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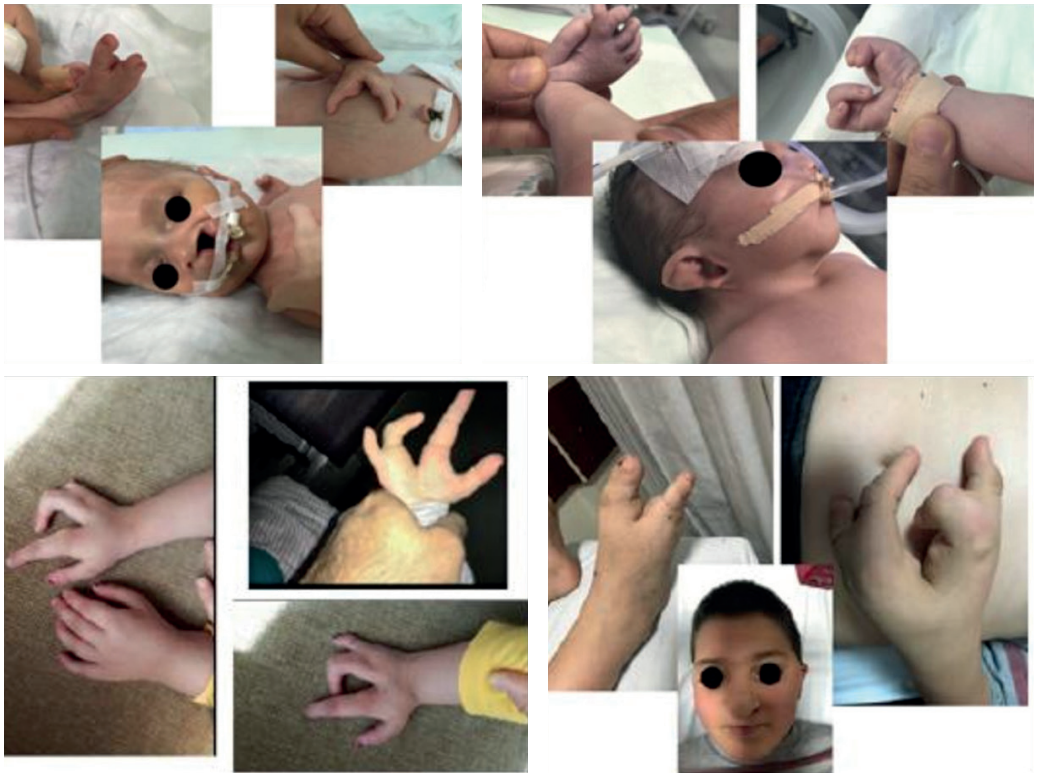

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Contents

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Review

Epidemiological and characteristic features of childhood fractures

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ABSTRACT

Childhood fractures are becoming an important public health problem around the world due to the increasing incidence. Fractures in children are more than twice as common as in adults. The incidence of pediatric fractures is affected by many factors such as the age and sex of the child and seasonal and sociocultural factors. One of the leading causes of childhood fractures is simple falls and approximately 50% of childhood fractures were reported to occur after a simple fall. On the other hand, childhood fractures are also very common at home or school and after traffic accidents. A child's bone has a lower density and more porous structure than an adult's bone. The periosteum of bone in children is thicker and stimulates new bone formation more strongly. As a result, new bone formation is completed in less time. The remodeling potential of a child's bone is also an advantage that differentiates pediatric treatment from adult treatment. Complications like delayed union, nonunion, re-fracture, myositis ossificans, and joint stiffness are also very rare in children. But physeal damage may cause serious complications like growth arrest or angular deformities. Despite the advancement in technology and increasing options for minimally invasive surgeries, closed reduction and conservative treatment methods are still the mainstay of treatment in children.

Keywords: Childhood fractures, remodeling, torus fracture, conservative treatment

INTRODUCTION

Childhood fractures are becoming an important public health problem around the world due to increasing incidence. Fractures in children are approximately more than twice as common as in adults. One in three children has a fracture at least once up to adolescence and the incidence of childhood fractures is affected by many factors such as the age and gender of the child and seasonal and sociocultural factors.[1,2]

Sex

While there is no difference in terms of sex in the first two years of life, boys are more prone to fractures after the age of two. It is reported that under the age of sixteen, the cumulative risk of a fracture is 27 % in girls and 42 % in boys. The increase in fractures in boys is due to several factors such as the use of sports equipment, cycling, or other sporting activities that are more common in boys.[3,4]

Trauma

One of the most common causes of childhood fractures is simple falls. Approximately 50 % of fractures in children are reported to occur after a simple fall.[3-5] On the other hand, childhood fractures are also very common at home or in the school environment and after traffic accidents. These accidental injuries can be reduced by various measures. Another important thing to keep in mind is that child abuse may cause childhood fractures. Long bone shaft fractures, burns, ecchymoses at different stages in various parts of the body, and late admission to health institutions should alert the physician to child abuse. Fractures without trauma or

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with minor trauma may be related to the pathology of the bone such as metabolic bone diseases, tumoral lesions, or infection.[6]

Anatomical Location

The most common fracture in children is at the distal end of the radius. It accounts for 15.3% to 30.4% of all fractures.[2,3,7] The reason for this localization is due to transient osteopenia during the rapid growth period of children.[8]

The most common fracture sites after the distal radius are the distal humerus, clavicle, tibia, and femur respectively.[3]

Social Factors

The incidence of childhood fractures is also affected by geographical and sociocultural conditions. According to the literature, children living in a low sociocultural environment are more affected by trauma than children living in a high sociocultural environment.[9] Similarly, there is also a difference in fracture incidence between the children living in high-rise apartments in cities and those living in rural areas.[3] Also, children with problematic parents, such as alcoholics, have a higher fracture incidence.[4]

Seasonal Factors

The incidence of childhood fractures is significantly affected by seasonal differences. Outdoor activities for children increase in sunny weather and hot seasons, and traumas and fractures in children become more common. According to Masterson et al., the number of fracture cases is 2.5 times higher in summer months than in winter months.[10] Fracture incidences also increase especially in the afternoon between two and three o'clock in the day.[10,11]

Biological Properties and Remodulation

As in adults, fracture healing in children is composed of three stages: inflammation, repair, and remodeling.[12] In the acute stage of inflammation, a fibrin-rich hematoma starts to form a collagen skeleton after vascular damage. Hematoma also contains cellular components such as osteoblasts and chondroblasts that will promote new bone formation. At the repair stage, the hematoma surrounded by fibrovascular tissue begins enchondral and intramembranous ossification and a temporary callus is formed.

In some fractures, the remodeling stage can take years. During this phase, new bone formation is completed. The main factors affecting the remodeling capacity are age, the proximity of the deformity to the physis, and the remaining growth capacity of the physis.[13] According to Wolf's law, the bone remodels according to the stress applied to it and the remodeling capacity is much greater if the deformity is in the same axis of the movement plan.[14]

Excessive elongation (overgrowth) at the remodeling stage of childhood fractures is usually encountered in the diaphysis of long bones, most commonly in the femoral diaphysis, and may be problematic. However, a difference of up to 2 cm as a result of excessive elongation is usually compensated.[15]

Local Features of Remodeling

Metaphyseal bone has a high capacity for remodeling. Spongious bone produced by the adjacent physis displaces the diaphysis with structurally stronger bone. This area has a high osteogenic capacity and is also rich in vascular activity.

Bone formation in the diaphysis is less active compared to other parts of the bone and there is a balance between endosteal bone reabsorption in the medullary canal and new bone formation. As a result, the remodeling capacity of diaphyseal bone remains limited due to the rigidity and relatively avascular structure of bone in this region.[15,16]

How Does Remodeling Happen?

Angulation in the physis: Until the skeletal development is complete, 75-80% of the angular remodeling is performed by the physis.[16] The physis adjacent to the fracture grows asymmetrically and perpendicular to the forces acting on it.[17,18] The concave side grows rapidly to regenerate the long axis of the bone. After the physis is aligned, symmetrical growth begins again.

Angulation in the diaphysis: There is an increased pressure that stimulates bone formation on the concave side of the diaphysis.[19] The convex side, on the other hand, stimulates bone resorption under the effect of distraction force. Only 20% of the angular remodeling takes place in the diaphysis.

Overgrowth

Although post-fracture bony overgrowth is known to be caused by increased blood flow to growth cartilage in the proximal bone segment, its relationship with age, fracture segment, and fracture position has not been demonstrated.[19]

Differences Between Child and Adult Fractures

A child's bone has a lower density and more porous structure than an adult's bone.[20] The periosteum of bone in children is thicker compared to adults and stimulates new bone formation more strongly by covering the fracture hematoma. More vascular structure and high osteoblastic capacity of bones in children cause the inflammatory response to be stronger. Thus, bone development is excessive and may lead to overgrowth. As a result, new bone formation is completed in less time compared to adults.[21,22] Complications such as delayed union, non-union, re-fracture, myositis ossificans, and joint stiffness are also very rare in children. On the other hand, physeal damage may cause serious complications such as growth arrest or angular deformities.

Torus Fractures

Torus is derived from the Latin word "tori", which means swelling or protrusion. The torus fracture is located at the metaphysis-diaphysis junction with intact periosteum and a single cortex fracture.[23] It is a wide spectrum, ranging from a mild deformity to a complete fracture of the cortex (Figure 1). Torus fracture treatment is usually conservative.[23,24] Fracture healing is rapid and three to four weeks of rigid immobilization is usually sufficient for pain relief.

Plastic Deformation

The size and shape of the bone may change under the influence of loads applied to the body. There are two types of deformation processes: reversible (elastic) and residual (plastic) deformation. In elastic deformation, the bone returns to its original shape when the load on the bone is removed. On the other hand, plastic deformation is permanent, and it cannot return to its original shape even if the load over the bone is removed. Thus, plastic deformation is non-recyclable and permanent.

Immature bone is not resistant to bending forces, but before the bone fractures, it absorbs a lot of energy that leads to plastic deformation.[25] Plastic deformation is generally seen in the forearm bones. Although there is a high capacity for major remodeling in cases of plastic deformation, some authors suggest reduction of the remodelling capacity in children older than four years and in deformities with more than 20° angulation.[26]

Greenstick Fractures

In the greenstick fracture, there is a plastic deformation with an intact periosteum in the cortex at the compressive site and a complete fracture in the cortex at the traction site (Figure 2). Thick periosteum is the main determinant of the development of greenstick fracture and this type of fracture is specific to the childhood period. Correction of the deformity is usually recommended in the treatment of greenstick fractures, although this topic has been discussed in the literature.[27]

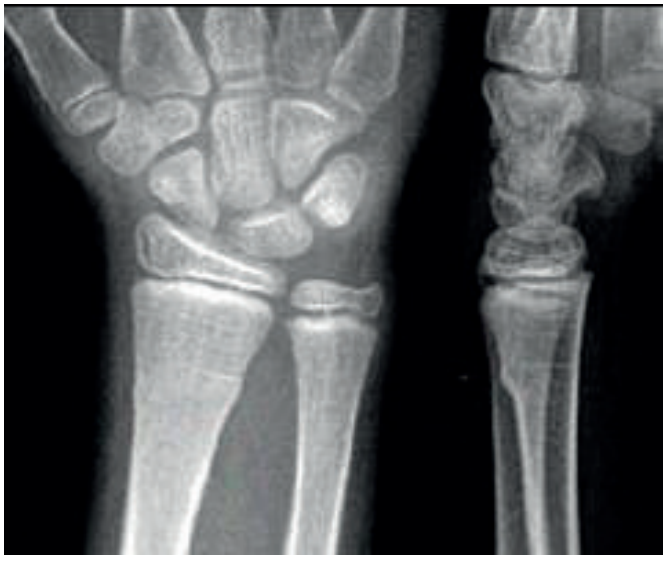

Figure 1. A-P and lateral radiograms of torus fracture

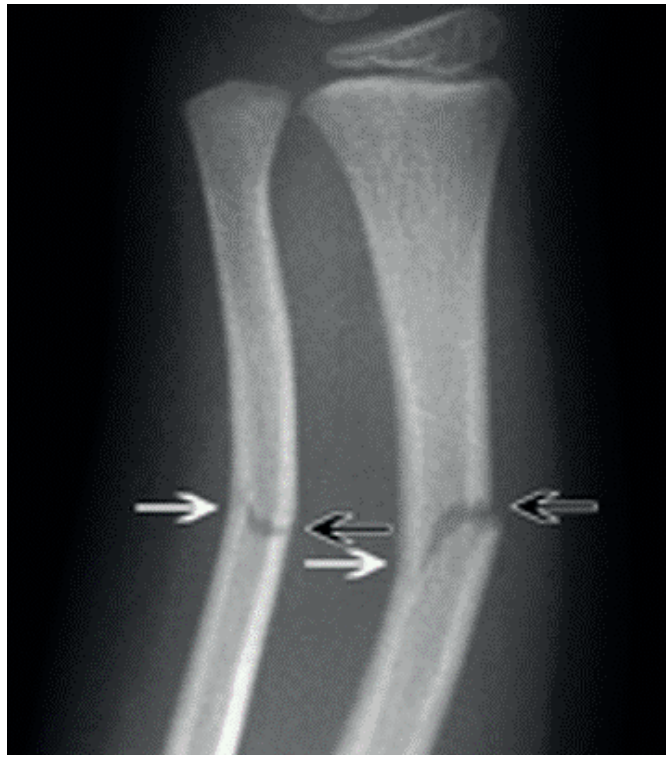

Figure 2. A-P radiogram of greenstick fracture

Treatment

Despite the advancement in technology and increasing options for minimally invasive surgery, closed reduction and conservative treatment methods, including casting, are still the mainstay of treatment for most of pediatric fractures. The incidence of childhood fractures that require surgery is only 16% of pediatric fractures.[7]

Conclusion

Childhood fractures are an important public health problem around the world due to the increasing incidence. Despite the high incidence of fractures in children, complications are very rare compared to adult fractures due to different properties of child bone such as the high potential of osteogenesis and remodeling capacity. Features that distinguish the child skeleton from the adult skeleton are having a thick periosteum and growth potential by the presence of physis. In this way, the healing time of fractures in children is shorter and they have a high remodeling potential.

On the other hand, prevention should be the mainstay of health strategy. Strict precautions should be taken in the environments where the children spend a lot of time, such as schools and playgrounds. All the children should be educated about traffic rules to minimize the risk of traffic accidents, starting from kindergarten through all grades..

Author contribution

Concept: BK, NK; Design: NK; Data Collection or Processing: BK; Analysis or Interpretation: BK, NK; Literature Search: BK, NK; Writing: BK, NK. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

The effects of transcatheter atrial septal defect closure on appetite, nutritional hormones and growth in children

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ABSTRACT

Objective: Children with congenital heart disease are at risk of malnutrition due to inadequate calorie intake, increased energy expenditure, pulmonary infections, and malabsorption. The aim of this study was to investigate the changes in appetite, nutritional hormones, and anthropometric measurements before and after the transcatheter closure of the atrial septal defect.

Method: The study included 27 patients whose atrial septal defect closed percutaneously and 25 children as a healthy control group. The initial symptoms, anthropometric measurements, and laboratory tests were recorded initially, and 1 month and 6 months after the closure.

Results: The mean age of patients and control group were 88.29 ± 58.25 months, 86.52 ± 55.81 months respectively. At the 1st month after the closure, all the symptoms in the patient group decreased compared to the initial visit except rapid breathing ($p < 0.05$). The percentage of patients who had a lack of appetite decreased from 45% to 5% at the 1st month visit. After the closure, the increase in weight for age, body mass index, and z-score were statistically significant at the 1st and 6th months ($p < 0.05$). Insulin-like growth factor-1 levels increased compared to the initial values at the 1st month ($p = 0.016$). A linear decrease in ghrelin levels and a linear increase in leptin levels were observed in the atrial septal defect group during the 6-month follow-up after the closure.

Conclusion: Children with atrial septal defect are at the risk of malnutrition. The primary prevention of malnutrition should be the goal of our treatment plan for these children; the timing of the interventional treatment is critical and has to be before the development of malnutrition.

Keywords: Atrial septal defect, children, ghrelin, growth, leptin, nutrition

INTRODUCTION

Atrial septal defects (ASD) are among the most common congenital heart diseases (CHD).[1] ASDs with a significant left-to-right shunt may increase the risk of malnutrition by leading to more frequent respiratory infections and hospitalizations.[2]

Ghrelin and leptin hormones, which affect appetite, have an important contribution to growth.[1,3-6] Ghrelin's function is to stimulate growth hormone secretagogue activity.[3-7] Eventually, ghrelin may signal the conservation of energy to prevent further weight loss and restore usual body weight by increasing food intake and reducing the use of fat.[8-10] Leptin is a peptide encoded by the obese gene.[11] Research on leptin has shown that leptin has effects that decrease food intake and increase adipose tissue. Besides, the effects of endocrinological factors such as growth hormone, insulin-like growth factors-1/2 (IGF-1/IGF-2), and insulin-like growth factors binding proteins on

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growth and nutrition were investigated in children with CHD. Most authors found the levels of these parameters to be low in these children.[12,13]

ASD closure is performed by transcatheter or surgical procedures in the presence of a significant left-to-right shunt. Since it is a less invasive method, transcatheter ASD closure should be preferred in cases suitable for treatment. It is a fact that the nutritional status and the growth of children improve significantly after the transcatheter closure. In this study, we aimed to demonstrate the effects of the transcatheter ASD closure treatment on appetite and growth through the changes in hormone levels such as ghrelin, leptin, IGF-1, and insulin-like growth factor binding protein-3 (IGFBP-3).

MATERIAL AND METHODS

Subjects

This case-control study was carried out at the outpatient clinic of Erciyes University Children's Hospital. Study approval was obtained from the ethics committee of Erciyes University (2017/347). Twenty-seven patients with ASD were included in the study. The main inclusion criteria of the patients were as follows: Secundum type ASD (diagnosed by echocardiography), Qp/Qs ≥ 1.5 (calculated during angiography), defects larger than 8 mm with sufficient rims.

Twenty-five healthy control children without malnutrition were included in the study after obtaining voluntary informed consent. Patients with chromosomal abnormalities, systemic diseases, and systemic infections were excluded from the study. We evaluated data of 20 patients, who came for regular follow-up in the 6th month. Unfortunately, seven of the patients did not come for their 6th month visit.

Measurements

Anthropometric measurements of patients: weight for age (WFA), height for age (HFA), body mass index (BMI) and their z-scores were recorded at the initial visit before the closure treatment, and at 1st and 6th month visits. These measurements were evaluated according to the World Health Organization (WHO) Anthro program for patients aged under 60 months, and according to WHO Anthro Plus program for patients aged 6 to 18 years were evaluated, which was established according to the WHO standards (https://www.who.int/tools/child-growth-standards/software).

Questionnaires

Questions about the symptoms, inadequate weight gain, lack of appetite, frequency of infection (frequent respiratory tract infections were defined as ≥ 6 events per year requiring antimicrobial treatment), respiration rate (using accessory respiratory muscles), fatigue were asked to all parents in two groups at initial visit. These questionnaires[14] and visual analogue scale (for lack of appetite) were repeated in the patient group at the 1st and 6th month visits. When asking questions about appetite to the families of children under the age of 6, the items in the questionnaire that were appropriate for our patient group were used. For children older than 6 years, the same procedure was performed by asking the patient himself/herself. The answer to the questions was asked to be shown on the visual analogue scale. The patient's lack of appetite was determined by applying a 100 mm long visual analogue scale (0-100 mm). The values close to '0' are composed of words and images expressing a decrease in the patient's appetite, while values close to '100' represent an increase in appetite. The cut-off value for lack of appetite was determined to be less than 50 mm. Answers to other questions were recorded as 'Yes' or 'No'.

