3-1.7)
BMI (m²)	21.5±5.0	20.9 (18.1-24.2)
Overweight		
Yes	28	25.9
No	80	74.1
Thyroid function		
Euthyroid	108	100.0
TSH (µIU/mL)	1.9±1.1	1.7 (1.1-2.3)
fT4 (ng/dL)	1.0±0.1	1.0 (0.9-1.1)
Anti-TPO		
Positive	15	13.9
Negative	93	86.1
Anti-TG		
Positive	16	14.8
Negative	92	85.2
Right thyroid volume (cc)	5.1±2.7	4.9 (3.2-6.5)
Right thyroid echogenicity		
Homogeneous	23	21.3
Heterogeneous	85	78.7
Isthmus thickness (mm)	2.3±0.9	2.1 (1.7-2.7)
Left thyroid volume (cc)	3.5±1.8	3.2 (2.1-4.4)
Left thyroid echogenicity		
Homogeneous	23	21.3
Heterogeneous	85	78.7
Total thyroid volume (cc)	8.6±4.2	8.0 (5.5-10.5)

Data were given as n (%), mean±SDS, median (25-75 percentile)

USG: Ultrasonography, SDS: Standard deviation score, BMI: Body mass index, BSA: Body surface area, TSH: Thyrotropin stimulating hormone, fT4: Free thyroxine, Anti-TPO: Anti-thyroid peroxidase antibodies, Anti-TG: Thyroglobulin antibodies, SD: Standard deviation

an obesity-related change. Among the possible causes of these changes observed in thyroid USG in obese children without autoimmunity is fat deposition in the thyroid gland and vasodilation caused by cytokines and inflammatory cells produced in the adipose tissue, and the increase in permeability of the thyroid vessels and plasma exudation in the thyroid parenchyma.[22,23] The improvement in thyroid morphology of obese patients after weight loss supports this view.[24] We associated these findings with overweight and classified them as changes related to weight gain. The sonographic findings of peripheral thyroiditis in patients with normal weight and negative autoantibodies were thought to be a precursor of autoimmune thyroiditis. We believe following up these children for possible autoimmune thyroiditis is advisable.

The incidence of thyroid nodules and cancer has increased significantly recently.[7] Most patients with thyroid nodules or thyroid cancer are asymptomatic at the time of diagnosis. Thyroid lesions of these patients are usually detected incidentally in a routine physical examination, during head and neck imaging, or during the evaluation of lymphadenopathy.[25] The incidence of thyroid nodules increases with age, but in contrast to adults, nodules detected in patients younger than 19 years have higher rates of malignancy (10-15% versus 20%25%, respectively).[11,26] Papillary thyroid cancer is the most common type of thyroid cancer in both adult and pediatric patients.[27] Since papillary cancer spreads through lymphatics, cervical lymph node metastasis is common at the time of diagnosis and is detected in 70% of pediatric patients.[27] Unlike papillary thyroid cancer, follicular thyroid cancer metastasizes by the hematogenous route. However, in the pediatric age group, follicular thyroid cancer has a milder course and remains confined to the thyroid gland.[12]

In this study, nodules were detected in 80 (74.1%) children. The incidence of thyroid nodules in pediatric literature is between 0.05%-5.1%.[11,12,28-31] In our screening program the incidence of thyroid nodules was very close to literature, which was 5.15% (80 cases out of 1,553). The TI-RADS-classification was used for the USG evaluation of these nodules. Although there are few studies in the literature in which the TI-RADS classification is used in the pediatric population, it has been concluded in these studies that the TI-RADS classification can be used easily and reliably for thyroid nodule risk classification in the pediatric population.[32-34] In accordance with the TI-RADS classification and the decision made in our pediatric thyroid nodule council in our institute, 9 of the 80 children underwent USG guided FNA (Table 5). One case was diagnosed with papillary thyroid cancer and invasion of central and lateral lymph nodes was detected (Figure 1).

Although thyroid cancer rates have increased significantly in the pediatric population recently, screening for thyroid nodules and cancer in children remains controversial. In a long-term follow-up study, Anderson et al.[35] found only a minimal increase (<1%) in thyroid cancer mortality in adolescents, suggesting that childhood thyroid cancer rarely causes death.[36] A study by Vaccarella et al.[37], examining the global pattern and incidence of thyroid cancer in children and adolescents, noted that the potential harms of diagnostic pressure outweigh the potential benefits in child and adolescent population. Furthermore, the study found that the increased incidence of thyroid cancer in this population was related to overdiagnosis.[37] Most children with thyroid cancer undergo total thyroidectomy. These children will undergo a lifelong therapy for thyroid hormone replacement, which often affects their quality of life. Thus, it has been debated that thyroid cancer screening should not be performed in asymptomatic children without risk factors.[37] However, this study diagnosed a case with papillary thyroid cancer that had metastasized to the

Table 2. Consistency evaluation of USG thyroid measurements between screening and detailed USG examination			
	Right thyroid volume	**Left thyroid volume**	**Total thyroid volume**
Mean of differences	-1.3	-0.3	-1.6
Upper limit of the 95% CI	-3.6	-2.0	-4.6
Lower limit of the 95% CI	1.1	1.5	1.5
Correlation coefficient	0.894	0.847	0.926
r	0.957	0.835	0.914
p	<0.001	<0.001	<0.001
USG: Ultrasonography, CI: Confidence interval			

Table 3. Characteristics of the groups with only nodules, only thyroiditis, and both pathologies				
	Nodule (n=28)	**Thyroiditis (n=28)**	**Nodule and thyroiditis (n=52)**	**p**
Gender				
Boy	13 (46.4)	10 (35.7)	20 (38.5)	0.688
Girl	15 (53.6)	18 (64.3)	32 (61.5)	
Age (years)	13.0 (8.0-15.5)	14.0 (10.0-15.0)	15.0 (12.5-16.0)	0.035
Height (cm)	150.4±20.7	155.3±15.1	160.2±12.4	**0.048**
Height (SDS)	0.0±0.9	0.1±1.2	0.0±1.0	0.781
Weight (kg)	49.7±22.3	58.7±22.0	54.4±15.1	0.268
Weight (SDS)	0.3±1.2	1.0±1.6	0.0±1.4	**0.015**
BSA (m^2)	1.4±0.4	1.6±0.3	1.5±0.3	0.211
BMI (kg/m^2)	20.7±5.3	23.6±5.5	20.8±4.1	**0.030**
Overweight				
Yes	6 (21.4)	12 (42.9)	10 (19.2)	0.058
No	22 (78.6)	16 (57.1)	42 (80.8)	
TSH (µIU/mL)	1.5 (1.1-2.1)	2.0 (1.1-2.5)	1.7 (1.1-2.3)	0.353
fT4 (ng/dL)	1.0 (0.9-1.1)	1.0 (0.9-1.1)	1.0 (0.9-1.1)	0.537
Anti-TPO				
Positive	0 (0.0)	8 (28.6)	7 (13.5)	**0.009**
Negative	28 (100.0)	20 (71.4)	45 (86.5)	
Anti-TG				
Positive	0 (0.0)	8 (28.6)	8 (15.4)	**0.014**
Negative	28 (100.0)	20 (71.4)	44 (84.6)	
Right thyroid volume (cc)	4.3 (2.2-5.6)	4.3 (3.1-7.4)	5.2 (3.7-6.8)	0.060
Right thyroid echogenicity				
Homogeneous	22 (78.6)	0 (0.0)	1 (1.9)	**<0.001**
Heterogeneous	6 (21.4)	28 (100.0)	51 (98.1)	
Isthmus thickness (mm)	2.1 (1.6-2.6)	1.9 (1.6-2.9)	2.3 (1.9,2.8)	0.371
Left thyroid volume (cc)	2.2 (1.6-3.7)	3.3 (2-4.7)	3.5 (2.7-4.5)	**0.009**
Left thyroid echogenicity				
Homogeneous	22 (78.6)	0 (0.0)	1 (1.9)	**<0.001**
Heterogeneous	6 (21.4)	28 (100.0)	51 (98.1)	
Total tytoid volume (cc)	6.8 (3.9-9.2)	7.5 (5.3-11.7)	8.7 (6.6-11.0)	**0.034**