Blood sampling

During the initial evaluation, approximately 6 mL of venous blood samples were collected from the patients between 9:00 a.m. and 10:00 a.m. after an average of 10 hours of fasting before the closure treatment. Four mL of the samples were centrifuged at 4000 rpm for 10 minutes in standard biochemistry tubes and their serums were separated. On the same day, IGF-1 and IGFBP-3 were measured at the central laboratory. A portion of the separated serum was then stored at -80° C to study leptin later. Two mL of venous blood sample was taken into tubes containing aprotinin. Plasma samples separated by centrifugation at 4000 rpm for 10 min were stored until the time of ghrelin analysis.

Ghrelin Human ELISA kit (Invitrogen, Catalog Number: BMS2192, USA) and Leptin Human ELISA kit (Invitrogen, Catalog Number: KAC2281, USA) were measured by the ELISA method. The lower limit of detection is 15.6 pg/mL for each hormone. IGF-1 was studied at cobas c 702 device at the Central Biochemistry Laboratory (Roche Diagnostics). IGFBP-3 was analyzed by IGFBP-3 Siemens kits in Immulite 2000 XPi device using the chemiluminescence method. We calculated IGF-1 and IGFBP-3 z-scores based on age- and gender-specific reference values for healthy Turkish children.[15] The laboratory tests of the patients were repeated at the 1st and 6th month visits.

Statistics

Data were analyzed using SPSS 22.0 computer software. The normality of the distribution of numerical variables was evaluated. Numerical data were compared between the groups using the Mann-Whitney U test (for not normally disturbed data) and sample t-test (for normally disturbed data). The chi-square test was used for categorical variables. We studied the correlation of the measured levels of individual hormones with anthropometric parameters, including z-scores of weight and height. For repeated measures, ANOVA was used in dependent groups for numerical variables matching normal distribution. After Bonferroni correction, pairwise comparisons were evaluated. Friedman test was used for numerical variables that did not conform to normal distribution. After Bonferroni correction, pairwise comparisons were evaluated. We used Pearson and Spearman's rank difference correlation to examine the correlation between hormone levels and anthropometric parameters. Statistical significance was determined according to a value of $p<0.05$.

RESULTS

Baseline characteristics

Twenty-seven (14 females, 13 males) patients with ASD fulfilling the inclusion criteria, and 25 (14 females, 11 males) healthy controls, who don't have any chronic diseases but have normal echocardiography findings, were included in the study. The age range of patients and healthy controls were 12-197 months (mean 88.29 ± 58.25 months) and 10-187 months (mean 86.52 ± 55.81 months), respectively. The baseline characteristics of the ASD group were summarized in Table 1. The mean size of the ASDs calculated by balloon sizing during angiography was 17.63 ± 5.48 mm. The patient group and control group were evaluated in terms of anthropometric measurements and hormone levels (Table 2). Ghrelin and leptin levels were higher, IGF-1 z-score and IGFBP-3 z-score values were lower at the initial visit compared to the control group, but there was no statistical significance. The WFA z-score, BMI, and BMI z-score were lower in the ASD group compared to the control group, but there was no statistical significance. Before the treatment, there were 9 patients (out of 20 patients) with an appetite score below 50. The mean appetite score was found to be 52.15±15.83 at initial visit.

Table 1. Baseline characteristics of atrial septal defect group

n=27	(%)
Age (month)	88.29 ± 58.25
Gender (female/ male)	14 (%52)/ 13 (%48)
ASD size (mm)	17.63 ± 5.48
Qp/ Qs	2.20 ± 0.66
PVR/SVR	0.14 ± 0.09
mean PAP (mmHg)	20.77 ± 5.50
ASD occluder devices:	
-Amplatzer septal occluder	10 (%37)
-Memopart septal occluder	6 (%22)
-Occlutech septal occluder	11 (%41)

ASD: Atrial septal defect, Qp/Qs: Pulmonary-systemic shunt ratio, PAP: Pulmonary arterial pressure, PVR: Pulmonary vascular resistance, SVR: Systemic vascular resistance

First month results

At the 1st month visit after the closure, all symptoms decreased in the patient group compared to the initial visit. The percentage of patients who had a lack of appetite decreased from 45% to 5% at the 1st month visit ($p= 0.002$). The mean appetite score was calculated to be 68.95±11.90. Only 1 patient with an appetite score below 50 was detected at the 1st month follow-up after ASD closure. The decrease in fatigue, inadequate weight gain, and frequency of infection was statistically significant (<0.001, 0.001, and 0.008 respectively). Nevertheless, the decrease in rapid breathing was not statistically significant.

After the closure, anthropometric measurements were found to be increased at the 1st month visit with a more prominent acceleration compared to the initial values (Table 3). The increase in WFA z-score, BMI, and BMI z-score was statistically significant ($p<0.05$).

At the 1st month visit, IGF-1 levels were significantly increased compared to the initial values (Table 3, $p = 0.016$). Ghrelin levels were found to be decreased, and leptin, IGF-1 z-score, IGFBP-3, and IGFBP-3 z-score levels were found to be increased at the 1st month visit compared to the initial visit. However, these differences were not statistically significant.

Sixth month results

At the 6th month visit after the closure, all the symptoms in the patient group decreased compared to the initial visit ($p<0.05$). The mean appetite score was calculated to be 70.95±12.50. At the 6th month follow-up after treatment, only 1 patient with an appetite score below 50 was detected, similar to the 1st month control. We found a statistically significant increase in WFA z-score, BMI, and BMI z-score at the 6th month visit when we compared to initial visit (0.05 vs 0.31 $p <0.001$, 17.80 vs 18.55 $p=0.001$, 0.17 vs 0.33 $p=0.002$, respectively). Laboratory tests

Table 2. Comparison of anthropometric measurements and laboratory tests between atrial septal defect group (before closure) and control group

	Atrial septal defect group (n=27)	Control group (n=25)	p value*
Weight for age z score	0.07 ± 1.37	0.10 ± 0.90	0.941
Height for age z score	-0.08 ± 1.10	-0.11 ± 0.79	0.919
Body mass index	18.94 ± 3.88	20.42 ± 2.25	0.236
Body mass index z score	0.18 ± 1.36	0.21 ± 1.29	0.158
Ghrelin (pg/mL)	636.00 (144.00-2208.00)	580.00 (212.00-2788.00)	0.603
Leptin (pg/mL)	4600.00 (441.00-55500.00)	3488.00 (996.00-38567.00)	0.862
IGF-1 (ng/mL)	95.50 (19.10-401.00)	82.00 (20.50-233.00)	0.680
IGF-1 z score	-0.98 ± 1.72	-0.59 ± 1.98	0.454
IGFBP-3 (ng/mL)	3877.77 ± 1850.70	3692.00 ± 1308.87	0.676
IGFBP-3 z score	0.42 ± 1.03	1.06 ± 1.59	0.097

IGF-1: insulin-like growth factor-1, IGFBP-3: insulin-like growth factor binding protein-3, Student's t-test was used in independent groups for numerical variables matching normal distribution. Non-parametric tests (Mann-Whitney U test) were used for numerical variables that do not confirm the normal distribution. p* <0.05 was considered statistically significant.

showed an increase in IGF-1 z-score at the 6th month visit when compared to the initial visit. Ghrelin levels showed a linear decrease; leptin levels showed an increase in the 6th month. These changes were not statistically significant.

Correlations

The correlation between initial hormone levels and anthropometric measurements of ASD patients was also evaluated in Table 4. The leptin, IGF-1 and IGFBP-3 levels, and IGF-1 z-scores were positively correlated with WFA and HFA. Similarly, there was a positive relationship between the IGFBP-3 z-score and WFA. The WFA z-scores were also weakly positively correlated with IGF-1 and strongly positively correlated with leptin levels. Ghrelin levels were strongly negatively correlated with WFA and HFA, and these results were statistically significant.

DISCUSSION

In this study, we investigated the symptoms, anthropometric measurements, hormonal levels, and their correlations in children before and after transcatheter ASD closure.

1. Symptoms and anthropometric evaluation

Rapid breathing, lack of appetite, frequency of infection, inadequate weight gain, and fatigue are frequently expected symptoms in patients with ASD that are hemodynamically significant. All the symptoms except rapid breathing decreased statistically significantly at the 1st month visit after the closure. These positive effects may be explained by changes in the morphology of the right ventricle that affects the left ventricle and the cardiac output. Therefore, pulmonary arterial blood flow and pulmonary congestion are reduced. A significant increase in appetite and food intake, a decrease in the frequency of infection, and a decrease in catabolism have been observed with ASD closure. Similar to our study, Knop et al.[16] and Sharma et al.[17] observed an increase in exercise capacity, a decrease in the frequency of infection, and an improvement in weight gain after transcatheter ASD closure. Narin et al.[18] evaluated 44 infants who underwent percutaneous ASD closure treatment with symptomatic ASD indication and they reported that 17 of the patients had a WFA z-score below -2 before ASD closure, their WFA z-scores had increased significantly after 12 months of follow-up, and only 3 patients had a WFA z-score below -2. Symptoms associated with heart failure should be considered in the timing of ASD closure and symptoms should be carefully evaluated at each visit.

Growth retardation and malnutrition are expected findings in children with CHD and have been reported since 1962. Mehrizi et al.[19] were the first to report it. Most patients with CHD present with growth retardation and malnutrition due to multifactorial reasons. Many patients with CHD have nutritional difficulties with decreased energy intake and increased energy requirements, provoking growth retardation. Malnutrition is not

Table 3. Comparison of anthropometric measurements and hormone levels of the atrial septal defect group before and after the closure

Atrial septal defect group	Initial time n=20	1st month n=20	6th month n=20	p value
Weight for age z score	0.05 ± 1.02	0.33 ± 1.34	0.31 ± 1.37	**0.008[a]** **<0.001*** 0.498† **<0.001‡**
Height for age z score	-0.11 ± 1.13	0.02 ± 1.22	0.06 ± 1.14	0.144[a] 0.068* 0.309† 0.054‡
Body mass index	17.80 ± 4.21	18.31 ± 4.00	18.55 ± 4.03	**0.015[a]** **0.013*** 0.389† **0.001‡**
Body mass index z score	0.17 ± 1.48	0.19 ± 1.33	0.33 ± 1.16	**0.012[a]** **0.009*** 0.086† **0.002‡**
Ghrelin (pg/mL)	763.00 (144.00-2208.00)	695.00 (192.00-1916.00)	436.00 (128.00-1436.00)	0.095[b] 0.102* 0.087† 0.061‡
Leptin (pg/mL)	3840.00 (441.00-55500.00)	6100.00 (690.00-59800)	9056.00 (447.00-51800.00)	0.198[b] 0.425* 0.126† 0.091‡
IGF-1 (ng/mL)	87.00 (19.10-401.00)	108.00 (15.00-429.00)	103.10 (26.20-539.00)	**0.027[b]** **0.016*** 0.258† 0.115‡
IGF-1 z score	-1.02 ± 1.66	-0.68 ± 1.53	-0.55 ± 1.47	0.225[a] 0.340* 0.668† 0.071‡
IGFBP-3 (ng/mL)	3720.48 ± 1620.30	4056.62 ± 1798.86	4040.50 ± 1845.74	0.569[a] 0.358* 0.843† 0.625‡
IGFBP-3 z score	0.40 ± 1.01	0.58 ± 0.94	0.43 ± 0.91	0.481[a] 0.287* 0.410† 0.793‡

IGF-1: insulin-like growth factor-1, IGFBP-3: insulin-like growth factor binding protein-3
*: p value between initial and 1st month, †: p value between 1st and 6th month, ‡: p value between initial and 6th month.
Table 3 shows the initial, 1st and 6th months control data of 20 patients who came to their follow-up regularly.
For repeated measures, ANOVA[a] was used in dependent groups for numerical variables matching normal distribution. After Bonferroni correction, pairwise comparisons were evaluated. Friedman[b] test was used for numerical variables that did not conform to normal distribution. After Bonferroni correction, pairwise comparisons were evaluated. p<0.05 was considered statistically significant.

Table 4. Correlation of nutritional and growth hormones with anthropometric measurements in the atrial septal defect group

n = 27 (initial levels)	Weight for age	Weight for age z score	Height for age	Height for age z score
Ghrelin	r = -0.683 **p < 0.001†**	r = -0.336 p = 0.087†	r = -0.704 **p < 0.001†**	r = -0.091 p = 0.651†
Leptin	r = 0.809 **p < 0.001†**	r = 0.647 **p < 0.001†**	r = 0.716 **p < 0.001†**	r=0.217 p=0.277†
IGF-1	r = 0.765 **p < 0.001†**	r = 0.386 **p = 0.047†**	r = 0.766 **p < 0.001†**	r = 0.154 p = 0.443†
IGF-1 z score	r = 0.582 **p = 0.001***	r = 0.310 p = 0.115*	r = 0.402 **p = 0.038***	r = 0.071 p = 0.725*
IGFBP-3	r = 0.792 **p < 0.001***	r = 0.293 p = 0.138*	r = 0.760 **p < 0.001***	r = 0.025 p = 0.903*
IGFBP-3 z score	r = 0.975 **p = 0.006***	r = 0.025 p = 0.902*	r = -0.102 p = 0.612*	r = -0.102 p = 0.612*

IGF-1: insulin-like growth factor-1, IGFBP-3: insulin-like growth factor binding protein-3
*Pearson Correlation test, †Spearman Correlation test p < 0.05 was considered statistically significant

expected in the early period of ASD. The characteristics of the acyanotic lesions such as coexisting pulmonary hypertension, failure to detect calorie intake, and use of medication due to heart failure may be an additive factor for malnutrition. Therefore, malnutrition is an expected finding in patients with hemodynamically significant ASD. Planning the most appropriate time for the defect closure is critical and it should be done before the onset of malnutrition.

Anthropometric measurements are substantial markers in investigating growth and the nutritional status.[8] Consequently, improvement in the weight status is the simple prominent data for the evaluation of growth. In our study, although not statistically significant, WFA z-score, BMI and BMI z-score values of patients were low compared to the control group. These results indicated that the time of closure in our patient group was well arranged that WFA z-score, BMI, and BMI z-score values had not been severely affected yet. Yilmaz et al.[20] found that the mean body mass index (BMI), WFA, and HFA of the control group were significantly higher compared to the CHD group in their study. This difference may be due to the variations in the study group. We observed a statistically significant increase in the WFA z-score, BMI, and BMI z-score at the 1st and 6th month follow-up compared to the initial visit measurement. This shows how effective transcatheter closure therapy is in the early phase and how it improves weight gain. This may be explained by the increased appetite of our patients after the closure. Similar to our study, Blasquez et al.[21] noted that the most important cause of insufficient growth in CHD was inadequate calorie intake. Soliman et al.[22] studied the linear growth of surgically treated children with CHD during the pre-operative and post-operative periods. They found a significant increase in HFA z-score and BMI z-score 1 year after the operation compared to the preoperative period. We also found an increase in the HFA z-score in our study, but it was not statistically significant. If we had followed-up the patients for 1 year instead of 6 months, maybe we might have obtained similar results. In our study, positive changes were observed in anthropometric measurements, especially in WFA, BMI and their z-scores at each visit. Thus, the cycle of negative metabolic balance can be considered broken.

2. Biochemical and hormonal evaluation

There are several hormones affecting growth such as growth hormone, IGF-1, ghrelin, leptin, etc. The role of ghrelin in CHD and its effects on growth have always been an interesting subject of research in the field of cardiology. The relationship among heart failure, growth, and ghrelin was first examined in 2010 by Kitamura et al.[6] They reported high ghrelin levels in patients with heart failure. Yilmaz et al.[20] found that ghrelin levels were higher in the CHD group compared to the control group. Therefore, they concluded that ghrelin may have an important role in metabolic balance such as growth retardation and malnutrition.[8,10] In our study, no statistically significant differences were found in ghrelin compared to the control group. Nevertheless, ghrelin levels of 20 patients with ASD were found to be lower at each visit compared to the previous value. This decrease in ghrelin levels may be associated with increased appetite and food intake after ASD closure.

In this study, no statistically significant differences were found in leptin levels compared to the control group at initial visit. After

transcatheter closure, leptin levels were increased gradually at the 1st and 6th month visits, compared to the initial visit. However, it was not statistically significant. This increase can be explained by an increase in fat tissue as a result of weight gain.

In our study, no significant differences were found in IGF-1 and IGFBP-3 values at the initial visit. In the 1st month, IGF-1 levels significantly increased compared to the initial visit. In the study of Surmeli-Onay et al.[23], the preoperative IGF-1 and IGFBP-3 levels were found to be higher in the control group compared to the children with CHD. They noted that IGF-1 and IGFBP-3 were important markers of nutrition. Similar to our study, Soliman et al.[22] also showed a significant increase in IGF-1 and its z-score values 1 year after the operation compared to the preoperative period. These findings support the view that the attained growth spurt after treatment is mediated by increased IGF-1 synthesis. So IGF-1 and IGFBP-3 values can be largely reversible after a nutritional intervention, these values are on an increasing trend in patients with weight gain after ASD closure. In our study, it is noteworthy that the rate of increase in IGF-1 and IGFBP-3 levels and related anthropometric measurements are more significant in the early period of the treatment, becoming evident by the 1st month. Parallel to this, the accompanying symptoms seemed to be resolved in a short time. These results may be explained by the increase in appetite and weight after ASD closure.

3. The correlations

We observed that ghrelin levels were low; leptin and IGF-1 levels and IGF-1 z-score were high in the patients whose weight and height for the age group were high. In a study[8], a negative correlation was found between ghrelin level and WFA z-score. Yilmaz et al.[20] found that ghrelin levels were negatively correlated with BMI. These results suggest that ghrelin is one of the most potent orexigenic and adipogenic agents that increase to compensate for weight loss. In a study by Hallioglu et al.[24] a significant positive correlation was found between the BMI and leptin levels of the patients. This correlation is explained by the positive relationship between leptin and the adipose tissue mass.

CONCLUSION

In summary, children with CHD are often at risk of malnutrition. The primary prevention of malnutrition should be the goal of our treatment plan for these children; the timing of the interventional treatment is critical and has to be before the development of malnutrition, which has a positive effect on hormonal status. Briefly, transcatheter ASD closure is important because it improves the symptoms, has positive effects on hormones that affect appetite and growth, and as a result, it contributes to somatic growth.

LIMITATIONS

The most important limitation of our study is that the study has the data from a single center with a relatively limited number of patients which restricts the generalizability of our results. The second limitation was the wide age range of the patients. It was so wide that some patients were infants and some were adolescents. Therefore, calculating the calorie intake specifically for those who are breastfed was impossible. The third limitation was that the symptoms of the patients were asked to their parents, which relied on their observations and can be subjective. The last limitation was that seven of the patients did not come to their 6th month visit.

Ethical approval

This study has been approved by the Erciyes University Clinical Research Ethics Committee (approval date 16/06/2017, number 2017/347). Informed consent forms were obtained from parents.

Author contribution

Surgical and Medical Practices: OT, ÖP, NN, AB; Concept: OT, ÖP; Design: NN, DBK; Data Collection or Processing: OT, DBK, SS, ÇV; Analysis or Interpretation: OT, SS, ÇV; Literature Search: OT, ÖP, NN; Writing: OT, ÖP. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Vascular involvement in pediatric inflammatory bowel disease

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ABSTRACT

Objective: Patients with inflammatory bowel disease (IBD) have a higher incidence of cardiovascular disease (CVD). Early diagnosis of arterial damage is essential to prevent future vascular risk. We aimed to assess the vascular involvement IBD by monitoring inflammation parameters, echocardiography, augmentation index (AIx); carotid pulse wave velocity (PWV), carotid intima-media thickness (cIMT), and blood pressure.

Method: The patient population included 25 subjects with a previously biopsy-proven diagnosis of IBD who had been on treatment for at least one year. Carotid PWV, AIx, and cIMT of the patients were measured.

Results: Twenty-five patients (15 female and 10 male) with IBD and 25 healthy controls were included in this present study. There was a significant difference between the carotid PWV values (mean 4.84±0.39, 4.49±0.17, respectively, p <0.001), but no differences were observed in the cIMT and AIx values.

Conclusion: The carotid PWV values assessing arterial stiffness may be effective, safe, and easy to detect subclinical atherosclerosis in children with IBD. Larger studies should be carried out to evaluate other indicators of early atherosclerosis and arterial stiffness such as cIMT and AIx.

Keywords: AIx, cIMT, children, inflammatory bowel disease, PWV

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory, dysfunctional immune-mediated disorder of the gastrointestinal tract in genetically predisposed children.[1-3] It is classified as Ulcerative Colitis (UC) and Crohn's Disease (CD).[1,3] Approximately, 20-30% of patients are diagnosed in childhood and adolescence.[4] In children with IBD, host factors, and genetic, environmental, and microbial effects result in a dysregulated mucosal immune response against the intestinal microbiota.[5] Consequently, IBD develops due to abnormal recognition of microbiota antigens by innate immune cells, resulting in inflammation in the bowel.[3] Inflammation plays a critical role in the pathophysiology of IBD.[6,7] Chronic inflammation causes an increase in reactive oxygen species (ROS). The production of free radicals leads to tissue remodeling and the intensification of the process of atherosclerosis.[8] Recently, a relationship between atherosclerosis and chronic inflammation has been identified, and early endothelial dysfunction has been observed in chronic inflammatory disorders such as IBD.[3] Patients with IBD have a higher incidence of cardiovascular disease (CVD).[9-11] The vascular disease risk in IBD is estimated to be three to four-fold higher than that in the general population.[2,4,7,8]

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Early diagnosis of arterial damage is essential to prevent future vascular risk considering that subclinical atherosclerosis can be reversed with early diagnosis and intervention. Measurement of increased carotid intima-media thickness (cIMT), carotid pulse wave velocity (PWV), and augmentation index (AIx) are early diagnostic tools. Carotid intima-media thickness, which is assessed using B-mode ultrasonography, is a valid surrogate marker of atherosclerotic disease.[12] Arterial stiffness due to reduced arterial compliance is one of the major signs of vascular aging. Arterial stiffness, the main index for estimating arterial elasticity, is assessed by carotid PWV and AIx measurement.[13] These methods are repeatable, reliable, easy, and noninvasive for early detection of increased arterial stiffness at an early stage.[14]

Several studies have investigated the relationship between cardiovascular and inflammatory bowel diseases so far. The present study aimed to assess the vascular involvement in pediatric inflammatory bowel disease by monitoring inflammation parameters, echocardiography, AIx; carotid PWV, cIMT, and blood pressure.

MATERIAL AND METHODS

This case-controlled study was performed at a single center between January 2018 and January 2019. The patient population included 25 patients with a previous biopsy-proven diagnosis of IBD who had been on treatment for at least one year and had come for follow-up visits between 2018-2019. There were no known co-morbidities such as hypothyroid, hypertension, dyslipidemia; systemic autoimmune disease, active infection, diabetes mellitus; and Mediterranean fever syndrome. The control group was selected from healthy pediatric nephrology outpatients of similar age and sex to the patient group (n=25) and without any chronic disease. The study was approved by the Ethical Committee of the Ege University Hospital, Medical School. Written informed consent was signed by parents or caregivers. The study was conducted in accordance with the Declaration of Helsinki guidelines.

Inflammatory bowel disease is diagnosed with a detailed clinical story, physical examination, laboratory tests, and gastrointestinal endoscopy/colonoscopy. Age at the time of IBD diagnosis, complaints, gender, and family history were recorded. The patients' weight, height, body mass index (BMI), and standard deviation scores (SD) at the initial and last visits were also recorded. All patients underwent a physical examination, including measurement of weight using a digital scale and height using a stadiometer. Their body mass index was calculated as weight in kilograms divided by height in meters squared. We used the standard deviation scores that were calculated according to the Turkish growth charts to evaluate the weight, height, and BMI values across different age and gender groups.[15]

Blood samples were drawn by venipuncture to assess routine blood parameters. Complete blood count, biochemical parameters, and acute phase reactant levels (sedimentation, C-reactive protein) were evaluated after overnight fasting for at least eight hours at the time of the last visit. The samples were analyzed in a local laboratory.

Blood pressure was measured in the rested sitting position using the Omron automatic blood pressure device and a suitable sized cuff. The average systolic and diastolic blood pressure values over %95 according to age, sex, and height were considered as hypertension after at least three measurements.[16]

Carotid pulse wave velocity (PWV), AIx, and cIMT of the patients were measured. Carotid-femoral peripheral wave velocity and AIx were calculated using Vicorder three times (Skidmore Medical Limited, Bristol, UK). AIx was calculated as the difference between the first and second systolic peaks of the central aortic waveforms and defined as the percentage of the wavelength. Siemens Acuson Antares instrument and VFX-7-13 MhZ linear probe were used for the measurements of cIMT.

Statistical analysis

Statistical analysis was performed using basic statistical methods. The distribution of the data was calculated using the Kolmogorov-Smirnov normality test. Independent sample t-test was used to compare numerical data between groups. Pearson test was used to calculate the correlation between cIMT, carotid PWV, and AIx with laboratory parameters. The significance level was accepted as $p<0.05$. Data were analyzed using IBM SPSS 22.0 software package (IBM Corp., Armonk, NY).

RESULTS

Twenty-five patients (15 female and 10 male) with IBD, mean age 14.12±4.04 years, were included in this present study. The mean duration of follow-up was 3.33±3.00 years. Twenty-five age-matched (mean 13.20±4.03 years) subjects were selected as healthy control. Of the healthy controls, 11 were female and 14 were male. The anthropometric measurements of IBD patients and the control group were presented in Table 1.

Eight (32.0%) patients had diarrhea, five (20.0%) abdominal pain, three (12.0%) weight loss; three (12.0%) diarrhea and abdominal pain, one patient (4.0%) fatigue, and five had (20.0%) all of the symptoms.

Table 1. Anthropometric measurements of IBD patients at the time of diagnosis			
Patient group	**Minimum**	**Maximum**	**mean±SD**
Height SD	-2.95	0.76	-0.94±1.20
Weight SD	-5.52	1.29	-1.26±1.69
BMI SD	-6.34	2.51	-0.89±1.97
Healthy controls			
Height SD	0.53	1.34	0.99±0.22
Weight SD	0.22	1.27	0.76±0.43
BMI SD	0.77	1.37	0.87±0.57

SD: standard deviation score, BMI: body mass index, cm: centimeter; kg: kilogram, IBD: inflammatory bowel disease

Based on the complaints, acute phase reactant, symptoms, and stool examination at the last visit; 15 (60%) IBD patients were considered to be in remission. The remaining 40% of the patients had active disease.

The mean value of three blood pressure measurements was normal in all of the IBD patients. Echocardiographic evaluation was normal in all IBD patients.

There was no significant difference in cIMT, Aix, and carotid PWV values between the two groups, and their weight SD and height SD were significantly lower, while the CRP and sedimentation values were significantly higher in patients with active disease compared to patients in remission (Table 2).

When the patient and healthy control groups were compared, there was a significant difference in carotid PWV values (mean 4.84±0.39, 4.49±0.17, p<0.001, respectively), while no difference was observed in cIMT and AIx values (Table 3).

There was no significant relationship between the CRP and sedimentation values and the carotid PWV, cIMT, and AIx levels in patients with inflammatory bowel disease.

Table 2. Comparative analysis of the demographic, anthropometric and biochemical data of the IBD patients according to disease activity			
	Patients with an active disease mean±SD	**Patients with remission mean±SD**	***p* value**
Age (year)	14.85±3.89	13.63±4.20	0.09
Weight SD	-2.26±1.02	-0.9±1.49	**0.019**
Height SD	-1.81±1.15	-0.47±1.23	**0.039**
BMI SD	-1.62±-0.31	1.39±1.47	0.085
CRP (mg/dL)	2.34±2.65	0.13 ±0.17	**0.004**
Sedimentation (mm/h)	35.00±16.79	10.23±3.70	**<0.001**
25 OH vitamin D (ng/mL)	19.50±12.79	22.62±9.03	0.631
Hemoglobin g/L	11.37±1.67	11.62±2.21	0.731
White blood cell 10*3/uL	11.605±6.421	10.188±4.971	0.540
Absolute neutrophils count 10*3/uL	7.705±3.930	6.469±5.147	0.527
cIMT (mm)	0.47±0.03	0.47±0.02	0.663
AIx	31.60±7.98	23.33±10.95	0.052
Carotid PWV (m/s)	4.85±0.17	4.81±0.48	0.652

SD: standard deviation score, BMI: body mass index, cm: centimeter; kg: kilogram, IBD: inflammatory bowel disease, CRP: C reactive protein, PWV: pulse wave velocity, cIMT: carotid intima-media thickness, AIx: augmentation index

Table 3. Comparative analysis of the cIMT, AIx, and carotid PWV values between the IBD patients and healthy control group			
	IBD patients mean±SD	**Healthy controls mean±SD**	**p value**
cIMT (mm)	0.47±0.07	0.47±0.02	0.819
Carotid PWV (m/s)	4.84±0.39	4.49±0.17	**<0.001**
AIx	26.80±10.10	23.24±8.37	0.181
SD: standard deviation score, IBD: inflammatory bowel disease, PWV: pulse wave velocity, cIMT: carotid intima-media thickness, AIx: augmentation index			

DISCUSSION

There are limited published data on vascular involvement in pediatric patients with IBD. The present study was the first to report the evaluation of preclinical atherosclerosis using carotid PWV, AIx, cIMT measurements; ECG and blood pressure values altogether in pediatric IBD patients.

Cardiovascular risk is a well-known complication of chronic inflammatory conditions. Systemic inflammation has been associated with premature endothelial dysfunction and atherosclerosis is considered as a chronic inflammatory process.[17,18] Although relatively rare in the pediatric IBD population, atherosclerosis is a significant comorbidity that requires early diagnosis and management. Early diagnosis of arterial damage is essential to prevent future vascular risk since subclinical atherosclerosis can be reversed with early diagnosis and intervention. In a study with pediatric patients[19], carotid PWV values were significantly higher in patients with IBD. In the present study, we similarly found that carotid PWV values were significantly higher than the control group (mean 4.84±0.39, and 4.49±0.17, respectively, p <0.001). We could speculate that the patients' high PWV values due to the changes in the vascular wall could be related to the inflammation underlying IBD, considering that many of our IBD patients are in the active phase (40%), unlike the healthy controls. Lurz et al. found that PWV was normal in children with IBD in remission or with mild disease activity.[20] Nonetheless, in our study, we found that our patients in remission had higher PWV values than control patients. We may have achieved such different results (60% vs. 68%, respectively) as the remission rate of our patients was lower than the rate in the study conducted by Lurz et al.[20] Another important finding in our study was the insignificant increase in AIx and cIMT in IBD patients compared to healthy controls. Similar to our study, Yildirim et al. found PWV to be more useful than the cIMT in detecting vascular damage in Behcet Disease.[21] Multicenter studies with a larger sample size may be needed to obtain a significant difference for these two parameters. We speculate that this insignificant result might be related to the overall high rate of clinical remission (60%).

When we compared the IBD patients in the active phase and those in remission, the latter group had higher AIx and carotid PWV values than the former. However, this difference was not significant. Chronic low-grade inflammation might be the cause of increased atherosclerotic burden and vascular aging in IBD patients despite remission. Chronic exposure to even moderate levels of inflammatory factors appears to promote atherosclerosis.[22,23]

When the IBD patients were compared according to disease activity, the SD of weight and height were significantly lower, and CRP and sedimentation values were significantly higher in the patients with active disease. We may have observed low weight SD values due to sudden weight loss as a result of increased catabolism and gastrointestinal loss during the active disease period. The tissue damage that ensues triggers a host of events including increased energy expenditure, fat mobilization, proteolysis, negative nitrogen balance, gluconeogenesis, and anorexia and weight loss. Increased CRP and sedimentation values due to inflammation may be observed. Cortisol, which is elevated during a chronic inflammatory response, can cause growth stunting by impairing protein synthesis.[24] Corticosteroids are anti-inflammatory agents which are effective and commonly used in the treatment of CD and UC in children.[1,2] The beneficial effects of corticosteroids as immunosuppressive and anti-inflammatory agents are accompanied by adverse effects on growth, especially when supra-physiological doses are administered long-term. The fact that our patients who were included in the study received steroid therapy over physiological limits until induction may have caused the height SD rates to be lower than normal for their age. Besides, as a limitation of our study, we did not know whether our patients with short stature suffered from structural short stature as their parent height was not recorded.

Interestingly, in IBD patients, there was no significant relationship between the CRP and sedimentation values and carotid PWV, cIMT and AIx levels. A more significant result could have been obtained if the sample group was larger. Another reason might have been the patients with protein and energy malnutrition, leading to impaired acute phase reactant response in our study.

In conclusion, the carotid PWV values assessing arterial stiffness may be effective, safe, and easy to detect subclinical atherosclerosis in children with IBD. Larger studies should be carried out to evaluate other indicators of early atherosclerosis and arterial stiffness such as CIMT and AIx.

Ethical approval

This study has been approved by the Ege University Medical Research Ethics Committee (approval date 17/12/2020, number 20-12.1T/35). Written informed consent was signed by parents or caregivers.

Author contribution

Surgical and Medical Practices: EKT, ST, ED, EL, SA, FÇ; Concept: EKT, MK, EL, FÇ; Design: EKT, ST, ED, MK; Data Collection or Processing: EKT, ST, ED, MK, İKB, EL, SA, FÇ; Analysis or Interpretation: EKT, MK, EL, FÇ; Literature Search: EKT, İKB, FÇ; Writing: EKT, İKB, SA, FÇ. All authors reviewed the results and approved the final version of the article.

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The authors declare that there is no conflict of interest.

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Original Article

Results confirming the efficacy of oral L-dopa on cortisol secretion in patients being evaluated for suspected growth hormone deficiency

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ABSTRACT

Objective: Adrenal insufficiency is a life-threatening disease and therefore, accurate diagnosis and prompt treatment are life-saving. The main purpose of this study was to retrospectively evaluate the serum cortisol levels measured during the L-dopa test in cases suspected GH deficiency and to compare the effect of L-dopa on cortisol secretion with the results of previous studies.

Method: Between January 2019 and January 2021, patients who underwent the L-dopa test for the evaluation of GH deficiency in our Pediatric Endocrinology Clinic and whose basal cortisol levels were measured at the baseline and at the 120th minutes of the test were included. The clinical, anthropometric, and laboratory data of the patients were obtained from the medical records.

Results: Eighty-five patients (38 girls, 47 boys) were included in the study. The mean age of the patients was 10.3 ± 3.5 years (range, 4.1 - 14.9 years). The mean serum cortisol level was 11.1 ± 3.6 µg/dL at baseline and 20.9 ± 3.8 µg/dL at 120th minutes (the mean cortisol increase was 9.8 ± 4.1 µg/dL). Cortisol response was adequate (> 18 µg / dL) in 76 cases (89.4%). Nausea/vomiting was observed in 53 (62.4%) of the patients during the L-dopa test. Peak cortisol responses of the cases with and without side effects were similar (20.9 ± 3.8; 20.8 ± 3.7; p = 0.945).

Conclusion: In conclusion, the L-dopa test is easy to apply, effective, and safe and can be performed to evaluate cortisol adequacy at least in patients being evaluated for suspected GH deficiency.

Keywords: Adrenal function, adrenal insufficiency, cortisol, cortisol deficiency, dopamine agonist, L-dopa

INTRODUCTION

Adrenal insufficiency is a life-threatening disease characterized by the lack of sufficient cortisol production in the adrenal glands, and accurate diagnosis and prompt treatment are life-saving.[1] Various pharmacological tests, including the insulin tolerance test (ITT), adrenocorticotropic hormone (ACTH) test, and glucagon tests, are widely used in the evaluation of the hypothalamic – pituitary – adrenal (HPA) axis.[2] Because of the possibility of a second pituitary hormone deficiency in patients with GH deficiency, adrenal insufficiency should be ruled out. ITT, ACTH, or glucagon test have been the most commonly used tools to measure cortisol secretion when evaluating the adrenal axis in patients with GH deficiency. Although ITT has been considered the gold standard, it is an unsafe test and serious neurological complications and even death have been reported.[2,3] On the other hand, the glucagon test has various disadvantages, including its long duration (180 minutes) and side effects such as vomiting and hypoglycemia.[4] In addition, although ACTH tests are effective, it does not allow us to evaluate GH secretion in addition to cortisol. Therefore, there is a need for an additional test to measure cortisol secretion in

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children with suspected growth deficiency. Some recent studies have suggested that L-dopa, which has been used for almost 50 years to measure GH deficiency, stimulates cortisol secretion and can be used in the diagnosis of adrenal insufficiency.[5,6] The results of our previous study investigating the effect of L-dopa on cortisol secretion in patients being evaluated for suspected GH deficiency confirmed the findings of previous studies.[7] Therefore, in our center, we started routinely using the L-dopa test to measure cortisol secretion in patients being evaluated for suspected GH deficiency. In addition to GH levels, we routinely measured serum cortisol levels at the baseline and 120th minutes in the patients who underwent the L-dopa test for suspected GH deficiency. In this study, we aimed to retrospectively evaluate the serum cortisol levels measured during the L-dopa test in cases suspected GH deficiency and to compare the effect of L-dopa on cortisol secretion with the results of previous studies.

MATERIAL AND METHODS

Between January 2019 and January 2021, patients who underwent the L-dopa test for the evaluation of GH deficiency in our pediatric endocrinology clinic and whose basal cortisol levels were measured at the baseline and at the 120th minutes of the test were included. All patients underwent a thorough physical examination and laboratory evaluation, including thyroid function tests to measure possible endocrine pathology. The clinical, anthropometric, and laboratory data of the patients were obtained from the medical records. Patients with chronic diseases (cardiovascular, gastrointestinal, and respiratory), a history of drug use (steroids and antipsychotics), endocrine pathology (Cushing syndrome and hypothyroidism), or suspected multiple pituitary hormone deficiency were excluded from the study. A Harpenden stadiometer with a sensitivity of 0.1 cm was used to measure height. Auxological evaluation was performed according to the Turkish National Growth Chart.[8] This study was conducted in accordance with the Declaration of Helsinki Ethical Principles, and approved by the Dr. Behçet Uz Children Hospital Clinical Research Ethics Committee (Protocol no:759 and Decision no: 2017/241). Each participant included in this study was informed about the scope of the study and written consent was obtained from the parents.

All experiments were performed as a routine diagnostic procedure in recumbent subjects in the morning between 7:30 and 8:00 a.m. after 10–12 h of fasting. The provocation tests were performed in the morning hours. On the morning of the study, subjects were not given breakfast, and a catheter was inserted into their antecubital vein; this system was kept open with saline. The patients were allowed to rest for 30 minutes before the stimulation test. For the test, a single oral dose of L-dopa (Madopar®, La Roche, Basel, Switzerland) was administered according to the weight of each subject (500 mg for children weighing > 30 kg, 250 mg for those weighing 15–30 kg, and 125 mg for those weighing < 15 kg). During the L-dopa test, serum GH levels were classically measured just before the administration of L-dopa and at the 30th, 60th, 90th, and 120th minutes, and in addition, serum cortisol levels were measured at the baseline and at the 120th minutes of the test. Side effects during the L-dopa test were recorded. All samples were analyzed immediately. Hormonal measurements were performed using electrochemiluminescence immunoassay procedures with the Cobas kit (Roche, Mannheim, Germany). Peak concentrations of cortisol exceeding 18 µg/ dL (496 mmol/L) were defined as an adequate response. A low-dose 1-microgram ACTH test was administered to the patients whose serum cortisol level was insufficient in the L-dopa test to investigate adrenal insufficiency.