Data were given as n (%), mean±SDS, median (25-75 percentile)

SDS: Standard deviation score, BMI: Body mass index, BSA: Body surface area, TSH: Thyrotropin stimulating hormone, fT4: Free thyroxine, Anti-TPO: Anti-thyroid peroxidase antibodies, Anti-TG: Thyroglobulin antibodies

Table 4. Comparison of different types of thyroiditis				
	Diffuse (n=25)	**Peripheral (n=45)**	**Obesity-related changes (n=10)**	**p**
Gender				
Boy	9 (36.0)	17 (37.8)	4 (40.0)	0.974
Girl	14 (64.0)	28 (62.2)	6 (60.0)	
Age (years)	15.0 (10.0-16.0)	15.0 (12.0-16.0)	13.0 (12.0-14.0)	0.308
Height (cm)	156.7±14.4	159.3±13.3	160.4±12.1	0.696
Height (SDS)	0.1±1.1	-0.1±1.1	0.4±0.6	0.436
Weight (kg)	59.8±22.6	52.2±12.8	66.9±19.5	0.072
Weight (SDS)	0.7±2.0	-0.3±0.9	1.9±1.3	**<0.001**
BSA (m^2)	1.6±0.3	1.5±0.2	1.7±0.3	0.190
BMI (kg/m^2)	23.8±6.0	20.2±3.1	25.5±5.1	*
Overweight				
Yes	11 (44.0)	1 (2.2)	10 (100.0)	*
No	12 (56.0)	44 (97.8)	0 (0.0)	
TSH (µIU/mL)	2.2 (1.1-2.8)	1.6 (1.1-2.2)	2.1 (1.7-2.7)	0.060
fT4 (ng/dL)	1.0 (0.9-1.1)	1.0 (0.9-1.0)	1.1 (0.9-1.1)	0.405
Anti-TPO				
Positive	15 (60.0)	0 (0.0)	0 (0.0)	*
Negative	10 (40.0)	45 (100.0)	10 (100.0)	
Anti-TG				
Positive	14 (56.0)	2 (4.4)	0 (0.0)	*
Negative	11 (44.0)	43 (95.6)	10 (100.0)	
Right thyroid volume (cc)	5.6 (3-8.7)	4.9 (3.6-6.5)	5.4 (3.7-7.6)	0.520
Isthmus thickness (mm)	2.2 (1.6-3.2)	2.1 (1.7-2.6)	2.6 (2-3.3)	0.394
Left thyroid volume (cc)	3.4 (2.3-5.7)	3.3 (2.7-4.2)	4 (2.4-5.1)	0.683
Total tyroid volume (cc)	10.1±5.4	8.7±3.2	10.5±5.3	0.393
Nodule				
Negative	15 (60.0)	9 (20.0)	4 (40.0)	**0.003**
Positive	10 (40.0)	36 (80.0)	6 (60.0)	
Nodule type				
Solitary	5 (50.0)	6 (16.7)	1 (16.7)	0.082
Multi-nodular	5 (50.0)	30 (83.3)	5 (83.3)	

*p-values were not calculated due to data characteristics.

Data were given as n (%), mean ± SDS, median (25-75 percentile).

SDS: Standard deviation score, BMI: Body mass index, BSA: Body surface area, TSH: Thyrotropin stimulating hormone, fT4: Free thyroxine, Anti-TPO: Anti-thyroid peroxidase antibodies, Anti-TG: Thyroglobulin antibodies

central and lateral lymph nodes, without any risk factors and were asymptomatic. It was considered that the relatively early diagnosis and treatment of this case contributed positively to the morbidity and mortality of this patient. With this one case in our screening program the incidence of thyroid cancer was 0.06% (1 case out of 1,553) in our population and this incidence was higher than that in the United States, which has an incidence rate of 0.014%.[38] Therefore, screening should be considered seriously in countries with a high incidence rate of thyroid cancer.

Study Limitations

Not being able to include all the patients where we detected pathology in our screening program, the possibility of missing potential indistinct pathologies (such as mild parenchymal

Table 5. The TI-RADS classification features of the detected thyroid nodules and pathological results of the nodules		
	n	%
TI-RADS classification (score)		
TI-RADS 1 (0)	49	61.3
TI-RADS 2 (2)	4	5.0
TI-RADS 3 (3)	9	11.3
TI-RADS 4 (4-6)	15	18.8
TI-RADS 5 (>6)	3	3.8
Histopathological results of the nodules		
Benign cytology	5	55.6
Follicular adenoma	1	11.1
Atypia of indeterminate significance	1	11.1
Papillary thyroid cancer	1	11.1
Non-diagnostic cytology	1	11.1
TI-RADS: The Thyroid Imaging Reporting and Data System		

heterogeneity, mild thyroiditis) using a hand-held USG device in the screening step, performing all USG examinations by a single radiologist and not being able to present long-term data on children included in this study were the limitations of the study. Being adequately representative of the regional population because it evaluates the pathologies detected due to the screening program in a large population, being able to evaluate pathologies in detail after the screening program and in case FNA is required, the fact that the FNA procedure is performed by the same radiologist who conducted the screening program, were study strengths.

CONCLUSION

In conclusion, this study showed that autoimmune thyroiditis and parenchymal changes in the thyroid gland due to obesity are common disorders in children. Also, thyroid nodules may have a high malignant potential and the chance of early diagnosis of thyroid cancers with screening is demonstrated.

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Ethics

Ethics Committee Approval: This study was approved by the Aydın Adnan Menderes University Faculty of Medicine, Clinical Research Ethics Committee (no: 2022/67, date: 07.04.022).

Informed Consent: Informed consent from the parents of the patients had already been obtained before including the patients to the screening programme.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.G., Concept: M.G., A.A., Design: M.G., A.A., Data Collection or Processing: M.G., R.D.S., S.Ö., Analysis or Interpretation: S.Ö., A.A., Literature Search: M.G., R.D.S., A.A., Writing: M.G., R.D.S., A.A.

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

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Original Article

Evaluation of the Knowledge and Awareness Level of the Pediatric Residents About the Diagnosis, Treatment and Follow-up of Urinary Tract Infection in Children

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ABSTRACT

Objective: In this study, we sought to assess pediatric residents' level of knowledge about the diagnosis, treatment, and follow-up of urinary tract infection in children.

Methods: This survey was a descriptive study applied to pediatric residents. In the study, a questionnaire form prepared by researchers consisting of questions about socio-demographic features, about the diagnosis, treatment, and follow-up of urinary tract infection in children was used.

Results: Eighty-eight physicians participated in this research. The percentage of participants who correctly indicated urine culture based on the results of routine urinalysis in the diagnosis of urinary tract infection ranged from 95.5% to 96.6. 54.5% of participants (n=48) correctly identified the indication for ultrasonography in children with acute urinary tract infection. 67.0% (n=59) of the participants answered that Mercaptuacetyltriglycin was not appropriate for initial evaluation of recurrent urinary tract infection under the age of one year, while 33.0% (n=29) answered the question incorrectly. In clinical scenarios, 48.9% (n=43.0) participants made the proper decision for treatment of extended spectrum beta-lactamase-positive *E. coli* treatment.

Conclusion: In conclusion, pediatric residents had appropriate training and experience in the diagnosis of urinary tract infection in children. However, over half of the residents lacked sufficient training in the management of resistant bacteria and additional radiological imaging techniques. Considering this, we believe it will be good to keep the knowledge updated concerning the treatment and follow-up of children with urinary tract infection through in-service training and post-graduate education.