Statistical analyses of the data were performed using the SPSS software package for Windows (Ver. 20.0; SPSS Inc., Chicago, IL, USA). The distribution of data was evaluated using the Kolmogorov-Smirnov test. For numerical comparisons, the Student's t-test or Mann-Whitney U tests was used to assess differences between the two groups according to the normal distribution of the measured parameters. Spearman's rho correlation was used to identify the associations between variables. Categorical data were expressed as frequency (%), while numerical data were expressed as mean ± standard deviation. In all statistical tests, *p*-values <0.05 were considered significant.

RESULTS

Eighty-five cases (38 females, 47 males) whose cortisol levels were measured during the L-dopa test were included in the study. The mean age of the cases was 10.3 ± 3.5 years (range, 4.1 - 14.9 years). According to Tanner staging, 54 of the cases were prepubertal and 31 were pubertal. The mean height SDS was -3.32 ± 0.84. The mean peak GH level was 5.8 ± 3.4 ng/mL.

Serum cortisol levels were 11.1 ± 3.6 µg/dL at baseline and 20.9 ± 3.8 µg/dL at 120th minutes (cortisol increase, 9.8 ± 4.1 µg/dL). The cortisol response was adequate (> 18 µg / dL) in 76 cases (89.4%) (Figure 1). In 9 cases with an inadequate cortisol response, ACTH test was performed and an adequate cortisol response was obtained, indicating that there was no patient with adrenal insufficiency among the subjects. The characteristics of 9 cases with a peak cortisol response of <18 µg/dL during the L-dopa test were presented in Table 1. Interestingly, three of the 9 cases with a peak cortisol level below 18 µg/dL at the 120th minute of the L-dopa test were found to have a baseline cortisol level above 10 µg/dL. Nausea/vomiting was observed in 53 (62.4%) of the patients during the L-dopa test. Peak cortisol

responses of cases with and without side effects were similar (20.9 ± 3.8; 20.8 ± 3.7, respectively; p = 0.945). On the other hand, no significant difference was found between the peak cortisol responses obtained during the L-dopa test of prepubertal and pubertal subjects (20.8 ± 3.7; 21.1 ± 3.8, respectively; p = 0.753). In addition, no significant correlation was found between age and peak cortisol (r = -0.065, p = 0.553).

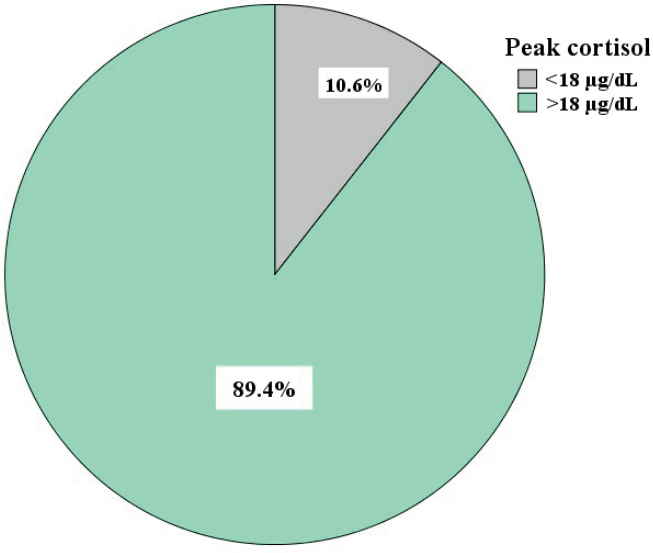

Figure 1. Determination of peak cortisol responses as adequate (>18 µg / dL) or insufficient (<18 µg / dL)

DISCUSSION

The effect of dopamine on cortisol secretion has been investigated for about 50 years. The first study was performed by King et al.[9] in 1959 in albino rats and showed that dopamine caused a significant increase in cortisol secretion. On the other hand, in the years following this study, various experimental studies conducted with a small number of subjects reported that intravenous or oral dopamine did not significantly increase serum cortisol secretion.[10-13] Subsequently, Stratakis et al.[14] demonstrated a moderate effect of dopamine on cortisol and ACTH secretion, and Philippi et al.[15] reported that dopamine had a significant stimulatory effect on cortisol secretion. Recently, in two different studies conducted by Marakaki et al., it was shown that 93% and 94.7% of cases had sufficient cortisol response with the L-dopa test.[5,6] However, the very small number of cases in our previous study and Marakaki's studies was the most important limitation. Similarly, in our previous study, the L-dopa test revealed that 26 of the 29 children (89.7%) had an adequate cortisol response (this rate was 79.3% in ITT, the gold standard test).[7] In the current study, in which the baseline and 120th-minute cortisol levels were evaluated in subjects who underwent the L-dopa test, the frequency of cases with an adequate cortisol response was found to be 89.4%. Considering the previous study results, the current study with a very high number of cases suggested that the stimulating effect of L-dopa on cortisol secretion is as effective as the gold standard test, ITT.

Dopamine, the dominant catecholamine neurotransmitter in the central nervous system, regulates various functions such as cognition, emotion, hunger/satiety, and the endocrine system (for example, prolactin suppression). While dopamine cannot

Table 1. The characteristics of 9 cases with a peak cortisol response of <18 µg/dL during the L-dopa test

Patient	Age (years)	Gender	L-dopa test		1-mcg ACTH test	
			Cortisol		Cortisol	
			Baseline (µg/dL)	120th minutes (µg/dL)	Baseline (µg/dL)	60th minutes (µg/dL)
1	5.1	Male	5.9	15.3	8.4	20.8
2	4.9	Male	7.9	16.8	9.8	19.9
3	11.5	Male	6.1	13.4	8.3	19.6
4	11.9	Female	8.1	14.9	16.8	26.3
5	14.0	Male	12.3	16.2	8.85	22.8
6	11.1	Female	5.4	9.4	7.92	24.5
7	14.3	Female	13.4	17.4	10.7	18.8
8	10.9	Female	7.9	8.9	9.2	21.1
9	4.3	Female	12.2	12.9	11.4	20.6

cross the blood-brain barrier directly, L-dopa, which is the precursor of dopamine, crosses the blood-brain barrier and binds to the dopamine receptor (known as D1-D5) in the central nervous system and displays its functions.[16] Administration of a dopamine agonist (bromocriptine) was demonstrated to increase the proopiomelanocortin (POMC) mRNA, a prohormone for adrenocorticotropic hormone (ACTH), concentration in the pituitary gland and hypothalamus.[17] Another study suggested that L-dopa is converted to norepinephrine by dopamine β-hydroxylase and, subsequently, stimulates the corticotropin releasing factor, which positively regulates the HPA axis.[18] The results of the experimental studies support that the dopamine agonist stimulates the HPA axis through various pathways and therefore increases the secretion of cortisol from the adrenal gland. In our previous study[7] and in the study by Marakaki et al.[5], ACTH levels were also shown to increase in correlation with serum cortisol responses during the L-dopa test, suggesting that the possible physiological mechanism of the cortisol-secreting effect of L-dopa is the increase in ACTH.

It has been demonstrated that the maturation of the HPA axis increases with age and with the progression of puberty, and as a result, cortisol secretion increases.[19,20] In the current study, similar to our previous study, no correlation was found between peak cortisol level and pubertal status or age. In addition, nausea/vomiting was observed in 53 (62.4%) of the patients during the L-dopa test, and peak cortisol responses were similar in patients with and without side effects. This finding was similar to the results of our previous study and the two studies of Marakaki et al.[5-7] Taken together, these findings suggest that the hypothesis that an increase in cortisol and ACTH secretion occurs as a result of side effects such as nausea/vomiting during the L-dopa test is not valid.

This study has some limitations. Considering the previous studies, it was shown that the peak cortisol response was obtained at the 120th minute in most of the cases during the L-dopa test.[5-7] Therefore, in our daily practice in our center, we measure serum cortisol at the baseline and at the 120th minute during the L-dopa test. Therefore, serum cortisol levels at these time-points were considered in this retrospective study. Since we did not measure cortisol levels at the 90th minute, we cannot exclude the negative impact of this on the peak cortisol responses. Furthermore, conditions affecting the bioavailability of oral L-dopa and thus peak cortisol levels were not considered in the current study.

In conclusion, the L-dopa test is easy to apply, effective, and safe and can be performed to evaluate cortisol adequacy at least in patients being evaluated for suspected GH deficiency. However, further studies are needed to evaluate its effectiveness in the diagnosis of adrenal insufficiency.

Ethical approval

This study has been approved by the Dr. Behçet Uz Children Hospital Clinical Research Ethics Committee (approval date 27/10/2022, number 759). Each participant included in this study was informed about the scope of the study and written consent was obtained from the parents.

Author contribution

Surgical and Medical Practices: TK, SA, BÖ, Concept: TK, SA, BÖ, Design: TK, SA, BÖ, Data Collection or Processing: TK, SA, ÖN Analysis or Interpretation: TK, ÖN, BÖ, Literature Search: SA, ÖN, Writing: SA, TK, BÖ. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

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Original Article

Risk factors and clinical features of osteopenia of prematurity: Single-center experience

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ABSTRACT

Objective: Osteopenia of prematurity is an important cause of morbidity in preterm newborns. The aim of this study is to evaluate the clinical and laboratory findings and risk factors of osteopenia of prematurity in the newborns followed up in our unit.

Method: This study was a retrospective, cross-sectional study. Newborns with a gestational age of ≤ 32 weeks, a birth weight of ≤ 1500g were included in the study.

Results: The study included a total of 50 newborns. In patients with osteopenia of prematurity, invasive/noninvasive respiratory support, and duration of total parenteral nutrition (TPN) were longer, the incidence of necrotizing enterocolitis, red blood cell (RBC) transfusion rates, use of diuretics and proton pump inhibitors (PPI) were higher ($p < 0.05$). Multiple regression analysis showed that prolonged duration of TPN was the most important risk factor for osteopenia of prematurity (OR: 1.484(1.009-2.182); p: 0.045).

Conclusion: This study shows that osteopenia of prematurity remains to be an important health problem in premature newborns. Patients with prolonged TPN infusions are at risk of developing osteopenia of prematurity. Adjustment of mineral supplements in parenteral nutrition according to calcium and phosphorus levels should be started early in life, and enteral nutrition should be encouraged by reducing the duration of TPN use. Further studies are needed to increase our awareness of osteopenia of prematurity and to clarify the relationship between PPI use and RBC transfusion and osteopenia of prematurity.

Keywords: Prematurity, osteopenia of prematurity, risk factor, proton pump inhibitor, red blood cell transfusion

INTRODUCTION

Osteopenia of prematurity, also known as a metabolic bone disease of the newborn, is defined as postnatal bone mineralization lower than intrauterine bone mineral density at the same gestational age.[1,2] Many hormonal, environmental, and genetic factors have been reported to affect bone mineralization in the fetal and postnatal periods.[3] Its clinical symptoms appear 6-16 weeks after birth, and if not diagnosed in time, various short and long-term problems may occur.[2] Osteopenia of prematurity has been reported to cause bone fractures, poor respiratory outcomes, insufficient weight gain, impaired growth, and predisposition to osteoporosis in adulthood.[4-9] The diagnosis is made by measuring biochemical markers such as serum calcium, phosphorus, alkaline phosphatase, parathormone, and vitamin D and/or detecting the presence of osteopenia or fracture radiologically.[1,2] However, none of them have diagnostic value on their own.[1]

The incidence of osteopenia of prematurity is not well known due to differences in terminology and diagnostic criteria.[3] It is estimated that the incidence may have increased as the survival

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rates of premature newborns have increased as a result of the developments in neonatology in recent years.[2] There are very limited data on osteopenia of prematurity in Turkey.[10-14] There may be differences in neonatal intensive care practices between countries due to demographic structure and economic reasons. There is a need for new studies in countries such as Turkey, which have a dispersed demographic structure and health care services. This study aimed to examine the clinical and laboratory findings of osteopenia of prematurity and the affecting risk factors in the premature newborns followed up in our unit.

MATERIAL AND METHODS

The study design was a retrospective, cross-sectional design. Cases with a gestational age of ≤32 weeks and a birth weight of ≤ 1500g, followed in our neonatal intensive care unit between January 1, 2020 and May 1, 2022 were included in this study. Premature newborns with congenital malformation, genetic disease, other metabolic bone diseases (such as osteogenesis imperfecta), and missing data were excluded from the study.

The demographic data (gestational age, birth weight, gender, mode of delivery), perinatal characteristics (preeclampsia, diabetes mellitus, premature rupture of membranes, small for gestational age (SGA)), clinical outcomes (necrotizing enterocolitis (NEC), patent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD), cholestasis, hypothyroidism, duration of mechanical ventilation, duration of total oxygen requirement, red blood cell (RBC) transfusions, hospital stay), history of medication use affecting calcium metabolism (postnatal steroid, diuretic (>2 weeks), caffeine, proton pump inhibitor (PPI) use), nutritional management (duration of parenteral nutrition, the first day of enteral nutrition, use of fortifying supplements, vitamin supplementation), physical examination findings (craniotabes, enlargement of cranial sutures, fractures, etc.), laboratory analyses (serum calcium, phosphorus, alkaline phosphatase, 25-hydroxyvitamin D, parathormone, and urinary phosphorus, creatine levels in the urine taken on the postnatal 28th day of the cases) were retrospectively investigated. Renal tubular phosphorus reabsorption (TPR) was calculated (TRP: 1- [(urine phosphorus/plasma phosphorus) x (plasma creatine/urine creatine)]x100 formula was used). On the postnatal 28th day, cases with serum alkaline phosphatase of ≥500IU/L and/or phosphorus of <5.5mg/dl and TRP of >95% were diagnosed with osteopenia of prematurity.[11] The cases were divided into two groups: those with and without osteopenia of prematurity, and their data were compared.

Bronchopulmonary dysplasia (BPD) was defined as an oxygen requirement >21% for at least 28 days.[15] Cholestasis was defined as a conjugated bilirubin value of >2.0mg/dl, or a conjugated bilirubin fraction of >20% of the total. The diagnosis of NEC was made based on clinical and radiological findings. Findings such as feeding intolerance, abdominal distention, gastric residue, bile vomit, and bloody stool were considered to be associated with NEC.[16] The study was approved by the local ethics committee (No:2022/39).

Statistical Analysis

Statistical analyzes were performed using IBM SPSS (Statistical Package for Social Sciences) statistical software, version 24 (IBM Corp, Armonk, NY, USA). Categorical data were presented with n and %, and numerical data with mean ± standard deviation if normally distributed, and median (IQR) if non-normally distributed. Descriptive statistics (kurtosis and skewness), visual methods (histogram), and analytical tests (Shapiro-Wilk's test) were used to determine the normal distribution of numerical variables. In the comparison of the two groups, the student's t-test was used if the data were normally distributed, and the Mann-Whitney U test was used if the data were non-normally distributed. Chi-square tests were used for the comparison of categorical data (Fisher's exact test was used when chi-square test assumptions did not hold due to low expected cell counts). Possible factors determined by univariate analysis were analyzed by logistic regression analysis to determine independent predictors. Odds ratios (OR) (95% CI) were used in the logistic regression analysis. A p-value <0.05 was considered statistically significant.

Our unit's parenteral and enteral nutrition policy:

In our unit, total parenteral nutrition (TPN) support is administered to all premature and very low birth weight newborns on the first day of life [Aminoasid (2g/kg; Primen-%10; Baxter, S.A. Belgium), lipid solution (2g/kg; ClinOleic-%20; Baxter, S.A. Belgium), and glucose]. Amino acid/lipid doses are gradually increased to 3g/kg on the third day. Phosphate supplementation was given if serum phosphate levels were persistently lower than 4 mg/dl. Elemental phosphorus was started at 20mg/kg per day and increased to a maximum of 40mg/kg/per day. If serum calcium levels were <8mg/dl, elemental calcium was started at 20mg/kg per day and increased to a maximum of 80mg/kg per day. Enteral nutrition is usually initiated with breast milk within the first two days of life, and the premature formula is added when breast milk is insufficient. If the baby tolerates, the amount of enteral feeding is increased by 20-30 ml/kg/day, and the amount of TPN is decreased proportionally. TPN support continues until 75% of the total volume is met by enteral nutrition. When the amount of enteral feeding is more than 100ml/kg/day, 1.1g of

Eoprotein (Aptamil Milupa breast milk fortifier) is added to every 30 ml of breast milk. When the baby is on full enteral nutrition, vitamin D (800 Units/day) support is administered.

RESULTS

The study population consisted of 50 premature newborns (25 male, 25 female) with a mean gestational age of 29.3±2.2 weeks and a mean birth weight of 1198.7±266.3 g. There were 26 cases in the group with osteopenia of prematurity (Group I) and 24 cases in the group without osteopenia (Group II). Group 1 had a lower birth weight and more male gender than group 2 (1101 vs 1304, p: 0.004; 58% vs 42%, p: 0.258, respectively). Osteopenia of prematurity was detected in 9 (69.2%) of 13 newborns with a birth weight of ≤1000 g and in 17 (45.9%) of 37 newborns with a birth weight of 1000-1500 g. Maternal and neonatal demographic characteristics of the groups are shown in Table 1. The most common clinical findings in Group I cases were related to the respiratory and gastrointestinal systems. In Group I cases, invasive/noninvasive ventilation times were longer, enteral feeding initiation times were later, transition to full enteral feeding took longer and NEC incidence was higher ($p<0.05$, Table 1). No fractures or rickets were found in any of the cases. RBC transfusion rates, use of diuretics, and PPI were found to be higher in Group I cases compared to Group II ($p<0.05$, Table 1). The cases in Group I had lower serum phosphorus and vitamin D levels, and higher serum alkaline phosphatase and parathormone levels and TPR levels (Table 2). Multiple regression analysis showed that prolonged duration of TPN is the most important risk factor for osteopenia of prematurity (OR: 1.484(1.009-2.182); p: 0.045) (Table 3).

DISCUSSION

Osteopenia of prematurity is a major cause of morbidity in premature and very low birth weight newborns.[11] Determination of risk factors for osteopenia of prematurity is vital for early detection and prevention of the disease.[11] The diagnosis is made in the presence of hypophosphatemia, high alkaline phosphatase, secondary hyperparathyroidism, and high TRP (>95%).[11,17] Our results are consistent with the findings in other studies. However, there is no consensus on the cut-off values yet. Therefore, the true incidence of the disease remains unclear.[3,17] The frequency of osteopenia of prematurity has been reported to increase inversely with gestational age and birth weight and is directly proportional to postpartum diseases.[1,17] It was reported that 55% of extremely low birth weight (≤1000g) and 23% of very low birth weight newborns (1000-1500g) have osteopenia of prematurity.[2,18] In our study, osteopenia of prematurity was detected in 9 (69.2%) of 13 newborns with a birth weight of ≤1000 g and in 17 (45.9%) of 37 newborns with a birth weight of 1000-1500 g. Our rates were high compared to the literature. This may be due to the different diagnostic criteria and sample sizes used to define osteopenia of prematurity in each of the studies.

In the present study, newborns with osteopenia of prematurity had lower vitamin D levels, and the time to start vitamin D supplementation was delayed. The low levels of vitamin D in newborns with osteopenia of prematurity in our study were associated with the frequent occurrence of feeding intolerance in these cases. Vitamin D deficiency may lead to osteopenia in newborns. If newborns do not receive or make enough vitamin D, calcium and phosphorous will not be properly absorbed.[19] Our results were consistent with those of Cho et al.[20] The study of Angelika et al.[9] reported that early vitamin D supplementation increased vitamin D levels and improved bone mineralization in premature newborns. Chan et al.[6] also indicated that starting vitamin D supplementation after 14 days is an independent risk factor for osteopenia of prematurity. In our study, vitamin D supplementation was initiated after the 14th day in most cases with osteopenia of prematurity. The result of our study is significant to emphasize the importance of providing vitamin D support to premature newborns in the early period in order to prevent osteopenia of prematurity.