Keywords: Pediatric residents, urinary tract infection, diagnosis, treatment, follow-up, radiological imaging

INTRODUCTION

Urinary tract infection (UTI) is a common bacterial infection during early childhood.[1] In the first eight years of life, 2% of boys and 7-8% of girls experience a UTI.[2] Prepubescent girls and boys are diagnosed with UTI at rates of 3% and 1%, respectively.[3] Moreover, approximately 7.8% of children aged between 2 and 19 years who have fever and/or urinary tract symptoms have UTI.[3] After the first few months of life, UTIs occur more frequently in girls than in boys, because of the shorter length of the female urethra.[4]

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Clinically, UTIs can range from asymptomatic bacteriuria to acute pyelonephritis, which can cause children to develop sepsis.[5] Lower UTIs are more prevalent, although infections at a young age frequently take the form of pyelonephritis. Childhood upper UTIs pose a significant risk of eventual kidney injury, hypertension, or kidney failure.[6] The infection can return frequently and result in morbidities such development retardation, kidney scarring, and high blood pressure in children, despite advances in medicine and the therapy of UTI. Therefore, it is crucial to identify UTI and treat it appropriately.[7]

In this study, we sought to assess pediatric residents' level of knowledge about the diagnosis, treatment, and follow-up of UTI in children and to identify their knowledge gaps.

MATERIALS AND METHODS

This descriptive study was conducted in 2022. A questionnaire was used to help gather the data. The researcher developed the questionnaire by reviewing the literature, and the data regarding the detection and treatment of UTIs was made by considering the most recent National Institute for Health and Clinical Excellence (NICE) guideline in England.[8] Pediatric residents were asked to fill out surveys while researchers watched. The practitioners were informed about the study before administering the surveys, and their verbal and written consent was obtained. The participants who took part in the survey received a questionnaire with 13 items on it, which they were requested to complete anonymously. The questions were written in the style of closed-ended, multiple-choice questions (Table 1). There is a brief piece in the questionnaire that asks about the physicians' socio-demographic traits and how long they have worked as assistants. The questions are divided into three primary categories: diagnosis, therapy, and patient follow-up.

Statistical Evaluation

Statistical analysis was performed using SPSS Statistical Software (version 25; SPSS, Chicago, IL, USA), and mean, standard deviation, number and percentage were used to define the data. Pearson's chi-square test and Fisher's chi-square test were used to compare discrete (discontinuous/uncountable) variables between groups. Statistical significance was set as $p<0.05$. This study was approved by the institutional board.

Ethics approval for this study was obtained from the Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital with the approval number of 736 and the date with 15.09.2022.

RESULTS

Eighty-eight pediatric residents participated in the research. The gender split among the participating physicians was 76.1% female (n=67) and 23.9% male (n=21). The average age was 24 to 30 years in 79 (89.8%) residents and 30 to 35 years in 9 (10.2%) residents. Participants in the survey were clinicians who were between the first and fourth years of their residency training, and 18 (20.5%) individuals were found to be in their first year of pediatric education, while 15.9% (n=14) were in their final year. Throughout their pediatric residency training, 71 (80.7%) of the residents had previously studied in the nephrology clinic (Table 2). Generally, the percentages of responses to the questions ranged from 98.8 to 94.3%. The percentage of respondents who said, "I have no idea," was computed to range from the lowest 1.1% (n=1) to the highest 5.7% (n=5).

Of the participants, 2.3% and 5.7% stated that they had no opinion on UTI identification and epidemiology, respectively.

Table 1. Major elements of the questions in the questionnaire
1. Choose the incorrect statement regarding the epidemiology of pediatric urinary tract infections.
2. Which of the following is not included in the definition of atypical urinary tract infection?
3. Which of the following is the most common causative agent for pediatric urinary tract infection?
4. Which of the following is not defined as a recurrent urinary tract infection?
5. Which of the following is true about the time it takes for the urine sample to be delivered to the laboratory after collection?
6. Which of the following routine urine examination findings would not consider taking a urine culture?
7. Which of the following is not an indication for urine culture?
8. Which of the following is false regarding imaging of urinary tract infection?
9. A boy younger than 1 year has a recurrent urinary tract infection. Which of the following examinations would you not want the patient to prioritize?
10. Which of the following patients with urinary tract infection does not have an indication for hospitalization?
11. In which patient group below would you not consider urinary tract infection prophylaxis as a priority?
12. Which of the following scenarios for urinary tract infection does not require treatment?
13. A 4-year-old girl, who was followed up by the otolaryngology department due to hearing loss, was diagnosed with leukocyte +3 and bacteria 1,037 in her urine, and a midstream urine culture was taken when she applied for fever and vomiting. The patient was started on prophylactic ceftriaxone. On the 3rd day of the hospitalized patient's treatment, while the fever continues, ESBL+ *E. coli* was detected in his culture, which of the following changes would you make first in his treatment?

Table 2. Socio-demographic characteristics of the residents	
Variables	**N (%)**
Gender	
Female	67 (76.1)
Male	21 (23.9)
Age range (years)	
24-30 age range	79 (89.8)
30-35 age range	9 (10.2)
Years of education in pediatric residency training	
0-1	18 (20.5)
1-2	20 (22.7)
2-3	21 (23.9)
3-4	15 (17.0)
4-5	14 (15.9)
Previously worked in the nephrology clinic during pediatric residency training	
Yes	71(80.7)
No	17(19.3)

Most participants (n=86, 97.7%) knew that *Escherichia coli (E. coli)* is the major cause of UTIs. The percentage of participants who properly answered the questions about the definition of recurrent UTI ranged from 54.5% (n=48) to 84.1% (n=74), whereas the percentage of participants who correctly answered the question about the diagnosis of atypical UTI remained at 52.3% (n=46).

The percentage of participants who correctly indicated urine culture based on the results of routine urinalysis in the diagnosis of UTI ranged from 95.5% to 96.6% (n=84 to n=85). 54.5% of participants (n=48) correctly identified the indication for ultrasonography (USG) in children with acute UTI. 60.2% (n=53) participants correctly responded to the question about when the laboratory should collect the urinary tract sample.

In the ninth question, was asked that "A boy younger than 1 year who had a recurrent UTI. Which of the following examinations would you not want the patient to prioritize?." Fifty-nine (67.0%) of the participants answered that Mercaptuacetyltriglycine (MAG3) was not appropriate for initial evaluation of recurrent UTI under the age of one year, while 29 (33.0%) answered the question incorrectly. Hospitalization indications in children with UTIs were accurately identified in 81 (92.0%) participants. In clinical scenarios that didn't require for treatment, it was shown that 96.6% (n=85) of the participants selected the right response, "Bacteriuria diagnosed in asymptomatic adolescent females." 48.9% (n=43.0) participants made the proper decision for extended spectrum beta-lactamase-positive *E. coli* treatment. It was noted that 96.6% (n=85) respondents correctly identified the question about the appropriate prophylactic indication. The rate of correct answers was 74.0% (683/923) in the residents who had pediatric nephrology rotation and 72.4% (160/221) in the residents who had no pediatric nephrology rotation (p>0.05).

DISCUSSION

One of the most significant childhood infections is UTI. It can cause hypertension, proteinuria, and end-stage renal disease if it is not identified and treated in a timely manner. Early detection and prompt treatment of UTIs in children are crucial for this reason. Due to this, this study aimed to evaluate pediatric residents' approaches to the diagnosis, follow-up, and treatment of UTIs using questions created in accordance with new developments in the literature. While the diagnosis of UTI had the highest rate of correct responses in the study, it was noted that the rate of correct responses was around 60.0%, particularly in the indications for requesting USG in the case of UTI and in the choice of advanced imaging method to be requested later.

In our study, we assessed how pediatric residents deal with UTI. Bunting-Early et al.[9] revealed that delays in urinalysis/culture, particularly in the diagnosis of UTI, resulted in difficulties in their survey research of physicians practicing in the United States. In our study, 95% of participants were aware of the urine culture indication for the diagnosis of UTI. It is crucial to remember that early detection is important, especially because an untreated UTI can lead to sepsis in the early stages and renal scarring or failure in the later stages.[10-12]

Kennedy et al.[13] revealed variations in UTI follow-up and thorough examination tests in a study that compared NICE recommendations and accepted practices. Particularly in the first approach, general practitioners, according to the provided scenarios, half of the participants reported having divergent views on whether to refer patients with UTI to an advanced center and the appropriate imaging techniques.[13] In accordance with NICE recommendations, USG should be used to look for structural anomalies in all febrile children with atypical infections who do not respond clinically after 3 days despite receiving the proper antibiotic treatment.[8] Half of the participants in our survey incorrectly identified the ultrasound indication. All children under the age of two should have USG at the first sign of UTI, according to American and Canadian standards.[14,15] NICE recommendations advocate USG for children under the age of six months, for atypical causative microorganisms, and for unresponsive UTIs.[8] In terms of cost-effectiveness, asking for USG imaging in the appropriate patient is crucial. This is also a tactic that will reduce the workload of radiologists.

A renal plasma flow agent called MAG3 is nearly entirely secreted in the proximal tubules and discharged there.[16] MAG-3 is used as an advanced step test in the assessment of UTIs, but when we take the patient's urinary tract blockages into consideration.[16,17] In our study 67% of the participants correctly identified MAG3 as not being among the first-line examinations when asked about other tests, which were not given priority while examining the 1-year-old infant kid with recurrent UTI.

Antibiotic resistance in UTI, as well as other infections, has been emerging globally and as a consequence increases the mortality and hospital costs.[18-20] A study in Turkey reported an increased

antimicrobial resistance at UTI, resulting in clinicians facing difficult to treat UTI in children.[21] In the treatment section of the survey, nearly half of the residents could not treat the UTI-associated extended spectrum beta-lactamase-positive *E. coli* in an appropriate way, which was critical for eradication of the bacteria.[22]

Study Limitations

This study contains limitations because of its design. It can't be stated that the number of participants represents all physicians working in this sector and limited in our institution because a sufficient sampling selection technique was not applied. The study provides additional information for designing strategies, although the approach and level of knowledge of pediatric residents on UTI have not been reviewed in the literature in Turkey.

CONCLUSION

In conclusion, pediatric residents had appropriate training and experience in the diagnosing of UTI in children. However, over half of the residents lacked sufficient training in the management of resistant bacteria and additional radiological imaging techniques. Considering this, we believe it will be good to keep the knowledge updated concerning the treatment and follow-up of children with UTI through in-service training and post-graduate education.

Ethics

Ethics Committee Approval: Ethics approval for this study was obtained from the Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital with the approval number of 736 and the date with 15.09.2022.

Informed Consent: The practitioners were informed about the study before administering the surveys, and their verbal and written consent was obtained.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.D., Concept: N.D., Design: F.D., N.D., Data Collection or Processing: F.D., D.B., B.P.Z., Ö.D., E.Y., Analysis or Interpretation: E.Y., Literature Search: F.D., Ö.D., E.Y., Writing: F.D.

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Case Report

Case Reports of Patients Diagnosed with Familial Hypocalciuric Hypercalcemia, A Disorder That Should be Kept in Mind in Hypercalcemia Cases

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ABSTRACT

Familial hypocalciuric hypercalcemia (FHH) causes hypercalcemia by three genetic mechanisms: Inactivating mutations in the calcium-sensing receptor (*CaSR*), G-protein subunit α11 or adapter-associated protein complex 2, sigma 1 subunit. In other cases, hypercalcemia causes significant morbidity and mortality, while FHH usually follows a benign course. Failure to diagnose FHH may result in unwarranted treatment or surgery for a false diagnosis of primary hyperparathyroidism, given the significant overlap of biochemical features. Patients carrying a heterozygous loss-of-function mutation in the *CaSR* gene are typically referred to as FHH-type 1 (FHH1). Although FHH1 causes lifelong hypercalcemia, it is usually benign and asymptomatic. FHH is the most common syndrome of *CaSR* gene mutation; it may sometimes be associated with a hypercalciuric tendency depending on the variant. Although hypercalcemia is a frequently encountered condition in our clinical practice, FHH is a clinic that we do not often think of. This paper presents a family diagnosed with FHH, having heterozygous *CaSR* mutations in three generations.

Keywords: Familial, hypercalcemia, hypocalciuric

INTRODUCTION

Familial hypocalciuric hypercalcemia (FHH) is a group of autosomal dominant genetic diseases. It is characterized by persistent hypercalcemia, hypophosphatemia, hypermagnesemia, normal or mildly elevated serum parathyroid hormone (PTH) levels, and low urinary calcium excretion.[1] FHH, also called familial benign hypercalcemia, was initially defined as a variant of primary hyperparathyroidism (PHPT).[2] FHH is a life-long condition; it is usually caused by one of many heterozygous inactivating mutations in the calcium-sensing receptor *(CaSR)* gene, which could up-regulate the set point of parathyroid cells. When the *CaSR* receptor is inactivated, PTH is not suppressed despite relatively high calcium, which makes FHH similar to PHPT. In PHPT, although the renal reabsorption of calcium is higher than normal due to the high PTH level, hypercalciuria still occurs[3].

Patients carrying a heterozygous loss-of-function mutation in the *CaSR* gene are typically referred to as FHH-type 1 (FHH1)[4]. FHH1 causes lifelong hypercalcemia, but it is usually benign and asymptomatic. FHH is the most common syndrome of *CaSR* gene mutation; it may sometimes be associated with a hypercalciuric tendency depending on the variant.

Although hypercalcemia is a frequently encountered condition in our clinical practice, FHH is a clinic we do not often consider. This paper presents a family diagnosed with FHH, having heterozygous *CaSR* mutations in three generations.

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Patient Information and Clinical Findings

A 10-year-old, 6-month-old male patient was referred to our outpatient clinic after detecting high calcium in his routine blood tests. There was no previously detected high calcium level or loss of appetite, vomiting, constipation, polyuria, muscle weakness, anxiety, depression, or neurocognitive disorders (confusion, stupor, coma). On physical examination, the patient's height was 142.3 cm (50-75p), weight 41.9 kg (75-90p), and there was no consanguinity between the parents in the family history. His general condition was good, and system examinations were normal. Systolic and diastolic blood pressures were within normal limits for age. Laboratory results were as follows: Ca: 11.31 mg/dL, ALP: 306 U/L, Mg: 2.15 mg/dL, P: 3.65 mg/dL, PTH: 73.6 ng/L, 25(OH)D: 11.4 ng /mL, fT4: 1.13 pg/mL, thyroid stimulating hormone: 3.27 mU/L and urinary calcium/creatine: <0.01 mg/dL. Kidney ultrasonography was normal. 24-hour urine analysis and serum measurements of the patient were performed, and the calcium/creatinine clearance ratio was calculated below 0.01. During the patient's follow-up, persistent hypercalcemia, normal PTH levels, and low urinary calcium were detected, and the family was screened (Figure 1). Incidental hypercalcemia was found in her 4-month-old sister, mother, and grandmother; therefore, genetic screening was performed for FHH (Table 1).

Genetic Evaluation

After the informed consent was obtained, we extracted whole blood samples of the proband and his family members and sent them to the Genetic laboratory for DNA testing. NextSeq500 system was used for whole exon sequencing after obtaining the target gene. Sanger sequencing was used to investigate the heterozygous mutation of *CaSR*. The *CaSR* gene mutation study of the proband revealed a mutation; *CaSR* gene mutation of c.2532_2539delCAGCTTT (p.Ser845fs*133) was identified as heterozygous.

The clinical diagnosis was considered to be FHH1. The pedigree of the family for *CaSR* is shown in Figure 1.

Interventions and Follow-up

Until today, we encountered nephrolithiasis only in the sister of the patients who did not receive medical treatment other than hydration. There was no additional complaint or need for treatment. Other family members did not show adverse events such as nephrolithiasis, nephrocalcinosis, and renal dysfunction. Our patients are followed up with annual biochemistry tests (serum calcium, phosphate, creatinine), 24-hour urinary calcium measurement, and biennial renal ultrasonography. Our male patient was transferred to adult endocrinology when he turned 21, and his follow-up continues uneventfully. Genetic counseling was given to all affected individuals.