In the study of Chan et al.[6], gestational age below 30 weeks and use of TPN for more than 28 days were reported as the main risk factors for osteopenia of prematurity. Mutlu et al.[11] also revealed the use of anticonvulsant drugs as the most critical risk factor. The significant effect of birth weight on osteopenia of prematurity demonstrates the importance of prenatal mineralization on bone mineral density.[3] Since mineral deposition in fetal bone occurs mainly in the third trimester of pregnancy, premature newborns are born with insufficient bone mineralization. Furthermore, low birth weight may be due to a condition associated with placental insufficiency.[3] Placental insufficiency may develop due to conditions associated with chronic placental damage, such as preeclampsia.[3] Any condition that impairs placental function and thus nutritional transfer may lead to an increased risk of osteopenia of prematurity. Angelika et al.[9] also reported that they detected a relationship between premature rupture of membranes and osteopenia of prematurity. However, our study did not find a difference in the frequency of preeclampsia, premature rupture of membranes, or SGA between the groups.

Drugs such as methylxanthines, diuretics, and steroids used in the treatment of neonatal diseases have been demonstrated to increase the risk of osteopenia of prematurity.[17,21,22] Hypercalciuric drugs such as furosemide and methylxanthines have been shown to decrease bone formation by increasing

Table 1. Demographic characteristics of cases and risk factors for osteopenia of prematurity			
Variables	**Group I (n:26)**	**Group II (n: 24)**	**p**
Gestational age (week)	30.0±2.2	28.6±1.9	0.084**
≤28 week, n (%) 29-33week, n (%)	10(38.5) 16(61.5)	5(20.8) 19(79.2)	0.174*
Birthweight(g)	1101±248	1304±248	**0.004¶**
Type of delivery NVD/C/S, n (%)	2/24(7.7/92.3)	4/20(16.7/83.3)	0.409*
Gender female/male, n (%)	11/15(42.3/57.7)	14/10(58.3/41.7)	0.258*
SGA, n (%)	8(30.8)	2(8.3)	0.077*
Gravidity	2	3	0.712**
Preeclampsia/eclampsia n (%)	4(15.4)	4(16.7)	1.000*
Diabetes Mellitus, n (%)	-	2(8.3)	
Premature rupture of membranes, n (%)	5(19.2)	4(16.7)	1.000*
IMV days	3	1	**0.007****
Non-IMV days	6	2	**<0.001****
Duration of total oxygen requirement, days	8.5	3	**0.001****
BPD, n (%)	6(23.1)	1(4.2)	0.100*
Steroid use, n (%)	6(23.1)	1(4.2)	0.100*
Diuretic use, n (%)	10(38.5)	2(8.3)	**0.013***
PPI use, n (%)	12(46.2)	3(12.5)	**0.009***
Caffeine use, n (%)	23(88.5)	17(70.8)	0.164*
Eoprotein use, n (%)	16(61.5)	19(79.2)	0.174*
NEC, n (%)	12(46.2)	1(4.2)	**0.001***
Anticonvulsive drug use, n (%)	1(3.8)	1(4.2)	1.000*
Hypothyroidism, n (%)	3(11.5)	4(16.7)	0.697*
Cholestasis, n (%)	5(19.2)	1(4.2)	0.192*
PDA, n (%)	5(19.2)	1(4.2)	0.192*
Red blood cell transfusions, n (%)	10(38.5)	3(12.5)	**0.037***
First enteral feeding time (days)	4	3	**0.013****
Full enteral feeding time (days)	36	12.5	**<0.001****
TPN days	25	8	**<0.001****
Weight on the 30th days, g	1222.5	1900	**<0.001****
Vitamin D supplementation, days	30	12.5	**<0.001****
<14 days of age, n (%)	3(11.5)	13(54.2)	
≥14 days of age, n (%)	23(88.5)	11(45.8)	
Hospitalization time, days	66	34	**<0.001****

Abbreviations: SGA, small for gestational age; IMV, invasive mechanical ventilation; BPD, bronchopulmonary dysplasia; PPI, Proton pump inhibitor; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; TPN, total parenteral nutrition. Categorical data were presentedwith n and %, and numerical data with mean ± standard deviation if normally distributed, and median (IQR) if non-normally distributed. In the comparison of 2 groups; Chi-square test*, Mann-Whitney U** test and Student's t-test¶ were used.

Table 2. Laboratory characteristics of osteopenia of prematurity

	Group I (n:26)	Group II (n: 24)	P
Serum calcium (mg/dl)	9.5±0.8	9.8±0.6	0.248*
Serum phosphate (mg/dl)	4.9	6.4	**<0.001****
Alkaline phosphatase (U/L)	569.9±204.6	343.4±60.1	**<0.001***
Parathyroid hormone (pg/mL)	85.6±51.9	82.2±63.2	0.845*
Vitamin D (ng/ml)	12.7	19.2	**0.017****
TRP (%)	96	92	**<0.001****

Abbreviations: TRP: Tubuler reabsorption of phosphate.
Numerical data were presented as mean ± standard deviation if normally distributed and median (IQR) if not normally distributed. In the comparison of 2 groups; Student's t-test* ve Mann-Whitney U test** were used.

Table 3. Risk factors of osteopenia of prematurity (multivariate analysis)

Variables	B	Wald	p	OR	%95 CI	
NEC	3.428	4.025	0.285	30.811	0.057	16574.852
PPI use	3.915	2.880	0.090	50.164	0.545	4614.347
Diuretic use	0.665	0.050	0.822	1.945	0.006	649.474
TPN days	0.395	4.025	**0.045**	1.484	1.009	2.182
Vitamin D supplementation at <14 days of age	0.517	0.138	0.710	1.677	0.110	25.523

Abbreviations: NEC, Necrotizing enterocolitis; PPI, Proton pump inhibitor, TPN, total parenteral nutrition; OR, odds ratio.
Hosmer – Lemeshow test: 0.933, **Nagelkerke R^2:** 0.718, **Cox – Snell R^2:** 0.539, **Omnibus test:** 0.001.

calcium loss, and steroids by inhibiting osteoblast growth and increasing osteoclast differentiation.[11,17] While Mutlu et al.[11] reported that caffeine and steroid use were risk factors for osteopenia of prematurity, they found no difference between the groups with regard to diuretic use. Chan et al.[6] stated that the use of aminophylline and diuretics increased the risk, but they did not find a difference with the control group in terms of steroid use. Avila-Alvarez et al.[3] also revealed that postnatal steroid use did not increase the risk of osteopenia of prematurity. Our study found that the use of diuretics was high in newborns with osteopenia of prematurity. However, we did not detect any difference between the groups with regard to caffeine and steroid use. Besides, our study did not determine a relationship between osteopenia of prematurity and BPD. However, although it was not statistically significant, we detected a higher incidence of BPD in babies with osteopenia of prematurity. Respiratory outcomes were also worse in the group with osteopenia of prematurity.

Factors such as the delay in establishing fully enteral feeding, prolonged parenteral nutrition, and the presence of NEC have been reported as risk factors in the development of osteopenia of prematurity.[17,21-23] Similarly, in our study, NEC was higher in the group with osteopenia of prematurity and the duration of TPN was longer in these cases. The present study found that prolonged TPN use was a risk factor for osteopenia of prematurity. Because the greatest need for mineral accumulation occurs during the developmental stage, calcium and phosphorus depositions in preterm neonates during the early postnatal period cannot meet the requirements of the intrauterine bone growth rate. Furthermore, the majority of premature newborns require prolonged TPN infusion due to difficulties with enteral feeding. TPN is a non-physiological route of nutrient delivery that bypasses the gastrointestinal tract and portal system. The effects of administering nutrients directly into the continuous venous blood are not fully known. Multiple factors may contribute to the development of bone disease associated with TPN. Inadequate mineral formulations, poor solubility of minerals, restricted intravenous fluid volume due to pre-existing diseases, and aluminum contamination of parenteral nutrition, frequently prevent sufficient mineral supply from TPN solutions. This seriously affects the bone health of newborns in both the short and long terms.[6,9,24,25]

Red blood cell transfusions are a crucial supportive treatment, especially in treating premature newborns. In our study, the rate of administration of RBC transfusions was higher in cases with osteopenia of prematurity. Avila-Alvarez et al.[3] also reported a

similar relationship between the development of osteopenia of prematurity and RBC transfusion. Iron overload resulting from multiple RBC transfusions in children and adults with thalassemia has been indicated to be one of the factors affecting the pathogenesis of osteoporosis.[26] Iron deposition in the bone can impair osteoid maturation and inhibit local mineralization, resulting in focal osteomalacia.[26] Premature newborns may also be exposed to iron overload caused by the destruction of transfused erythrocytes when they receive multiple RBC transfusions.[27,28] However, we did not have sufficient information on the iron levels of the cases in our study. Further studies are needed to confirm the relationship between osteopenia of prematurity and RBC transfusion.

A new and interesting finding of this study is that PPI use is higher in cases with osteopenia of prematurity. PPIs are frequently used to treat gastrointestinal diseases such as gastroesophageal reflux in newborns. In recent years, studies performed on adults and adolescents have reported a relationship between PPI use and bone fractures.[29,30] It has been reported that PPI exposure in the first year of life in children is associated with an increase in bone fractures in the first five years.[31] To our knowledge, there are no studies on this subject in premature newborns. Several hypotheses have been proposed to explain the relationship between PPI therapy and bone metabolism. One of them is that using PPIs causes hypochlorhydria, resulting in a decrease in calcium absorption from the small intestine and a decrease in bone mineral density.[32] Another hypothesis is that PPIs inhibit gastric H^+-K^+-ATPase as well as the vacuolar H^+-ATPase pump in osteoclasts. As a result, osteoclast function is impaired, and abnormal osteoclast-mediated bone resorption and osteoporosis develop.[31] The present study is pioneering in demonstrating the relationship between osteopenia of prematurity and PPI use. Physicians should be more cautious when using PPI, the lowest effective dose possible should be preferred in patients with appropriate indications, and patients using PPI should be screened for osteopenia. Due to the small number of cases in our study, PPI use may not have been determined as a risk factor for the development of osteopenia of prematurity. We think that this issue should be further investigated and the findings should be supported by larger studies.

Our study has several limitations. These include retrospective planning, a small number of cases, insufficient information about RBC transfusion (frequency, indications, iron, iron binding capacity, ferritin levels of the cases), and lack of bone imaging methods for osteopenia.

CONCLUSION

This study shows that osteopenia of prematurity remains to be an important health problem in premature newborns. Patients with prolonged TPN infusions are at risk of developing osteopenia of prematurity. Adjustment of mineral supplements in parenteral nutrition according to calcium and phosphorus levels should be started early in life, and enteral nutrition should be encouraged by reducing the duration of TPN use. Further studies are needed to increase our awareness of osteopenia of prematurity and to clarify the relationship between PPI use and RBC transfusion and osteopenia of prematurity.

Ethical approval

This study has been approved by the Kanuni Training and Research Hospital Clinical Research Ethics Committee (approval date 27/06/2022, number 2022/39). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: BSH; Concept: BSH; Design: BSH; Data Collection or Processing: BSH; Analysis or Interpretation: BSH; Literature Search: BSH; Writing: BSH. The author reviewed the results and approved the final version of the article.

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Conflict of interest

The author declares that there is no conflict of interest.

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Original Article

Balloon angioplasty for postoperative aortic recoarctation in children: A 10-year, single-center experience

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ABSTRACT

Objective: Coarctation of the aorta is a congenital anomaly observed in 8% to 10% of all cases of congenital heart disease. In patients with postoperative aortic recoarctation, reoperation is associated with high morbidity and mortality risk, and percutaneous balloon angioplasty is widely accepted as a first-line option in these patients regardless of the primary surgery or recoarctation anatomy. Our aim in this study was to share our experience with balloon angioplasty in patients who developed recoarctation after surgery for aortic coarctation.

Methods: A total of 39 patients aged 0-18 years who underwent percutaneous balloon angioplasty in the Pediatric Cardiology Department of Ege University between January 2010 and January 2020 were included in the study. All of the patients developed aortic recoarctation after surgical repair of aortic coarctation and were referred from various centers.

Results: On echocardiography performed before balloon angioplasty, the mean pressure gradient between the ascending and descending aorta was 50±11 mmHg. Transcatheter peak systolic pressure gradient between the ascending and descending aorta was 35 ± 13 mmHg before the procedure and decreased to 8 ± 11 mmHg after the procedure. The mean balloon diameter used for balloon angioplasty was 10 ± 4 mm. Adequate gradient reduction was achieved in all patients during balloon angioplasty. No major complications were observed.

In our study, after balloon angioplasty, the prevalence of recoarctation was 7%.

Conclusion: In conclusion, balloon angioplasty can be used safely in the treatment of postoperative recoarctations.

Keywords: Recoarctation, balloon angioplasty, aortic, surgery

INTRODUCTION

Coarctation of the aorta is a congenital anomaly observed in 8% to 10% of all cases of congenital heart disease. It refers to a segmental narrowing of the aorta that can occur at all levels, but most frequently (in 98% of cases) in the aortic arch, just distal to the origin of the left subclavian artery and directly opposite the insertion of the ductus arteriosus.[1] Patients with untreated aortic coarctation are at high risk of mortality and morbidity due to heart failure, intracranial hemorrhage, aortic rupture, and myocardial infarction.[1]

The first successful surgical treatment of aortic coarctation was performed by Crafoord and Nylin in 1945 by resection and a direct end-to-end anastomosis technique.[2] More recently, various other techniques have been described and successfully applied in the surgical treatment of aortic coarctation.[3-6] The risk of recurrent CoA is increased when surgery is performed in young

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infants, especially in those requiring prostaglandin infusions, which are thought to modify the arch anatomy and may mask the appropriate resection boundaries.[7] Meticulous, wide resection of ductal tissue should therefore be performed. The underlying substrate of significant arch hypoplasia in neonates who are significantly symptomatic enough to require surgery also increases the probability of residual or recurrent CoA. On the other hand, there is an increased risk of hypertension and long-term atherosclerotic heart disease if the repair is delayed until late childhood or adolescence.[6] Up to 30% of repaired adults require further intervention.

Since it was first reported in 1982, percutaneous transcatheter balloon angioplasty has been used as an alternative to surgery for the treatment of native coarctation and recoarctation in neonates, infants, children, and adolescents.[8-10] In patients with postoperative aortic recoarctation, reoperation is associated with a high risk of morbidity and mortality, and percutaneous balloon angioplasty is widely accepted as a first-line option in these patients regardless of the primary surgery or recoarctation anatomy.[11-13] Our aim in this study was to share our experience with balloon angioplasty in patients who developed recoarctation after surgery for aortic coarctation.

METHODS

Patient selection

A total of 39 patients aged 0-18 years who underwent percutaneous balloon angioplasty for postoperative aortic recoarctation in the Department of Pediatric Cardiology of Ege University between January 2010 and January 2020 were included in the study. Ethics committee approval was obtained from the Scientific Research Ethics Committee of the Ege University Faculty of Medicine. The parents or caregivers of all participants were informed in writing and provided informed consent before inclusion in the study. All of the patients developed aortic recoarctation after surgical repair of aortic coarctation and were referred from various centers. Patients who underwent stent implantation for recoarctation and those who underwent balloon angioplasty for native coarctation were excluded.

Definitions

Recoarctation

The diagnosis was made by physical examination, upper/lower limb arterial blood pressures, telecardiography, electrocardiography, echocardiography, and cardiac catheterization. Recoarctation was diagnosed in patients with an upper-lower limb blood pressure gradient ≥ 20 mmHg and an instantaneous peak pressure gradient ≥ 20 mmHg across the coarctation on echocardiography, with or without a diastolic tail pattern on continuous-wave Doppler.

Indications for balloon angioplasty

Regardless of the patient's age, balloon angioplasty of aortic recoarctation was performed in patients with suitable anatomy and a transcatheter systolic (peak-to-peak) coarctation gradient of > 20 mmHg. Balloon angioplasty for recoarctation is indicated in the presence of significant collateral vessels and suitable angiographic anatomy, irrespective of age, as well as in patients with univentricular heart or with significant ventricular dysfunction.

Balloon angioplasty procedure

All balloon angioplasty procedures were performed under sedation, with access via the femoral artery. Anteroposterior, 15-20° left oblique, and lateral angiographic images were obtained before and after the procedure. Systolic, diastolic, and mean arterial pressures in the ascending and descending aorta were measured before and after the procedure in all patients. A balloon diameter no larger than the diameter of the descending aorta at the level of the diaphragm and equal to or 1-2 mm larger than the diameter of the aorta at the left subclavian artery was selected for the procedure. Under fluoroscopic guidance, the balloon was positioned at the coarctation and inflated 2-3 times for less than 10 seconds until the waist disappeared. Balloon inflation pressure was not increased above the values specified by the manufacturer. In patients who did not show sufficient expansion of the coarctation and whose pressure gradient across the coarctation did not decrease below 20 mmHg at the end of the procedure on radiographic and hemodynamic evaluation, the procedure was repeated using a second balloon that was 1 or 2 mm wider but did not exceed the diameter of the descending aorta at the level of the diaphragm.

Follow-up after balloon angioplasty

After the procedure, patients were evaluated on days 1 and 15, at months 1-6, year 1, and annually thereafter. Clinical findings, upper/lower limb blood pressures, and transthoracic echocardiography results were evaluated at the follow-up visits. Patients with an upper-lower limb pressure gradient ≥ 20 mmHg at the clinical follow-up and patients with an instantaneous peak systolic pressure gradient ≥ 20 mmHg at the coarctation site in echocardiographic follow-up were diagnosed as having recoarctation.[14]

Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 21 (IBM Corp., Armonk, N.Y., USA). Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

RESULTS

Demographic findings

Of the 39 patients who underwent balloon angioplasty, 19 (48.7%) were female and 20 (51.3%) were male. The mean age at first diagnosis was 31.3 ± 40.7 months (range: 0-144). Some patients were diagnosed prenatally thanks to advances in fetal echocardiography techniques. The mean age at balloon angioplasty was 67 ± 10 months. The mean weight of the patients at the time of balloon angioplasty was 24 ± 14.5 kg. The follow-up period after balloon angioplasty ranged from 6 to 120 months (Table 1).

Primary operative procedure

All patients who underwent balloon angioplasty had previously undergone surgical repair of aortic coarctation. These procedures were performed in various centers and included extended end-to-end or end-to-end anastomosis in 34 patients, aortoplasty with a pericardial patch in 1 patient, aortoplasty with a Dacron patch in 1 patient, and tubular grafting in 3 patients (Figure 1). Coarctation repair with simultaneous patent ductus arteriosus (PDA) division was performed in 14 patients and pulmonary banding was performed in 1 patient.

Table 1. Demographic, echocardiographic and angiographic evaluation results of patients who underwent balloon angioplasty for aortic recoarctation

Age (month)	31.3 ± 40.7
Gender	
Female	19 (%48.7)
Male	20 (%51.3)
Weight (kg)	24 ± 14.5
First diagnosis age (month)	31.3 ± 40.7
Mean age at balloon angioplasty (month)	67 ± 10
Follow-up range (month)	6-120
Ejection fraction value mean (%)	68 (range 35-82)
Mean balon diameter (mm)	10 ± 4
Mean pressure gradient between the ascending and descending aorta (mmHg)	
Echocardiography gradient	50 ± 11
Angiography gradient	35 ± 13
Post-procedure gradient	8 ± 11

Echocardiography and comorbidities

Left ventricular ejection fraction was measured by a pediatric cardiologist using two-dimensional echocardiography (Vivid E9, GE-Vingmed Ultrasound AS, Horten, Norway). The same pediatric cardiologist evaluated the patients for concomitant congenital heart disease. Left ventricular ejection fraction was calculated using the Simpson method. The mean ejection fraction value of the patients was 68% (range: 35%-82%). On echocardiography performed before balloon angioplasty, the mean pressure gradient between the ascending and descending aorta was 50±11 mmHg. No concomitant anomalies were detected in 22 (56.4%) of the patients. The bicuspid aortic valve was diagnosed by echocardiography in 10 patients (25.6%), ventricular septal defect (VSD) in 5 patients (12.8%), secundum atrial septal defect in 1 patient (2.5%), and mitral stenosis in 1 patient (2.5%).