DISCUSSION

CaSR is mainly expressed in the parathyroid gland, kidney, and bone; acts as the primary regulator of calcium homeostasis.[5] The best-characterized role of *CaSR* is in the parathyroid gland, where it senses various factors that suppress the release and production of circulating ionized calcium (Ca2+), particularly PTH. Endogenous agonists of *CaSR* include Ca2+, Mg2+, other divalent ions that activate intracellular pathways, and polyamines such as spermine; Gq/11-mediated signals leading to the formation of inositol monophosphate (IP1) are the main pathway.[6,7] Loss-of-function mutations in *CaSR* reduce the capacity of the parathyroid gland and kidney to detect changes in serum Ca2+ concentrations.[4,8] Various mutations have been identified in *CaSR*, and functional effects depend on the affected site; these lead to varying degrees of *CaSR* inactivation.[9] Regarding FHH, more than 200 mutations identified in *CaSR* were detected; however, no strong correlation was found between genotype and phenotype in case-specific *CaSR* mutations.[10] The phenotype of

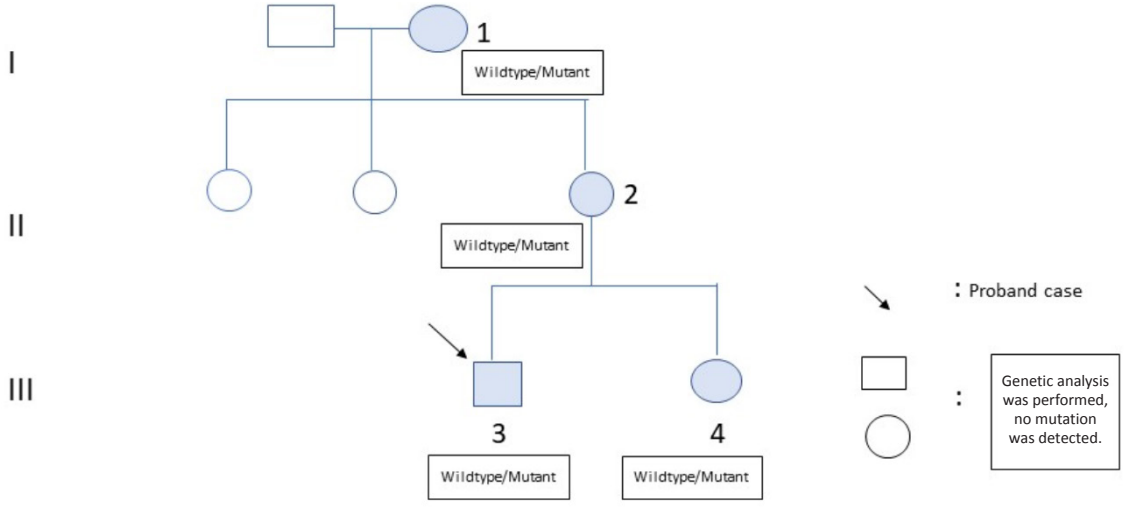

Figure 1. Pedigree. Blue filled symbols are family members with FHH, having *CaSR* mutation

Table 1. Genetic screening for FHH

	Pedigree no	Gender	Age	Ca (mg/dL)	P (mg/dL)	PTH (pg/mL)	Ca/Crea in spot urine (mg/dL)	Treatment	Clinic	*CaSR* gene analysis
Grandmother	I-1	Female	72	11.2	3.45	12.1	<0.01	Hydration	Asymtomatic	[c.2532_2539delCAGCTTT (P.sER845fs*133)]
Mother	II-2	Female	42	11.1	3.55	10.4	<0.01	Hydration	Asymtomatic	[c.2532_2539delCAGCTTT (P.sER845fs*133)]
Sister	III-3	Female	6	10.6	3.70	10.6	<0.01	Hydration	Asymtomatic	[c.2532_2539delCAGCTTT (P.sER845fs*133)]
Brother	III-4	Male	21	11.31	3.65	12.3	<0.01	Hydration	Asymtomatic	[c.2532_2539delCAGCTTT (P.sER845fs*133)]

FHH: Familial hypocalciuric hypercalcemia

most patients with *CaSR* mutation is normal, and most of them are asymptomatic. Many *CASR* mutations have been identified before, but the heterozygous mutation c.2532_2539delCAGCTTT (p.Ser845fs*133) has not been reported in the literature. FHH is usually inherited in an autosomal dominant manner, but recessive cases have also been reported.[9] The genetic inheritance in our patients was autosomal dominant, as in most reported cases. We described 3 generations of a family associated with a heterozygous *CaSR* mutation [c.2532_2539delCAGCTTT (p.Ser845fs*133)]. The co-existence of hypocalciuria, normal or high PTH, and hypercalcemia (in the absence of vitamin D deficiency) in carriers of c.2532_2539delCAGCTTT (p.Ser845fs*133) in the *CaSR* gene is a strong indicator of FHH1.[11-17] All heterozygous family members had elevated serum ionized calcium levels and normal PTH levels, which is fully consistent with hypocalciuria and the FHH1 phenotype. In 98% of the cases, the Ca/Creatinine ratio is below <0.001. In our cases, the Ca/Creatinine ratio was <0.001, which is consistent with the literature. In addition, the detected genotype of our case was clinically compatible with FHH and contributed to the literature in this respect. It is thought that 20% of the mutations implicated in FHH genetics have not been identified yet.[18] Lietman et al.[19] and Szczawinska et al.[20] reported two different families carrying the *CaSR* Q459R mutation. All heterozygous carriers of the mutation had normal biochemical values, including serum calcium levels that were within or rarely above the reference range. Likewise, there was no accompanying biochemical disorder in our cases. In the study of Kobayashi et al.[21], it was suggested that the hypercalcemia observed in heterozygous carriers was masked by the low calcium intake generally found in the Japanese population. No studies have been conducted on low calcium intake in our country, but we know that our patients follow a diet rich in calcium. In plasma, calcium may bond to proteins (less than 50%) or may form complex bonds with anions such as phosphate, citrate, or sulfate (10-15%) or may be present as ionized calcium (about 50%). Among those, ionized calcium is critical because it is the biologically active part.[22] Ong et al.[23] showed that 45% of cases with hypercalcemia would be missed by measuring only total calcium in patients with high total calcium and/or ionized calcium. Patients with primary HPT and FHH usually have a similar phenotype, but FHH rarely requires treatment, while primary HPT often requires parathyroid gland surgery. A recent study suggested that the Pro-FHH equation is better than 24-hour CaCl/CrCl to differentiate Primary HPT and FHH patients.[24] Hypercalcemia has many causes; differential diagnosis covers hypocalciuric hypercalcemic syndrome types 2 and 3, HPT (especially familial HPT), vitamin D metabolism disorders, and low glomerular filtration rate. Hypocalciuric hypercalcemia syndrome type 2 is associated with mutations of the *GNA11* gene located on chromosome 19p13.3, encoding one of the G-protein subunits (G-α11). This form constitutes 10% of familial benign hypercalcemia cases.[25] Type 3, on the other hand, consists of mutations in the *AP2S1* gene located on chromosome 19q13.3, usually at the arginine level at position 15. AP2S1 mutations are responsible for approximately 20% of FHH cases.

This form is associated with a more severe variant of FHH. FHH1 has a heterozygous inactivating mutation on the 3rd chromosome, on the *CaSR* gene. This syndrome is also called Marx-Auerbach syndrome or Familial benign hypercalcemia. The prognosis of this type is quite good, and it has been reported that there is no significant decrease in life expectancy. It may be because most of the cases, who are asymptomatic, cannot be detected clinically.[26] Hypercalcemia incidentally detected in our patients also supports the literature. The absence of hypermagnesemia in our cases ruled out FHH2 in diagnosis. FHH3 has mutations in the adapter-related protein complex-2 and sigma-1 subunits encoded by the *AP2S1* gene.[10,18,26-29] Some publications indicate that learning difficulties and neuropsychiatric findings may also occur in types 2 and 3.[30] In our cases, the absence of these features does not support the possible diagnosis of type 2 and 3 FHH. Regarding the cases with FHH reported in the literature, recurrent pancreatitis attack that may develop due to hypercalcemia is another issue to consider. For this reason, abdominal pain, laboratory evaluation, and amylase follow-up are important in symptomatic cases.[26] It can lead to symptomatic hypercalcemia with hypophosphatemia, a PTH increase with age, low bone mineral density, and cognitive dysfunction.[31,32] Approximately 20% of hypocalciuric hypercalcemia cases are unrelated to the defined genes, suggesting that other yet unknown genes play a role.[33]

Except for gene mutations that play a role in type 2 and 3 FHH, FHH syndromes associated with *CaSR* gene mutation should be differentiated from HPT with normal PTH.[34]

In hypocalciuric hypercalcemia syndromes, the familial character of hypercalcemia and the calcium/creatinine clearance ratio <0.01 support familial benign hypercalcemia rather than HPT despite the gray area.

There are other autosomal dominant genetic forms of familial hypercalcemia; they are associated with tumors, especially HPT associated with tumor suppressor gene mutations.[35]

Along with confirmatory genetic testing, appropriate screening of family members diagnosed with FHH1 and providing genetic counseling are crucial to avoid unnecessary treatment. Symptomatic individuals should be treated to prevent exacerbation of hypercalciuria and accompanying complications (nephrocalcinosis, nephrolithiasis, and impaired renal function). In symptomatic patients, treatment aims to relieve symptoms with the lowest possible dose of calcium and active vitamin D analog rather than to achieve normocalcemia. Thiazide diuretics can be combined with calcitriol to reduce renal calcium excretion. We did not need to use thiazide diuretics in our patients. Treatment of hypercalcemia should target the etiology and serum calcium level. Treatment was not started because our patient was asymptomatic. It has been reported that cinacalcet therapy may be considered if the patient is symptomatic, or serum Ca is >11.2 mg/dL, or 1 mg/dL higher than the Ca upper limit. In deciding to continue the drug, the disappearance of symptoms and returning serum calcium levels to normal values in an average of 8-12 weeks were considered an adequate response to the treatment.[23] However, it should be noted that the safety and efficacy of cinacalcet use are not known in cases under 18, as there is no FDA approval.

CONCLUSION

In this study, we examined a family with FHH and showed that the possible pathogenic cause behind FHH is a mutation in the *CaSR* gene (c.2532_2539delCAGCTTT (p.Ser845fs*133). The history of hypercalcemia in the family should prompt physicians to consider rare familial causes in patients with hypoparathyroidism. These diagnoses have critical implications regarding the management, screening, and genetic counseling of affected individuals.

Ethics

Informed Consent: The informed consent was obtained.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Concept design: A.D.B., Y.Y., A.C.C., Data Collection or Processing: A.D.B., Y.Y., A.C.C., Analysis or Interpretation: A.D.B., Y.Y., A.C.C., Literature Search: A.D.B., Y.Y., A.C.C., Writing: A.D.B., Y.Y., A.C.C.

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Case Report

Are Genetics Involved in the Development of Multisystem Inflammatory Syndromes in Children?

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ABSTRACT

The relationship between Multisystem Inflammatory Syndrome in Children (MIS-C) and genetic predisposition is not well established. The aim of this article emphasize the presence of genetic predisposition in MIS-C by presenting two sibling cases from two separate families with a diagnosis of MIS-C. The patients applied with complaints of fever, abdominal pain, diarrhea and maculopapular rash. While the coronavirus disease-2019 (COVID-19) polymerase chain reaction test was negative in all cases, three had both IgM and IgG positivity, and the other case had only IgG positivity. Patients who did not define any other infection were diagnosed with MIS-C according to the Centers for Disease Control and Prevention criteria. The patients were discharged with full recovery. The fact that siblings share the same genetic background and the same environmental factors suggests that MIS-C syndrome occur in individuals with a genetic predisposition. Further genetic studies with a large MIS-C series are needed to determine which genotypic trait may cause the development of MIS-C in COVID-19 infection.

Keywords: Children, COVID-19, genetic, MIS-C, siblings

INTRODUCTION

The severe global effects of the coronavirus disease-2019 (COVID-19) (severe acute respiratory syndrome-coronavirus 2) epidemic are still being experienced, with it officially being declared a pandemic by the World Health Organization (WHO) on March 11, 2020. At the end of April 2020, a novel syndrome-made appearance, and was understood to be linked to COVID-19; the findings were similar to that of Kawasaki disease (KD), toxic shock syndrome and macrophage activation disease, reported initially in case studies from the UK, then in the United States and Central Europe. This disease was first termed pediatric inflammatory multisystem syndrome temporarily by the Royal College of Pediatrics and Child Health and was associated with COVID-19; it was later called COVID-19-associated Multisystem Inflammatory Syndrome in Children (MIS-C) by the Centers for Disease Control and Prevention (CDC) and WHO. Although the immunopathogenesis of MIS-C is still unclear, it is classified as a hyperinflammatory condition that develops approximately 1-6 weeks after a COVID-19 infection.[1] The relationship between MIS-C development and genetic predisposition is not well established.

This article aimed to emphasize the presence of genetic predisposition in MIS-C by presenting two previously healthy siblings from two separate families, who were not consanguineous marriage and followed up with the diagnosis of MIS-C.

Case 1

A nine-year-old girl with no prior complaints was admitted to our clinic with a fever and rash. The patient experienced fever (39 ºC), abdominal pain and headache for 4 days. The patient had a history of contact with his uncle, who previously had an active

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COVID-19 infection three months prior. During this time, COVID-19 symptoms were also present in the patient's parents, but they had not been tested. The patient's physical examination revealed maculopapular rashes on the extremities and torso. There was widespread abdominal tenderness present. COVID-19 testing showed that COVID-19 real time-polymerase chain reaction (PCR) was negative, COVID-19 IgM negative and COVID-19 IgG positive. Laboratory evaluation was as follows: C-reactive protein (CRP): 136 mg/L, sedimentation: 40 mm/hour, d-dimer: 2.43 mg/L, ferritin: 265 µg/L, procalcitonin: 0.33 µg/L, white blood cell (WBC): 10420/mm^3, neutrophil: 8640/mm^3, lymphocyte: 1080/mm^3, proBNP: 800 ng/L, fibrinogen: 631 mg/dL. Due to the presence of fever, skin lesions and hematological, gastrointestinal and cardiovascular involvement, the patient was diagnosed with MIS-C with respect to the CDC criteria. Low molecular-weight heparin and intravenous immunoglobulin were administered. The patient's clinical findings improved during the eight-day follow-up and she was discharged with full recovery.

Case 2

A seven-month-old male patient, who was the brother of the first case, presented with fever and restlessness that lasted for 3 days. The fever started about 10 days after her sister's symptoms first appeared. Physical examination showed widespread maculopapular rash and non-purulent conjunctivitis in the eyes. After further evaluation, COVID-19 PCR was found to be negative, but COVID-19 IgG and IgM were positive. Laboratory testing was as follows: d-dimer: 3.09 mg/L, fibrinogen: 163 mg/dL, CRP: 1.49 mg/L, procalsitonin: 0.12 ug/L, ferritin: 70 µg/L, proBNP: 525 ng/L, WBC: 11210/mm^3, neutrophil: 590/mm^3, lymphocyte: 9640/mm^3. Cardiovascular evaluation showed no signs of pathology other than a high-ProBNP level. Similar to his sister, the male patient was diagnosed with MIS-C according to CDC criteria and was administered low molecular-weight heparin and intravenous immunoglobulin. The patient's clinical findings improved in the follow-up and he was discharged with full recovery.