Angioplasty results

The transcatheter peak systolic pressure gradient between the ascending and descending aorta was 35 ± 13 mmHg before the procedure and decreased to 8 ± 11 mmHg after the procedure. The mean balloon diameter used for balloon angioplasty was 10 ± 4 mm. Of the potential complications that can occur during and after balloon angiography, none of the patients developed aneurysm, peripheral artery thrombosis, bleeding requiring transfusion, cerebrovascular events, severe arrhythmias, or death.

Follow-up and recurrence

Three patients required surgery for aortic recoarctation detected by physical examination and echocardiographic evaluation after balloon angioplasty. In our center, 2 patients underwent left subclavian-descending aortic bypass with a Dacron tube graft and 1 patient underwent coarctation repair surgery with a Dacron graft (Figure 1). Patients who developed restenosis after balloon angioplasty were treated surgically; balloon angioplasty was not repeated. Because of other accompanying cardiac anomalies, 2 patients underwent discrete subaortic membrane resection, 1 patient underwent VSD closure, and 1 patient underwent mitral valve repair. No major complications or death occurred after coarctation balloon angioplasty or other surgical procedures.

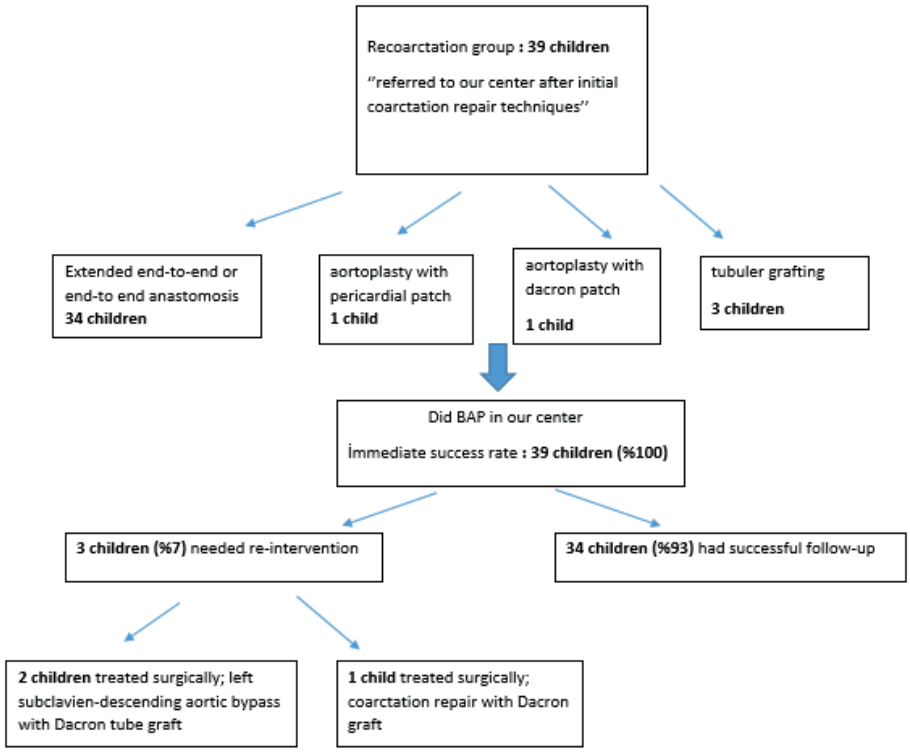

Figure 1. Detailed management and outcome of the study cohort

BAP : Balloon angioplasty

DISCUSSION

Although aortic coarctation is diagnosed across a wide age range, it is usually detected at 3-6 months of age, with a small proportion of patients diagnosed in adolescence and adulthood. Aortic coarctation is associated with intracardiac and extracardiac anomalies. Bicuspid aortic valve, VSD, PDA, and transposition of great arteries are among the most common. The bicuspid aortic valve is the most common intracardiac anomaly, with a prevalence of 45% to 62%.[15-17]

In most centers, surgical treatment is primarily chosen for symptomatic young infants and patients with long segment coarctation regardless of age. In asymptomatic and incidentally detected cases, elective coarctation repair is performed between 6 months and 2 years of age.[18] Younger age at surgery increases the risk of recurrence, while older age at surgery increases the risk of persistent hypertension.

The timing and choice of therapeutic intervention in patients with aortic coarctation depend on the presence of ductal patency in a symptomatic newborn, the anatomy and severity of the coarctation, the patient's age, size, and symptoms at the time of diagnosis, and other concomitant cardiac anomalies. In patients with a large VSD, coarctation repair and palliative pulmonary banding can be performed, or in patients with a smaller VSD, coarctation repair can be performed with the aim of reducing the left-to-right shunt and facilitating defect closure. In some centers, the choice of surgical or transcatheter methods in neonates and infants is controversial. The risk of recurrence and re-intervention after balloon angioplasty is higher in this patient group.[19]

Surgical techniques consist of extended end-to-end anastomosis, end-to-end anastomosis, subclavian flap repair, patch aortoplasty, and interposition grafting. Extended end-to-end anastomosis is the most preferred method and is thought to allow normal development of the transverse arch and isthmus.[20] In our patient group, end-to-end anastomosis techniques were used most frequently.

The most important factors affecting the formation of recoarctation are low weight, young age, need for PGE1 infusion at birth, abandonment of ductal tissue, and presence of aortic arch hypoplasia.[21] The older age at coarctation diagnosis in our patient group compared to the literature increased the risk of recoarctation. Acute postoperative complications, including bleeding, injury to the recurrent laryngeal nerve, chylothorax,

hypertension, and the need for prolonged mechanical ventilation, are more common in patients with intracardiac abnormalities.[22]

While balloon angioplasty was initially used for recurrent aortic coarctations, with increasing experience it has also been used more frequently in native coarctation patients. Balloon angioplasty reduces the coarctation pressure gradient to within normal limits in 80% of cases. Rates of recoarctation and aneurysm are below 10%.[23] In our study, the prevalence of recoarctation was 7%. Patients with native coarctation and recoarctation had similar restenosis rates in follow-ups.[23]

Aneurysm formation in and around the area of stenosis may be observed in the early and late periods following balloon angioplasty in children. The reported frequency of aneurysm development varies considerably, but some studies have found the rate ranging from 0% to 5%.[24,25] Although it is difficult to establish a causal relationship with the factors in aneurysm development, the use of large balloons, incorrect catheter, and guide wire maneuvers, tears in the intima and media layers of the vessel during angioplasty, and the formation of cystic medial necrosis have been implicated.[26,27] Apart from this, as with the likelihood of restenosis, the risk of aneurysm development is higher in patients who undergo balloon angioplasty in the first 3 months of life.

Femoral artery injuries are the most common early problem in children undergoing balloon angioplasty, especially in neonates and infants, and complete occlusion occurs in approximately 8% of these cases.[12] Although these patients develop good collaterals in the long term, they should be monitored for the sequelae of occlusion. These complications can be reduced by using balloons with a smaller diameter and lower profile, placing a smaller sheath in the artery[28], and using different access routes (umbilical artery or antegrade route in neonates). Patients undergoing balloon angioplasty due to aortic coarctation may rarely experience bleeding requiring blood transfusion, cerebrovascular events, and death. Mortality is uncommon except in the neonatal period. The mortality rate in children undergoing balloon angioplasty is reported to range from 0.7% to 4.5%, and most of these deaths are believed to be attributable to concomitant heart disease.

In conclusion, balloon angioplasty can be used in the treatment of postoperative recoarctations. Balloon angioplasty for recoarctation is effective and is associated with the accelerated growth of the dilated segment at follow-up in many patients. In many patients, it provides a permanent improvement in hypertension.

Acknowledgments

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Ethical approval

This study has been approved by the Ege University Medical Research Ethics Committee (approval date 24/03/2022, number 22-3.1T/45). The parents or caregivers of all participants were informed in writing and provided informed consent before inclusion in the study.

Author contribution

Surgical and Medical Practices: ED, EL; Concept: ED, ZÜ, EL; Design: ED, ZÜ, EL; Data Collection or Processing: ED, ZÜ; Analysis or Interpretation: ED, DA, ZÜ; Literature Search: ED, DA; Writing: ED, DA. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

A new marker for the evaluation of nutrition in pediatric critical care patients: Zonulin

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ABSTRACT

Objective: Zonulin is a biomarker of increased intestinal permeability. Malnutrition is strongly associated with prolonged length of stay, increased infection, and mortality. This study aimed to determine how the serum zonulin level is affected in patients in PICU, and evaluate the relationship between pre-albumin and Vitamin D.

Method: 35 critically ill pediatric patients were included in the study. The control group was formed of 25 healthy children. The albumin, pre-albumin, Vitamin D, and zonulin levels were examined in patients with findings of infection that regressed during ICU follow-up.

The differences between prealbumin levels, Vitamin D, and zonulin were analyzed with the Mann-Whitney-U Test.

Results: The most common reason for admission to the PICU was respiratory failure in 12 patients. The Vitamin D level was determined to have a mean of 28.8±12.3ng/mL and <29ng/mL in 9 patients. The albumin level was determined to be mean 3.3±0.6 mg/dL, and the pre-albumin level was mean 17.8±7.4mg/dL. The serum zonulin levels in critically ill patients were statistically significantly higher than in the control group. The difference between the zonulin levels of patients with pre-albumin values was statistically significant. The zonulin levels of patients with a Vitamin D value <20 were found to be statistically significantly higher than the zonulin levels of patients with a Vitamin D value >20

Conclusion: The higher zonulin level in critically ill pediatric patients may be associated with prolonged catabolic processes, exposure to oxidative and hypoxic stress, and bacterial translocation development associated with all of these. The results of the current study showed a statistically significant negative correlation between Vitamin D and zonulin levels. Therefore, the relationship between low Vitamin D values and a high zonulin level may be useful in evaluating chronic malnutrition.

The serum zonulin level selected as a biomarker for the surveillance and management of nutrition in critically ill pediatric patients is not an appropriate marker.

Keywords: Zonulin, malnutrition, pediatric critical care, prealbumin, vitamin D

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INTRODUCTION

Malnutrition develops more easily and rapidly in children as they have low nutrient reserves, a fast metabolism, and depletion of energy reserves in a shorter time due to metabolic stress. Acute or chronic malnutrition is seen in 24-55% of patients followed up in pediatric intensive care units (PICU).[1] While malnutrition is determined in some of these patients at the time of admission, others may develop malnutrition secondary to deficient nutrient intake associated with the disease during the treatment process in ICU.[2] Malnutrition in children with severe diseases is associated with the need for mechanical ventilation, a prolonged period of mechanical ventilation, prolonged length of stay in ICU and hospital, increased infection, and increased mortality.[3,4]

The patient's body weight must be measured on the first day of admission and followed up with regular measurements throughout hospitalization to evaluate the nutritional status of patients and identify acute changes. The energy requirements of critically ill pediatric patients must be evaluated on an individual basis, and the appropriate amount of energy support must be provided, but it is not easy to determine and measure the energy consumption and manage the appropriate nutritional content and amount in these patients. Various monitoring of nutrition methods such as the follow-up at regular intervals of anthropometric measurements, albumin, pre-albumin, and retinol-binding protein are recommended to obtain the ideal nutritional targets for critical pediatric patients.[4]

Low albumin is known to be a marker of malnutrition. Low pre-albumin is also one of the markers of poor nutrition, but as both albumin and pre-albumin levels are affected by inflammation, neither is accepted as a good marker of poor nutrition.[5] Therefore, none of these methods and markers have been determined as the ideal method in the follow-up of nutrition.

Zonulin is accepted as a biomarker of increased intestinal permeability, which is to a large extent regulated by tight junctions in the intestinal epithelium, and zonulin has an important role in the regulation of these tight junctions. Zonulin is bound to specific receptors in the intestinal epithelium and is found in the structure of the intercellular tight junctions. Separation of this protein from the tight junctions causes an increase in intestinal permeability. When the sensitively regulated zonulin mechanism is genetically damaged, it can cause intestinal and extra-intestinal, autoimmune, inflammatory, and neoplastic disorders in some individuals.[6] Increased intestinal permeability has been associated with conditions such as dysbiosis, chronic systemic inflammation, insulin resistance, and metabolic syndrome. When there are problems in the intestinal barrier and increased intestinal permeability, serum zonulin levels increase.[7] Elevated zonulin levels have been associated with a greater waist circumference, diastolic blood pressure, fasting glucose, and an increased risk of metabolic disease.[8]

This study aimed to determine how the serum zonulin level is affected in patients in PICU, to evaluate the relationship between anthropometric measurements and biochemical parameters, primarily pre-albumin and Vitamin D, and to determine the utility of the serum zonulin level in the follow-up and management of nutrition.

MATERIAL AND METHOD

The study included 35 critically ill pediatric patients treated in the tertiary-level PICU of Hatay State Hospital. The control group was formed of 25 healthy children who presented at the Pediatric Health and Diseases Polyclinic for routine examinations. For the children in PICU, a record was made of the diagnoses on admission, PIM-3 score, PELOD-2 score, body weight, and height on the first day of admission and on discharge, demographic data, complications that developed during the follow-up period, and the daily calorie intake. The albumin, pre-albumin, Vitamin D, and zonulin levels were examined in patients with findings of infection that regressed during ICU follow-up. Patients with trauma, malignancy, weight >97th percentile, or active infection were excluded from the study. 2. It should be stated how and why it was decided that there was no active infection in excluded patients. Since the children we compared in the control group were healthy children without infection and also because the zonulin level may be affected by the infection, we excluded the patients with active infection. The serum zonulin levels were measured using the Bio-Tek ELX-800 ELISA method in the Health Sciences Vocational Further Education School Research and Application Laboratory of Van Yüzüncü Yıl University. Our study was approved by our hospital's Ethic Committee. All procedures were carried out following the ethical rules and the principles of the Declaration of Helsinki.

Statistical Analysis

A normality test of zonulin values was done with Shapiro-Wilk. The correlation between demographic data, blood parameters, and zonulin was calculated using Spearman's rho. The differences between prealbumin values >20 and <20 and zonulin were analyzed by the Mann-Whitney U Test. Differences between vitamin D values >20 and <20 and zonulin were analyzed by the Mann-Whitney U Test

RESULTS

The 35 patients included in the study were 19 males and 16 females, with a mean age of 48.1 ± 41.8 months and a median length of stay in PICU of 19 (min:13-max:33) days. The reasons for admission to PICU were respiratory failure in 12 patients, central nervous system-related causes in 9 patients, cardiac causes in 8, renal failure in 4, and gastrointestinal bleeding in 2. Blood samples were taken from the patients, and three were fed parenterally and 32 enterally. At the time of admission, the weight percentile was <3% in 11 (31.4%) patients and in the normal range in 24 (68.6%) (normal range: 3-97%). Throughout ICU follow-up, 14 (40%) patients reached at least 90% of the target calories. The PIM-3 score of the patients was determined to have a mean of 29.8±25.6 and a median of 19 (min:0.5, max: 89). The PELOD-2 score was determined to have a mean of 8.9±4.2 and a median of 9 (min:1, max:18) (Table 1).

The Vitamin D level was determined to have a median of 29 (min: 19- max: 38) ng/mL and <29ng/mL in 9 (25.7%) patients. The albumin level was determined to have a median of 3.4 (min:3 – max:3.8) mg/dL, and the pre-albumin level have a median of 19 (min:11 – max: 22) mg/dL. The CRP level was determined to have a median of 3 (min:1.6 – max: 5.3) mg/L.

Table 1. Demographic data

		n	% Mean ± SD
Male		19	%54.1
Weight Percentile	<3	11	%31
	3-10	7	%20
	10-25	9	%26
	25-50	3	%9
	50-75	3	%9
	75-90	1	%3
	90-97	1	%3
Age (Month)		35	48,1 ± 41,8
Length of Stay		35	24,1 ± 16.4
PELOD 2 score		35	8,7 ± 4.2
PIM 3 score		35	29,8 ± 25,6

Table 2. Evaluation of Zonulin levels

	Study Group	Control Group	p
Zonulin	12.8±7.2	6.6±2.3	0.001*

* p<0.05, Evaluated with the Mann Whitney U Test.

The serum zonulin level was found to have a mean of 12.8±7.2 in the critically ill patients and a mean of 6.6±2.3 in the control group. The serum zonulin level in the critically ill patients was statistically significantly higher than in the control group (p=0.001) (Table 2).

There was no statistically significant correlation between zonulin and pre-albumin in critically ill pediatric patients (r=-0.117, p=0.502). The difference between the zonulin levels of patients with pre-albumin values <20 and >20 was found to be statistically significant (13.1±6.7 vs. 12.2±8.4, p=0.484 Mann Whitney U-test). The zonulin – pre-albumin distribution is shown in Figure 1.

A low level significant negative correlation was determined between the zonulin level and Vitamin D level in critically ill pediatric patients (Spearman r=-0.386, p=0.022). The zonulin levels of patients with Vitamin D value <20 (16.5±5.4) were found to be statistically significantly higher than the zonulin levels of patients with Vitamin D value >20 (11.5±7.4) p=0.033, Mann Whitney U-test). The zonulin – Vitamin D distribution is shown in Figure 2.

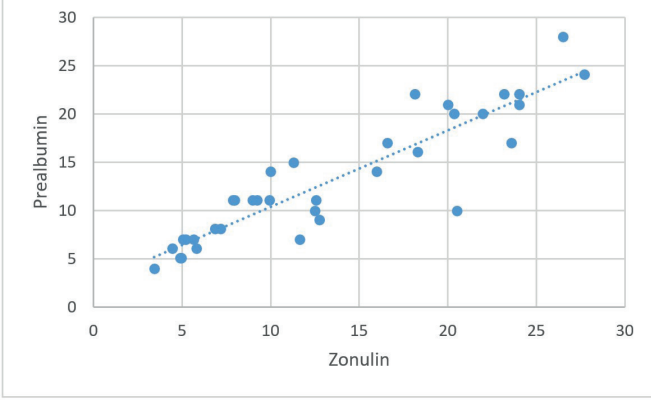

Figure 1. Zonulin – prealbumin distribution chart

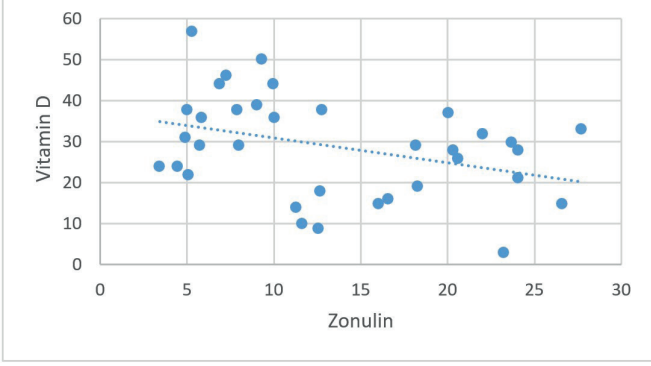

Figure 2. Zonulin – vitamin D distribution chart

No statistically significant correlation was determined between zonulin and creatinine in critically ill pediatric patients (Spearman r=0.231; p=0.182). No statistically significant correlation was determined between the zonulin value and BUN (r=0.329; p=0.053), AST (r=0.251; p=0.146), and ALT (r=-0.061; p=0.726) levels.