Case 3

A six-year-old male patient was admitted to the emergency department complaining of fever, abdominal pain and diarrhea. The patient's complaints had been present for 2 days. His mother and father had an active COVID-19 infection one week prior. On physical examination, the patient exhibited no findings other than abdominal tenderness. A few days prior, the family stated that the boy had red eyes and dry and cracked lips. The patient's COVID-19 evaluation revealed a negative PCR, but positive COVID-19 IgM and IgG. The patient's laboratory results were as follows: CRP: 253 mg/L, procalcitonin: 1.38 µg/L, d-dimer: 1.82 mg/L, WBC: 15830/mm^3, neutrophil: 12740/mm^3, lymphocyte: 1860/mm^3, proBNP: 218 ng/L, ferritin: 104 µg/L. During the follow-up, the patient's cultures exhibited no signs of microbial growth. The patient had positive COVID-19 serology and high proBNP as well as cardiovascular, hematological and gastrointestinal involvement. Since no other infective agent could reasonably explain these findings, the patient was diagnosed with MIS-C according to the CDC criteria. Low molecular-weight heparin and intravenous immunoglobulin were administered. The patient's clinical findings improved in the follow-up and he was discharged with full recovery.

Case 4

A 3-year-10-month-old male patient, who was the brother of case 3, presented to our outpatient clinic complaining of fever, abdominal pain and diarrhea that had been present for a day. Physical examination revealed no findings other than abdominal tenderness. The patient was found to have a negative COVID-19 PCR and positive COVID-19 IgM and IgG. Laboratory testing was as follows: CRP: 73.9 mg/L, procalcitonin: 0.90 µg/L, d-dimer: 1.50 mg/L, WBC: 15110/mm^3, neutrophil: 12200/mm^3, lymphocyte: 2120/mm^3, proBNP: 384 ng/L, sedimentation: 26 mm/hour, fibrinogen: 125 mg/dL, ferritin: 71 µg/L. All of the patient's culture results were negative. The patient exhibited cardiovascular, hematological and gastrointestinal involvement as well as positive COVID-19 serology and since no other infective agent could be considered, the patient was diagnosed with MIS-C with respect to CDC criteria, similar to his brother. Furthermore, the patient was administered low molecular-weight heparin and intravenous immunoglobulin. The clinical and laboratory characteristics of the patients are presented in Table 1.

DISCUSSION

Our article is the first article in the literature to present two siblings (4 cases) from two different families diagnosed with MIS-C. The patients were diagnosed with MIS-C according to the CDC criteria. They all were administered intravenous immunoglobulin and low molecular-weight heparin. In a comprehensive seroconversion study, median seroconversion times of total antibody, IgM, and IgG were found to be 11, 12, and 14 days, and seroconversion rates were 93.1%, 82.7%, and 64.7%, respectively. Additionally, the study stated that the sensitivity of the test was 66.7% in the early stage of the disease (within 7 days after contact), however, this number increased upon the 8th day after the onset of symptoms and exceeded 90% on the 12th day. It was reported that the sensitivity for total antibody, IgM and IgG in samples taken in the days after were 100%, 94.3%, and 79.8%, respectively.[2] All of our cases were presented in the early period (the first 7 days after the onset of symptoms). While the COVID-19 PCR test was negative in all cases, three had both IgM and IgG positivity, and the other case had only IgG positivity. Due to the clinical and laboratory similarity between KD and MIS-C, understanding the etiology of can provide us with new information regarding the pathogenesis of MIS-C in COVID-19. For this purpose, data about families with KD were analysed; some infectious pathogens may trigger KD in familial cases, and it should be emphasized that these cases have a higher risk of KD development compared with the general population. Our case is the first in the literature in which familial MIS-C has been reported. These results suggest that in patients with a COVID-19 infection, genetic factors can affect the

Table 1. The clinical and laboratory characteristics of the patients

	Case 1	**Case 2**	**Case 3**	**Case 4**
Age (month)	104	7	77	46
Sex	Female	Male	Male	Male
Relation	Case 2	Case 1	Case 4	Case 3
CDC diagnosis				
1. Fever ≥38° C or subjective for ≥24 hours	4 day	3 day	2 day	1 day
2. Laboratory inflammation				
CRP (mg/L)	136	1.49	253	73.9
Sedimentation (mm/hour)	40		12	26
Procalsitonin (µg/L)	0.33	0.12	1.38	0.9
Fibrinogen (mgdL)	631	163		125
D-dimer (mg/L)	2·43	3.09	1.82	1.5
Ferritin (µg/L)	265	70	104	71
Neutrophil (/mm^3)	8640	590	12740	12200
ProBNP (ng/L)	800	525	218	384
3. Severe illness requires hospitalization	Yes	Yes	Yes	Yes
4. ≥2 organ systems involved (cardiac, renal, respiratory, hematological, gastrointestinal, dermatological and neurological)	Cardiac (ProBNP ↑) Hematological (D-dimer ↑) Dermatological (maculopapular rash) Gastrointestinal (abdominal pain, abdominal tenderness)	Cardiac (ProBNP ↑) Hematological (D-dimer ↑) Dermatological (maculopapuler rash)	Cardiac (ProBNP ↑) Hematological (D-dimer ↑) Gastrointestinal (abdominal pain, diarrhea)	Cardiac (ProBNP ↑) Hematological (D-dimer ↑) Gastrointestinal (abdominal pain, diarrhea)
No other plausible diagnosis	No	No	No	No
SARS-CoV-2 infection or exposure defined as				
COVID-19 PCR	Negative	Negative	Negative	Negative
COVID-19 IgM	Negative	Positive	Positive	Positive
COVID-19 IgG	Positive	Positive	Positive	Positive

CDC: Centers for Disease Control and Prevention, CRP: C-reactive protein, SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, COVID-19: Coronavirus disease-2019, PCR: Polymerase chain reaction

severity of disease, characteristics of the symptoms and severity of the host immune response to this infection. In their studies on twins, Williams et al.[3] reported that 50% of the COVID-19 infection phenotype variance was caused by genetic factors. Additionally, they had previously expressed that the anosmia symptom showed 48%-inherited characteristics.[3] Hoffmann et al.[4] stated that the symptoms occurring in a COVID-19 infection may be linked to genes encoding angiotensin-converting enzyme-2 receptors, and that these genes may reflect the genotypic status in a COVID-19 infection as it is required for viral attachment. Although the immunopathogenesis of MIS-C is still not clearly understood, its good response to immunomodulation therapy may imply that the disease is due to immune dysregulation.[5] While the molecular similarity between COVID-19 antigens and body cells cannot be shown, autoimmune response with macrophage activation is another mechanism suggested to play a role in the development of cytokine storm. However, the genotypic features associated with MIS-C development are currently a mystery.

In conclusion, our patients are siblings who share the same genetic background, are exposed to the same environmental factors and the same viral strain, suggesting that MIS-C syndrome is an indicator of the excessive immune response that occurs in individuals with genetic predisposition after a COVID-19 infection. However, it is not known which genotypic trait may cause MIS-C development in COVID-19 infection. Therefore, genetic studies with large MIS-C series are required.

Ethics

Informed Consent: The informed consent was obtained.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.İ., U.U.G., Concept design: S.İ., Data Collection or Processing: U.U.G., Analysis or Interpretation: S.İ., Literature Search: S.İ., U.U.G., Writing: S.İ., U.U.G.

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Case Report

Nephrotic Syndrome as An Unusual Presentation of Hodgkin Lymphoma in A 7-Year-Old Boy

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ABSTRACT

Hodgkin lymphoma may present with nephrotic syndrome, but this coexistence is rare. Some hypotheses have been proposed, however, the reason of is not fully known. The patient was a 7-year-old boy who presented with the complaint of edema in the legs and around the eyes. Laboratory tests revealed hypoalbuminemia, hyperlipidemia, and nephrotic range proteinuria. Hodgkin lymphoma was found in the biopsy performed due to the detection of mediastinal enlargement and lymphadenopathy on X-ray and computed tomography. At the end of chemotherapy responding to Hodgkin lymphoma, nephrotic syndrome resolved without the need for other immunosuppressant treatment. Clinicians should keep in mind that the first evidence of Hodgkin lymphoma may be a nephrotic syndrome and the importance of the use of imaging methods.