The mean zonulin level was found to be 11.4±7.1 in the patients who reached the target calories and 13.7±7.3 in the patients who did not reach the target calories, and the difference between these two groups was not statistically significant (Mann Whitney U-test, p=0.429). The mean Vitamin D level was significantly higher at 36.9±9.8 in patients who reached the target calorie intake compared to 23.4±10.8 in the patients who did not reach the target calories (Independent Paired Samples t-test, p=0.001). There was no statistically significant difference in mean pre-albumin levels between the patients who reached and did not reach the target calories (19.4±7.3 vs.16.8±7.4) (Independent Paired Samples t-test, p=0.302). There was no statistically significant difference in mean albumin level between the patients who reached and did not reach the target calories (3.4±0.5 vs. 3.3±0.6) (Independent Paired Samples t-test, p=0.794).

DISCUSSION

Zonulin is accepted as a biomarker of increased intestinal permeability. To a significant degree, intestinal permeability is regulated by tight junctions in the intestinal epithelium, and zonulin has an important role in regulating them. The regulation of tight junctions is thought to be responsible for the movement of fluid, macromolecules and leukocytes between the bloodstream and the intestinal lumen.[8]

In a study by Küme et al., zonulin was found to be significantly higher in obese children than in healthy children, which showed the potential role of zonulin in the etiopathogenesis of obesity and related disorders.[9] In a similar study, energy and carbohydrate intake greater than the daily requirement was shown to play a role in increasing intestinal permeability and increased zonulin levels.[10] In the current study, the zonulin level of critically ill pediatric patients was determined to be higher than that of the healthy control group. The determination of a higher zonulin level in critically ill pediatric patients may be associated with delayed gastric emptying, an abnormal motility pattern, deterioration in the intestinal barrier, prolonged catabolic process, exposure to oxidative and hypoxic stress, and bacterial translocation developing associated with all of these.

Pre-albumin is a plasma protein, a large part of which is synthesized from the liver, which has a half-life approximately two days shorter than that of albumin. Although used in the evaluation of nutritional status in PICUs, it is not accepted as an ideal marker as it is a negative acute phase reactant and production is decreased in inflammation.[11,12] No significant correlation was determined between zonulin and pre-albumin in the current study. The fact that zonulin was determined to be high in patients with normal pre-albumin levels and low in those with low pre-albumin levels suggests that zonulin cannot be used in the evaluation of acute malnutrition and the monitoring of nutrition.

In 2019, Merker et al. evaluated hospital in-patients and showed a correlation between Vitamin D deficiency and chronic malnutrition.[13] The results of the current study showed a statistically significant negative correlation between Vitamin D and zonulin. Therefore, the relationship between low Vitamin D and high zonulin levels may be useful in the evaluation of chronic malnutrition.

Serum creatinine levels in children with chronic malnutrition have been previously shown to be lower than in children who are not malnourished.[14] Therefore, considering that the relationship between low creatinine and high zonulin levels may be useful in the evaluation of chronic malnutrition, this relationship was evaluated in this study, but no significant correlation was determined. Finally, since no significant difference was found between the zonulin levels of patients who reached and did not reach the targeted calories, this demonstrated that zonulin would not be a good marker in nutritional surveillance in critically ill pediatric patients.

Limitations of this study are the relatively low number of patients and that basal zonulin levels were unknown. Finally, in our study, the mortality rate in the PICUs was found to be 8.57%. The mortality rates were found to be similar to those in developed countries.

CONCLUSION

This is the first study in the literature to evaluate zonulin as a marker of the nutritional status in critically ill pediatric patients. According to the findings of the study, the serum zonulin level selected as a biomarker for the monitoring and management of nutrition in critically ill pediatric patients is not an appropriate marker. However, this study can be considered valuable in measuring the zonulin level in critically ill pediatric patients for the first time and providing a reference value.

Ethical approval

This study has been approved by the Hatay Mustafa Kemal University Ethics Committee. Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: AK, YÇ; Concept: AK, GOT, AUK; Design: AK, YA; Data Collection or Processing: SA, TTK; Analysis or Interpretation: YÇ, SA, AUK; Literature Search: YÇ, GOT; Writing: AK. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Retrospective evaluation of candida infections in pediatric intensive care units

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ABSTRACT

Objective: *Candida* species are the most common infectious agents among the pathogens responsible for nosocomial fungal infections. Transmissions in intensive care units account for a significant proportion of the mortality and morbidity associated with candida infections. The present study evaluates the prevalence, type, treatment approach, underlying risk factors, and outcomes of candida infections in patients treated in a pediatric intensive care unit in Türkiye with a dense population of children who have fled the war in Syria.

Methods: The study was conducted in the 14-bed tertiary pediatric intensive care unit of a city hospital between March 2018 and March 2019.

Results: Candida species were reproduced in the studied samples of 28 (15.7%) of the 176 patients treated in the intensive care unit during the study period. Mortality occurred in six (21.4%) patients with invasive candidiasis of varying species, namely: *C. lusitaniae* (n=2); C. *parapsilosis* (n=2); *C. krusei* (n=1), and *C. albicans* (n=1), and candida was considered the cause of mortality in five of the six non-survivors. Resistance to liposomal amphotericin-B was observed in the *Candida* species isolated from the non-survivors.

Conclusion: In the present study, a prolonged stay in the intensive care unit, a higher number of indwelling medical devices, the use of broad-spectrum antibiotics, the presence of an underlying condition, and renal failure were observed to increase incidence of candida infection.

Keywords: Candida, pediatric, intensive care, mortality, evaluation

INTRODUCTION

Recently, there has been a significant increase in the incidence of nosocomial fungal infections in adults and children treated in intensive care units (ICUs). The advanced life support systems in ICUs, the increased number of invasive procedures, the prevalent use of cytotoxic therapies and broad-spectrum antibiotics, chronic diseases, and prolonged stays in ICUs are considered to be the main reasons for the increase in such infections.[1]

Candida infections are one of the most prevalent nosocomial fungal infections. The genus *Candida* includes around 150 species, the most commonly isolated of which are *C. albicans*, *C. glabrata*, *C. parapsilosis, C. tropicalis* and *C. krusei,* in descending

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order.[2] These species can cause infections in human at different ages, with, for example, *C. parapsilosis* being identified more commonly in newborns than other species.[3] *Candida* infections are considered a significant problem in ICUs worldwide, and their prevalence is increasing. Candidiasis is associated with high mortality and morbidity in which the sources of transmission in the ICU play an important role.

A study in Switzerland reported that one-third of *Candida* cases picked up the infection during treatment in the ICU. Compared to other therapeutic hospitalizations, patients are 5-10 times more likely to become infected with *Candida* species during intensive care treatment.[4] In the United States, C*andida species are* mostly isolated from the blood and result in bloodstream infections, accounting for 8-10% of cases, while *Candida* infections are the 6-10th most common infection in Europe, accounting for 2-3% of the transmissions through the bloodstream.

The present study evaluated the prevalence of various C*andida* species and investigated the treatment approaches, underlying risk factors, and outcomes in pediatric ICU patients in Hatay, a city in Türkiye that is host to many children who have fled the war in Syria.

MATERIALS AND METHOD

The study was conducted in a 14-bed public hospital with a tertiary pediatric ICU between March 2018 and March 2019. *Candida* growths in the blood, urine, and tracheal aspirate cultures of patients treated in the unit were analyzed retrospectively, as well as the agents (species), treatment approaches, time to negativity (days), and the effect on mortality. The study was approved by the Hatay Mustafa Kemal University ethics committee (approval number: 10/13, date: 8/9/2022). Informed consent was not required due to the retrospective study design.

Statistical analysis

Microsoft Excel 2010 was used for the analysis of the descriptive statistics of the study data.

RESULTS

A total of 176 patients treated in the ICU in the specified one-year study period, *Candida* growth was detected in 28 (15.7%). In the data analysis of the 28 patients, the mean age was 24.9±26.1 months and the female-to-male ratio was 11/17 (Table 1). The mean pediatric logistic organ dysfunction (PELOD II) score was 32.8±4.68, the mean pediatric risk of mortality (PRISM III) score was 27.3±7.38, and the mean MODS score was 18±6. Of the

Table 1. Demographic and clinical data of patients with positive cultures for *Candida*

	n (%)
Gender	
Female	11 (39.3%)
Male	17 (60.7%)
Age	24.9 ± 26.1 months
Growth distribution by anatomic region	
Blood	10 (35.7%)
Urine	6 (21.4%)
TAC	3 (10.7%)
Blood-urine	3 (10.7%)
Urine-TAC	3 (10.7%)
Blood-TAC	3 (10.7%)
Central Venous Catheter	
Yes	21 (75.0%)
No	7 (25.0%)
Intubation	
Yes	21 (75.0%)
No	7 (25.0%)
Uriner Catheter	
Yes	22 (78.6%)
No	6 (21.4%)
Systemic findings	
Yes	21 (75.0%)
No	7 (25.0%)
Prevalence of risk factors in patients (%)	
Chronic disease	20 (71.4%)
Neutropenia	-
Renal failure	20 (71.4%)
Postoperative surgery	5 (17.9%)
Immunosuppressive therapy	-
Broad spectrum antibiotics	28 (100%)
Parenteral nutrition	16 (57.1%)
Hemodialysis	17 (60.7%)
Mechanical ventilation	21 (75.0%)
Central venous catheter	22 (78.6%)
Urinary catheter	23 (82.1%)

patients, three were Turkish and 25 were Syrian. The Syrian patients had been under treatment in the war zone in Syria and were transferred to our hospital to continue with the therapy, or due to a deterioration of their clinical condition. All patients had underlying chronic conditions and at least one had chronic organ failure. The chronic conditions included respiratory failure related to hypotonicity secondary to genetic disorders, multi-drug resistant epilepsy, congestive heart failure secondary to complex cardiac anomalies, chronic kidney disease, sepsis, and acute liver failure.

Antifungal therapy was not initiated in five patients with positive cultures due to the absence of systemic findings, while 20 patients with suspected *candida* infections were initiated on empirical fluconazole therapy. The treatments were modified based on the results of susceptibility tests, and appropriate antifungal therapies were initiated targeting the pathogens identified in antibiotic susceptibility tests.

Of the 28 patients with candidemia, 20 had used inotropic agents. All of the non-survivors had been on inotropic therapy. After the identification of underlying chronic conditions, three patients were placed on continuous venovenous hemodiafiltration (CVVH) and one on therapeutic plasmapheresis (TPE). No patient received CVVT or TPE due to candida sepsis.

The length of stay of the sample in the ICU was 39.6±21.8 days. Of the patients with positive cultures for *Candida* (n=28), the organism was recovered from the blood, urine, and tracheal aspirate cultures in 16 (57.1%), 12 (42.8%), and nine (32.1%) patients, respectively, and the same agent was isolated from samples obtained from two different anatomical regions in nine patients (Tables 1 and 2).

The cultures did not become negative until death in three patients who died during their stay in the ICU, while the mean time to culture negativity was 11.37±6.80 (3–30) days for the other patients. Systemic findings were identified in 21 (75%) of the patients (Table 3, 4).

Table 2. Distribution of *Candida* species by infection localization

	Blood	Urine	TAC
C. peliculosa	1 (6.3%)	-	-
C. albicans	4 (25.0%)	5 (41.7%)	7 (87.5%)
C. lusitanie	2 (12.5%)	1 (8.3%)	-
C. parapsilosis	3 (18.8%)	-	-
C. spp	2 (12.5%)	-	-
C. tropicalis	4 (25.0%)	3 (25.0%)	1 (12.5%)
C. glabrata	-	1 (8.3%)	-
C. krusei	-	2 (16.7%)	-

In the present study, C. *albicans* was the most frequently (35.7%) isolated agent causing candidemia. Among the *non-albicans* species, C. *tropicalis* was the most commonly (25%) isolated species, followed by C. *parapsilosis* (10.7%). The proportion of *candida* species that could not be identified to a species level was 10.7%.

C. *lusitaniae* (n = 2), C. *parapsilosis* (n = 2), C. *krusei* (n = 1), and C. *albicans* (n = 1) were identified in the six (21.4%) non-survivors with a *candida*-positive culture result. Of those who died of *candidemia,* the pathogens were resistant to fluconazole and liposomal amphotericin B. In these patients, the *Candida* species were isolated from the blood, and five of the six exitus patients died due to *candida* sepsis. The same candida species were reproduced in both the blood and urine or the tracheal aspiration fluid culture of four of the six non-survivors. Hospital-acquired bacterial pathogens had previously been reproduced in the cultures of these patients, although candida species were only reproduced in the final culture tests. The candida species were either resistant to the antifungal therapies, or the therapy was initiated too late. It was seen that one candida species had no effect on mortality. Because the patient had a metabolic disorder, which was thought to be a mitochondrial disease and the main cause of death in this patient.

Table 3. Duration of antifungal therapy (days)

	n	Mean ± SD (days)	Min–max (days)	Candida species
Fluconazole	20	13.3 ± 7.6	1–26	*C. albicans/ krusei/ parapislosis/ tropicalis/ pelluculosis*
Micafungin	2	10.5 ± 9.2	4–17	*C. krusei/ albicans/ tropicalis*
Amphotericin B	1	17	-	*C. parapsilosis*
Caspofungin	2	6	-	*C. lusitania*
No agent administered	5	-	-	*C. krusei/ albicans/ spp.*

Table 4. Rates of antifungal agents according to patients	
Antifungal agents	**n**
Micafungin	2 (7.14%)
No agent	5 (17.85%)
Liposomal Amphotericin B	1 (3.5%)
Fluconazole	18 (64%)
Fluconazole + Caspofungin	2 (7.14%)

Of the other non-survivors, two had inoperable complex cardiac arrhythmia; one had hemolytic uremic syndrome and suffered a sustained cerebral infarction; one had neurogenic bladder, malnutrition, and external ventricular drainage, and had previously been fitted with a ventriculoperitoneal shunt; and one presented with acute hepatic failure of unknown origin and developed multiorgan failure after hospitalization.

DISCUSSION

A multicenter point-prevalence study conducted in adult intensive care units (ICUs) in Türkiye reported a rate of 4.7% for *Candida* species identified in sepsis cases in which the cause of sepsis could be identified.[5] In the present study, a total of 176 patients were treated in the ICU over the course of one year, and *Candida* growth was detected in 28 (15.7%). Broad-spectrum antibiotics, central venous catheters, parenteral nutrition, renal replacement therapies, neutropenia, and malignancy are the major risk factors for candidemia.[1] In the present study, high rates of central venous catheters, broad-spectrum antibiotic therapy, and renal failure were identified, and so the rate of candida growth was found to be higher than reported in the literature.

In Türkiye, the rate of *Candida* infection was reported to be 42% in blood cultures and 57% in urine cultures among pediatric patients treated in a tertiary pediatric ICU over an 11-year period.[6] In the present study, the rate of growth in blood and urine cultures was 57.1% and 42.8%, respectively, and this higher rate in the blood and urine cultures compared to other anatomical regions supports the findings of previous studies.

A study conducted in adult ICU patients identified C. *albicans* as the dominant species (47.9%), while the species most commonly associated with sepsis was identified as *C. parapsilosis*.[7] Other studies have reported *C. albicans* as the most common pathogen, followed by C. *parapsilosis*.[6,8,9] The present study also identified *C. albicans* (35.7%) as the dominant species, while the second most commonly isolated species was *C. tropicalis* (25%) and the third was *C. parapsilosis* (10.7%). The study by Omrani et al. reported C. albicans as the most common species followed by *C. tropicalis*.[10] A review of the literature reveals that there has been an increase in *non-candida albicans* species, although *C. albicans* is still the most common. Among the *non-albicans* species, the second most common species varies in different studies, with *C. parapsilosis, C. glabrata, C. krusei* and *C. tropicalis* all having been reported.[3,4,11,12]

In Türkiye, the mortality rate of adult ICU patients with candidemia has been reported to be 83%, and invasive *Candida* infections in the ICU setting have been identified as an independent risk factor for mortality.[13] The reported mortality rate associated with candidemia in pediatric ICU patients ranges from 7% to 26% in different studies.[12,14,15] One study reported a mortality rate of 13.7% in pediatric ICU patients[6], while the present study found a mortality rate of 21% in patients with candidemia. The difference in mortality rates associated with candidemia may be attributed to several factors, such as patient age, the presence of underlying diseases, the candida species, and the patient's physiological condition.

Based on moderate-quality evidence, IDSA strongly recommends empirical therapy for the treatment of invasive candidiasis in ICU patients with the presence of a high clinical index of suspicion.[16] In the present study, patients with underlying chronic conditions who were unresponsive to broad-spectrum antibiotherapy and with accompanying thrombocytopenia were initiated on prophylactic antifungal therapy.

The *Candida* species associated with mortality were different, although all species that led to mortality were resistant to liposomal amphotericin B and fluconazole. These species have been reported to be susceptible to micafungin, although recent guidelines recommend echinocandins or L amphotericin B as the first-line therapy for patients with suspected candidemia/invasive candidiasis.[17] A recent study supports the use of micafungin due to the fewer side effects, the safety of the drug, and the resistance to fluconazole and amphotericin B among *Candida* species.[6]

In the present study, the analyses conducted during the infection period revealed some pathogens to be resistant to fluconazole, flucytosine, caspofungin, and liposomal amphotericin B, and the infections in the non-surviving patients were all caused by the antifungal-resistant strains. Nevertheless, all *candida* species were found to be susceptible to micafungin. As the number of patients in our study was very small, the information is provided solely to contribute to the literature.

In conclusion, based on the findings of the present study, micafungin may be considered a promising antifungal agent against the increasing resistance to amphotericin B and

fluconazole. However, due to the small number of patients in the present study, this finding cannot be generalized and requires careful consideration.

Ethical approval

This study has been approved by the Hatay Mustafa Kemal University Non-Invasive Clinical Research Ethics Committee (approval date 08/09/2022, number 10/13). Informed consent was not required due to the retrospective study design.

Author contribution

Surgical and Medical Practices: GOT, TTK; Concept: YÇ, AK, TTK; Design: GOT, YA, SA, TTK; Data Collection or Processing: YÇ, AK, GOT, YA, SA, TTK; Analysis or Interpretation: YÇ, AK; Literature Search: YÇ, AK, TTK; Writing: YÇ.

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Conflict of interest

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Original Article

Poisonings in childhood: A 5-year experience of a tertiary city hospital in İstanbul

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ABSTRACT

Objective: Poisoning is a substantial public health problem preventable with basic precautions. This study aims to contribute to the literature by analyzing the demographic variables, epidemiological characteristics, and prognosis of children brought to the pediatric emergency department of our center due to poisoning in the last five years.

Methods: We retrospectively evaluated the medical records of 1928 patients who were under-18 years old and admitted with acute intoxication diagnosis to our tertiary hospital's pediatric emergency department in Istanbul between 2016 and 2021. Patients were divided into two groups by poisoning factors: drug and non-drug substances.

Results: We included all 1928 patients (55.1% male, 44.9% female). The median age was 30 (20-49) months, and 85.5% (n=1650) of patients were under 72 months old. There was a male gender dominance (62.4%) among patients aged 3-6, all of whom had accidental poisoning (100%). Poisonings among patients older than 12years of age were more common in girls (59.8%) and were mainly suicidal attempts (65.2%). We detected drug exposure in 58.9% (n=1047) of patients; the most common drugs were analgesics (13.5%, n=269), psychotropics (6.2%, n=102), and hormone preparations (4.5%, n=86). We also detected non-drug exposure in 41.1% (n=792) of patients; the most common non-drug substances were corrosive-caustic substances (14.6%, n=284), and detergent poisonings (5.5%, n=106). None of the patients died.