Keywords: Hodgkin lymphoma, nephrotic syndrome, proteinuria, X-ray

INTRODUCTION

Nephrotic syndrome (NS) is one of the important chronic diseases of childhood, characterized by edema, heavy proteinuria, hypoalbuminemia, and hypercholesterolemia.[1] NS, mostly idiopathic in childhood, may also occur secondarily due to some rare causes like malignancy as a paraneoplastic phenomenon.[2]

In rare cases, NS can be the first manifestation of Hodgkin lymphoma (HL) with an incidence of 0.5-1% reported in the literature.[3] Although the relationship between HL and NS is not fully clarified, hypotheses are accusing T-cell dysfunction.[4] Polyanions are important in maintaining glomerular permeability. Polyanions are damaged by decreased synthesis of cytokines because of dysfunction of T-cells. It has been stated that this may result in proteinuria because of disruption of the glomerular barrier.[1]

However, strong evidence derived from extensive studies on this relationship is lacking since the current data are mainly from limited case series or individual reports.

Here, we describe a seven-year-old male patient who presented with clinical and laboratory features of NS and was eventually diagnosed with HL.

CASE REPORT

A seven-year-old, previously healthy boy presented with bilateral periorbital and pretibial edema. He had no history of weight loss, night sweats, or persistent fever. On physical examination, body temperature was 36.4 °C, respiratory rate 20/minute, oxygen saturation in room air was 98% and blood pressure was 102/61 mmHg, which was within normal limits for his age. No lymphadenopathy (LAP) or hepatosplenomegaly was observed.

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Laboratory tests were leukocytes; 6.83×10^3/µL; hemoglobin g/dL; platelet count: 350×10^3/µL; albumin: 2.0 g/dL; total cholesterol: 424.9 mg/dL; erythrocyte sedimentation rate: 91 mm/hour; lactate dehydrogenase: 367 U/L; uric acid: 3.2 mg/dL; creatinine; 0.51 mg/dL. Serum electrolytes were within normal limits, while serology for hepatitis B and hepatitis C were negative. Spot urinalysis showed proteinuria (+3) and the protein/creatinine ratio was 4.0 mg/mg. Mediastinal lymph node enlargement was found on a chest X-ray which was performed to identify a pleural effusion without symptoms. Based on these findings, along with conglomerated LAPs in the chest tomography compressing the superior vena cava, pushing the trachea to the left posterior, and compressing the right main bronchus lymph node biopsy was performed, eventually diagnosing nodular-sclerosing HL. On the initial F-18-fluorodeoxyglucose (18 F-FDG) positron emission tomography/computed tomography (PET/CT) scan, multiple LAPs showed increased FDG uptake in both supra-infraclavicular lymph nodes and the spleen, indicating stage IIIA HL. He was given ABVD chemotherapy (Adriamycin 25 mg/m^2, bleomycin 15 mg/m^2, Vinblastine 6 mg/m^2, Dacarbazine 375 mg/m^2, on days 0 and 14). At the end of the first course of ABVD, we observed no pathological findings on physical examination, renal function tests, albumin, and cholesterol levels were normal, and proteinuria disappeared. In term 18 F-FDG PET/CT scan after three cycles of ABVD chemotherapy showed a complete metabolic response (Figure 1). During the follow-up, NS findings disappeared after ABVD treatment without the use of corticosteroids. The patient's NS was still in complete remission after four cycles of chemotherapy.

DISCUSSION

This case initially presented only with edema attributed to NS with no other specific complaints or symptoms suggesting HL. In a French study, it was shown that HL patients with NS mostly had LAP on physical examination at their first admission.[5] They also emphasized that if NS developed before the diagnosis of HL, resistance to steroids and other immunosuppressants may develop due to the glomerular permeability factor produced by Hodgkin cells. A chest X-ray was obtained to detect possible pleural effusion. Although there was no sign of pleural effusion on the chest X-ray, this led to the simultaneous diagnosis of HL and NS. Therefore, we believe that essential imaging methods such as X-rays can be an important part of diagnostic studies in children with NS.

In studies, it has been reported that systemic symptoms in HL patients with NS are higher than in those without NS.[5,6] The diagnosis of HL may be delayed if there are no systemic symptoms. In fact, our case was diagnosed with HL without systemic symptoms. Especially, kidney biopsy can be performed in patients whose NS is not cured because of unable to receive specific treatment for HL. We think that it is important to consider HL in patients presenting with NS clinical features without systemic symptoms to conserve patients from unnecessary invasive procedures and complications.

In this study, NS and HL were diagnosed simultaneously. However, NS may occur before or after HL.[7] There have been reports of cases with HL occurring years after the diagnosis of NS and a link between them.[8] It has also been reported that HL occurs when NS relapses in these patients and is completely cured after chemotherapy.[5] Therefore, we think that it is important to keep in consider that HL may occur in cases such as frequent relapses and resistance to treatment in the follow-up of patients with known NS.

The histopathological subtype of our case was found to be nodular sclerosing. Different results were found as the relationships between the histological subtypes of HL and NS were examined. In a study, NS was more frequently associated with nodular sclerosing histology, while in another study, the mixed cellular subtype was most common in NS.[5,9] It is thought that further studies in terms of histopathological frequency may be valuable in terms of determining the prognostic features of this association.

Investigation of HL as a possible etiologic cause in patients diagnosed with NS may also be beneficial in terms of response to treatment. If patients presenting with NS have underlying HL as a predisposing disease and cannot be diagnosed simultaneously, patients may unnecessarily receive long-term corticosteroid therapy. Furthermore, delayed diagnosis may complicate NS with resistance and frequent relapses.

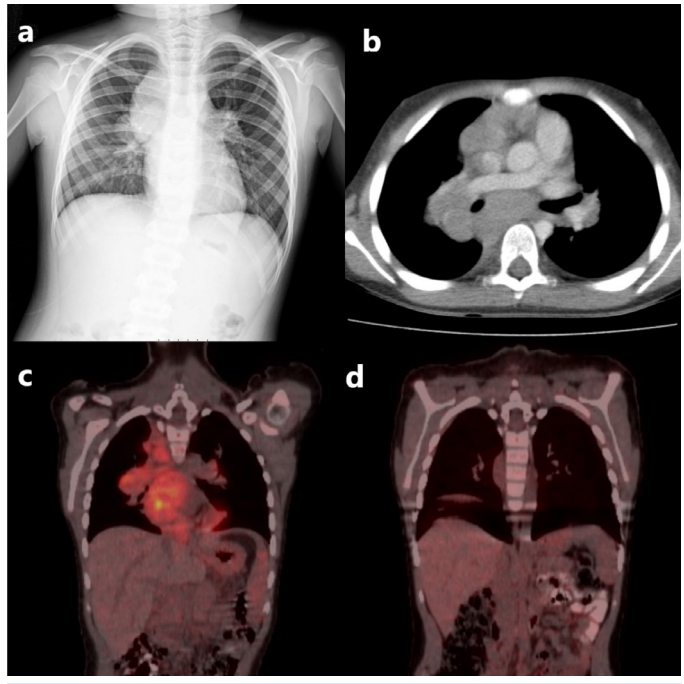

Figure 1. (a) Mediastinal enlargement on a chest X-ray at diagnosis. (b) Conglomerate LAPs and compression of the trachea on chest tomography. (c) PET/CT with increased FDG uptake before treatment. (d) PET/CT with the complete metabolic response after treatment

LAP: Lymphadenopathy, PET/CT: Positron emission tomography/computed tomography, FDG: Fluorodeoxyglucose

HL may rarely present with NS. Therefore, lymphoma should be considered in the etiology of children NS, and early diagnostic steps should include appropriate imaging techniques to identify HL.

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Ethics

Informed Consent: A written informed consent was obtained from the patient's family.

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Authorship Contributions

Concept: K.D., F.K., Design: K.D., F.K., Data Collection or Processing: K.D., F.K., U.D., Analysis or Interpretation: K.D., F.K., U.D., Literature Search: K.D., F.K., U.D., Writing: K.D., F.K., U.D.

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