Conclusion: Patients in the under 6 years old group admitted due to poisoning were predominantly male, and all cases were accidental. Whereas poisonings above the age of 12 were more common in girls and were usually due to suicide. Our study also showed that poisonings in children passed with milder symptoms, and we discharged most of the children after a short observation without the need for hospitalization. Well-balanced clinical management may prevent unnecessary hospitalization and unnecessary medical interventions.

Keywords: Children, poisoning, intoxication, emergency department, suicide

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INTRODUCTION

Although poisoning may result in mortality and morbidity, it is a substantial public health problem preventable with basic precautions.[1] It constitutes approximately 0.5-2% of the reasons for applying to emergency outpatient clinics in childhood.[2-4] For effective and rapid treatment, it will be helpful to have information about the common types of poisoning and their symptoms.[5]

Most poisonings are seen in children and adolescents. According to American Poison Control Center, 58% of the cases in the USA were under the age of 20.[6] Likewise, according to the National Poison Information Center report, approximately 60% of the admissions to emergency due to poisoningin Turkey are in children.[7] Studies have shown that poisoning is most common in children under the age of five.[5,8] According to the data of the Turkish Statistical Institute, injuries due to external factors and poisoning are responsible for 29.5% of the deaths in children under the age of 18 in Turkey.[9]

The causes and types of poisoning vary according to age, gender, season, socioeconomic status, and geographical region.[10] Even in the same province, the demographics and agents of poisoning can change over time.[5] Therefore, following these changes related to childhood poisonings will help physicians, and other healthcare professionals working in the emergency room to recognize poisoning cases without wasting time and manage treatment effectively. Early diagnosis and treatment play a crucial role in the clinical results of poisoning cases.[11]

Our study aims to contribute to the literature by retrospectively analyzing the causes, demographic variables, epidemiological characteristics, and prognoses of children brought to the pediatric emergency service of our center due to poisoning in the last five years.

MATERIAL AND METHODS

Permission for the study was obtained from the ethics committee of Istanbul Kartal Dr. Lütfi Kırdar City Hospital with the file number 2021/514/204/14. The study was carried out in accordance with the Declaration of Helsinki.

We retrospectively analyzed the medical records of 2368 patients who were under the age of 18 and admitted to the Pediatric Emergency Outpatient Clinic ofIstanbul Kartal Dr. Lütfi Kırdar City Hospital with poisoning between January 2016 and January 2021.

We excluded patients who were misdiagnosed or applied with the complaint of swallowing foreign objects like coins or toys. In addition, we could not reach some patients' data, so we included all eligible 1928 patients whose data was available in the study. Patient data werescanned from the hospital database and recorded in an Excel file.

We assessed patients by gender, age, the reason for exposure to poisoning (accidental or suicide), factor(s) causing poisoning, route of exposure to poisoning, place of poisoning, time of poisoning (hour, month, and day), hospital arrival time, treatment modality in pediatric emergency observation, duration of emergency department observation and pediatric emergency outcomes. The poisoning factors of the patients who applied for suicidal poisoning were also analyzed.

Patients who applied to the Pediatric Emergency Outpatient Clinic due to poisoning were divided into two groups according to the poisoning factors: drug and non-drug substances. After that, the patients were divided into subgroups according to the specific substances. In addition, we divided patients into different age groups and evaluated the causes of poisoning and its relationship with other variables according to age groups in our study.

Statistics

We presented the descriptive results with normal-distributed data as mean ± standard deviation and skewed data as median (interquartile range (IQR) 25/75). We used the One-way ANOVA test to compare more than two groups with normal distribution and homogenous variance and the Kruskal-Wallis test for non-normally distributed data. Tukey and Dwass-Steel-Critchlow-Fligner tests are used for pair-wise comparison, respectively. Type 1 error of <0.05 was considered statistically significant. We also built a binomial regression model with factors defined in the literature. We selected the predictors that may be statistically significant ($p<0.1$) by the "forward selection" method. Variance inflating factor test is used for collinearity assumption. We interpreted the R2 McFadden and the X2 value of likelihood ratio tests in the binomial regression model. Moreover, we presented binomial test results with an "estimated marginal means" table and a graph. We used the R-based statistical package program JAMOVI 2.2.5.

RESULTS

The number of patients admitted to the pediatric emergency department was approximately 660,000 in five years-period, and 0.35% (n=2368) of the admissions were due to poisoning.

We included 1928 patients (55.1% male, 44.9% female) in our study. The median age was 30 months (20-49 months). 85.5% (n=1650) of the patients were under 72 months. There was a male gender dominance (62.4%) among patients aged 3-6, all of whom had accidental poisoning (100%). As we divide patients into two groups by age (12 years), poisonings over the age of 12 were more common in girls (59.8%) and were mostly suicidal attempts (65.2%) (p<0.001, chi-square test). Drugs constituted 57.7% of poisonings in children younger than 12 years of age, while this rate was 75.8% for patients above 12 years of age (p<0.001, chi-square test).

As we evaluate the route of exposure to poisoning, 93.9% of the patients were poisoned orally, 1.9% by inhalation, 1.3% by skin, and 0.4% by the ocular route. The route of exposure was unavailable in the records of 2.5% of the patients. While 5% of the patients applied because of suicidal attempts, the rest (95%) were poisoned accidentally. While the most common place of

Table 1. Medication-related poisoning agents

	Accidental poisoning	Self-inflicted poisonings	Total n (%)	% of All Patients
Analgesics				
-Non-steroidal anti-inflammatory	152	1	153 (13.5)	8
-Paracetamol	92	5	97 (8.5)	5
-Other	18	1	19 (1.7)	0.5
Myorelaxants	25	2	27 (2.4)	1.4
Psychiatric drugs				
-Antidepressants	49	9	58 (5.1)	3
-Antipsychotic drugs	41	4	45 (4)	2.4
-Other	12	3	15 (1.3)	0.8
Neurological drugs				
-Anti epileptic drugs	24	2	26 (2.3)	1.4
-Other	10	0	10 (0.8)	0.5
Gastrointestinal drugs	56	4	60 (5.3)	3.1
Cardiovascular drugs				
-Antihypertensive drugs	65	2	67 (5.9)	3.5
-Other	8	0	8 (0.7)	0.4
Antihistamines	49	1	50 (4.4)	2.6
Antimicrobials	45	1	46 (4.1)	2.4
Cold medications	64	5	69 (6.1)	3.6
Antitussive and mucolytics	34	2	36 (3.2)	1.9
Hematological drugs	35	0	35 (3.1)	1.8
Hormone preparations	84	2	86 (7.5)	4.5
Vitamin derivatives	54	1	55 (4.8)	2.9
Antineoplastic drugs	5	0	5 (0.4)	0.3
Topical medications	50	0	50 (4.4)	2.7
Multiple drug intake	62	43	105 (9.3)	5.5
Unidentified drugs	13	1	14 (1.2)	0.7
Total	1047	89	1136 (100)	58.9

poisoning was at home (93.9%), 2.4% of poisonings occurred outside the home. We could not reach data for the remaining 3.7% of the patients.

Drugs were the common cause of poisoning (58.9%), however 41.1% (n=792) of the patient poisoned by non-drug substances. The factors causing poisoning are presented in Table 1. Analgesics and antipyretics constituted the largest group in drug poisonings. Non-steroidal anti-inflammatory drugs (NSAID) were the most common analgesic drugs (8%). The second most common poisoning agent was psychiatric drugs (6.2%) (antidepressants, antipsychotics, and sedative agents), followed by hormone preparations (4.5%). In addition, multi-drug use constituted 5.5% of the admissions (Table 1). In non-drug poisonings, corrosive-caustic substances accounted for 14.6% of all poisonings and 5.5% of detergent poisonings (Table 2).

Gastric lavage and activated carbonare major treatment approaches for poisoning in the pediatric age group. We administered activated carbon, gastric lavage, and specific antidotes to 21.8% (n=420),20% (n=386), and 1.6% (n=31) of the patients, respectively. 27 of these 31 patients had paracetamol intoxication, and N-acetylcysteine (NAC) was given as an antidote. Other patients were administered Flumanezil after benzodiazepine intoxication and atropine after organophosphate poisoning.

In Table 3, the patients were divided according to age groups and compared in terms of gender, type of poisoning agent, and hospital arrival time.

70.7% of the patients were discharged from the emergency room, 22.5% were hospitalized in the pediatric service, and 3.7% continued treatment in our pediatric intensive care unit. 1.8% of the patients did not accept the treatment and left the hospital, and 1.1% were referred to the pediatric surgery service. As we divided the age groups into two groups, more than 70% of the patients under 12 years of age were discharged from the emergency department, while this rate decreased to 49% over 12 years of age ($p<0.001$). In addition, while intensive care need was below 5% in children under 12 year-olds, this rate increased to 33.3% in children older than 12 ($p<0.001$). None of the patients died or had chronic sequelae in patients treated in our services. The mean hospital arrival time was 60 (30-105) minutes for all ages, and this time lap increased as the patient's age increased.

Table 2. Non-medication related poisoning agents

Substances	Frequency	Percent	% of All Patients
Caustic-corrosive substances	281	35.5	14.6
Mushrooms	5	0.6	0.3
Pesticides and insecticides	36	4.5	1.9
Hydrocarbons	26	3.3	1.4
Carbon monoxide and gas poisoning	24	3	1.2
Zoic	3	0.4	0.2
Herbal	24	3	1.2
Food poisoning	26	3.3	1.4
Mercury	5	0.6	0.3
Detergents	106	13.4	5.5
Alcohol	64	8.1	3.2
Antiseptic	20	2.5	1
Dye poisoning	13	1.6	0.7
Thinner	30	3.8	1.6
Narcotic	12	1.5	0.6
Cosmetic	39	5	2
Other non-drug substances	33	4.2	1.7
Unknown	45	5.7	2.3
Total	792	100	41.1

Table 3. Comparison of poisonings by age groups

		Age (month)					
		<12 n=95	**12-35 n=1028**	**36-71 n=527**	**72-143 n=146**	**>144 n=132**	**p**
Gender (%)	Female	49.5%	47.3%	37.6%	38.4%	59.8%	<0.001
	Male	50.5%	52.7%	62.4%	61.6%	40.2	
Drug/non-drug (%)	Drug	33.7%	54.7%	70.2%	49.3%	75.8 %	<0.001
	Non-drug	66.3%	45.3%	29.8%	50.7%	24.2%	
Poisoning time of day (%)	Night	22.1%	28.3%	32.4%	28.8%	38.9%	0.044
	Day-time	57.1%	52%	44.4%	55.9%	42.6%	
	Evening	20.8%	19.7%	23.1%	15.3%	18.5%	
Poisoning place (%)	Home	95.8%	96.7 %	82.6%	84.9%	86.4%	<0.001
	Outside	-	1.3%	1.5%	8.9%	9.1%	
	Unknown	4.2%	2%	5.9%	6.2%	4.5%	
Suicidal attempt (%)		%0	%0	%0	%7.5	%65.2	<0.001
Ending (%)	Discharged	72.6%	70.7%	74.6%	74.7%	49.2%	
	Ward	23.2%	22.5%	21.4%	16.4%	33.3%	
	NICU	1.1%	3.2%	2.5%	4.8%	13.6%	
	Referred	-	1.6%	0.4%	1.4%	1.5%	
	Unknown	3.2%	2%	1.1%	2.7%	2.3%	
Hospital arrival time (minute)		42.5 (20-60)	55 (30-90)	60 (30-120)	90 (45-240)	90 (50-180)	<0.001

*Chi-square test

Table 4. Estimated Marginal Means table for age (month) and gender

Gender	**Age (month)**	**Probability (%)**	**Lower CI (%)**	**UpperCI (%)**
Female	94.7 (-1 SD)	5.19	2.129	12.1
	134.3 (mean)	32.42	22.21	44.63
	173.8 (+1 SD)	80.79	70.931	87.88
Male	94.7 (-1 SD)	1.78	0.672	4.6
	134.3 (mean)	13.68	8.114	22.14
	173.8 (+1 SD)	58.15	43.932	71.13

*Estimated Marginal Means table of binomial regression model

Suicide attempts were usually performed with drugs (91.8%). It is noteworthy that "multiple drug intake" (48.3%) ranked first. Psychiatric drugs (18%) and analgesics and pain relievers (7.9%) ranked first and second in "single drug poisoning", respectively in single-drug poisonings took second order.

We did not observe any suicide attempts before 72 months, so we considered patients over 72 months as a separate group for interpreting the suicidal attempts and subjected the gender and age to multivariate analysis as these are possible risk factors for suicide attempts according to the literature (Table 4).[4] The predictors affecting the likelihood of admission due to a suicidal attempt were gender (female odds: 3.03; p=0.001) and age (odds ratio: 1.06 per month; p<0.001).

DISCUSSION

Poisoning is one of the most common but preventable causes of emergency admission in childhood.[12] Our study is a retrospective study in a tertiary hospital in Istanbul, including five years

of data, and very comprehensive in terms of the number of cases. In this study, we analyzed the patients who applied to the pediatric emergency outpatient clinic due to poisoning and aimed to update existing information, determine preventive measures accordingly, and plan treatment management quickly and effectively.

In our study, the number of patients who applied to our pediatric emergency outpatient clinic due to poisoning constituted 0.35% of the total admissions. This rate was reported between 0.5% and 0.7% in recent studies conducted in Turkey.[13-15] In a study conducted in our clinic between 2010 and 2011, this rate was 1.01% .[16] We can attribute this change to the increased patient admissions to the emergency department for reasons other than poisoning. At the same time, raising public awareness of poisonings reduces this rate. In addition, in recent years, research by pharmaceutical companies in Turkey regarding the safety caps have been aimed at this purpose.

In our study, 85.5% (n=1650) of the patients admitted with poisoning were under 72 months of age, which is consistent with the literature.[3,12,17] Similar to our study, studies have emphasized that the male gender was predominant, and the cause of poisoning was mostly accidental in poisonings under 12 years of age.In contrast, poisonings above 12 years of age were more common in females and were usually due to suicide.[3,4,14] The 2019 data of the American Poison Control Center, which includes the data of approximately 2.5 million patients published in 2020 by Gummin et al.[6], showed parallel results with our study on age and gender. The incidence of poisoning cases under the age of 6 was high because children in this age group are more curious due to their attitudes toward exploring the environment.[2,18]

In addition, we took the cases over the age of 6 as a separate group and subjected the gender and age, which are possible risk factors for suicide, to multivariate analysis.[4]This binomial model (suicide or accidental poisoning) calculated that each monthly increase in patient age increased the suicide odds by 1.006 times (or 0.6 %). Additionally, the female gender increased the suicide odds by 3.03 times. Lin et al.[4] reported 10.5 years of age as the cut-off value for suicide. In the study that included 10 years of data conducted by Kline et al.[19], it was shown that the likelihood of suicide increased as age increased and it was mostly seen in girls. In this study, it was emphasized that education and health policies should be developed for high school-age children in order to reduce the suicidal tendency in adolescents.[19] Clinicians should investigate the possibility of suicide in older girls who come to pediatric emergency outpatient clinics with suspicion of poisoning, plan emergency management by considering suicidal attempts, and refer these patients to child psychiatrists in addition to clinical treatment.

Consistent with studies, the majority of our patients were poisoned by ingestion.[2,6,20] In parallel with the literature, we observed that 93.9% of poisonings occurred at home.[2,6,14] This result is not surprising we knowing that 85.5% of our patients admitted with poisonings were under 72 months, most of the potential poisoning agents were reached at home, and the behavior of putting small foreign objects into the mouth was more common in this age group.

In our study, intoxications with drugs (58.9%) were higher than non-drug agents (41.1%), consistent with other studies.[16,17,21,22] The causes of poisoning vary according to socioeconomic status and geographical region.[10] Analgesics and antipyretics constituted the largest group in drug poisoning in our study. NSAIDs were the most common analgesic drugs. The second most common poisoning agent was psychiatric drugs (6.2%), followed by hormone preparations (4.5%). Multiple drug intake accounted for 5.5% of the admissions. In the study conducted in our hospital in 2011 by Dündar et al.[16], Central Nervous System drugs (psychiatric drugs, anti-epileptic) constituted the majority of drug poisoning, while analgesic and antipyretic drugs were the second most common. Thus, we can attribute this change over the years to the obligatory prescription of most CNS drugs, the easy accessibility of analgesic-antipyretic drugs, and the inappropriate use of drugs. In many studies, analgesics and antipyretics were the most common factors in medication-related poisoning.[2,17,23,24] In our study, the most common cause of non-pharmaceutical poisoning was corrosive-caustic substances, in line with the recent studies conducted in Turkey.[3,25] In the second place, poisoning with detergents came forth. Esophageal injury should be considered after poisoning with corrosive-caustic substances.[5]

Suicidal drug intake constituted 5% of total poisonings and 10.1% of drug-related poisonings. In a study conducted in our hospital in 2011, this rate was 12.4% in drug-related poisonings.[16] In suicidal attempts, multiple drug intake draws attention in the literature similar to our study.[5,10] In our patient group, psychiatric drugs were ranked first in single-drug poisonings.

The time elapsed between poisoning and the patient's admission to the emergency department is crucial for the management and prognosis of the treatment. In a 3-year study conducted in Qatar, Ahmed et al.[17] reported that admission to the emergency department was less than one hour in 255 of the poisoning cases. According to studies conducted in our country, admission to the emergency department was 60 minutes at the utmost.[10,14] In our patient group, the time until arriving at the emergency department after poisoning was 60 (30-105) minutes, and it was noteworthy that this time increased as the patient's age increased. We think that the increase in the suicide rate with

age in children causes a prolongation of the time to apply to the emergency department after the poisoning in older children. In addition, the fact that our hospital has many transportation opportunities and its central location has enabled patients to reach the hospital quickly.

In our study, 21.8% of the cases were treated with activated carbon, 20% with gastric lavage, and 1.6% with the specific antidote. NAC was administered as an antidote to 27 patients with paracetamol poisoning. A study from Turkey reported that they applied gastric lavage in 24.5%, activated carbon in 30.9%, and specific antidote in 2% of the cases (more than half were NAC).[14] In a study conducted in Singapore, 3.5% of the patients who applied to the emergency department after poisoning were treated with gastric lavage, 25% activated carbon, and 7.7% antidote (mostly NAC).[2] The use of activated carbon and gastric lavage in children depends on the poisoning agent and the time elapsed between poisoning and the patient's admission to the emergency department.[26]

We evaluated the need for hospitalization in the service and intensive care unit retrospectively to assess the clinical status of patients presenting with poisoning. In our study, 70.7% of the patients were discharged from the emergency room, 22.5% were hospitalized in the pediatric health and diseases service, and 3.7% were admitted to the pediatric intensive care unit for further treatment and follow-up. In the study published by Lee et al.[5] in 2019, it was reported that 17.2% of the patients who applied to the emergency outpatient clinics due to poisoning were followed-up in the pediatric health and diseases service, and 3.6% in the pediatric intensive care unit. In a study published in Iran in 2013, 5.8% of patients who applied to emergency outpatient clinics with poisoning needed pediatric intensive care services.[27] In a study similar to ours and containing 3-year data in Italy, most patients were hospitalized in the pediatric intensive care unit for follow-up of vital functions.[26] We did not observe any death due to poisoning in our patient group, which is compatible with studies in children.[2,3,26,28] Since most of the poisonings in children are accidental, the mortality rate is lower than that of the adult patient group.[26] In the study conducted by Akin et al.[20] in our clinic between 2005 and 2007, 2 patients died due to poisoning. We think raising awareness of poisoning in the community and minimizing the duration of admission to the emergency department are critical subjects to prevent death due to poisoning. Compared to other studies conducted in our clinic, this period was shorter in our study.[16,20] The increase in transportation opportunities to our hospital over time is also an important factor in this.

The main limitation of the study was that it was retrospective. We recorded the patient data by accessing the hospital information system and files. Nevertheless, in our retrospective single-center study conducted in a tertiary hospital, we could not reach all of the medical practices performed in previous health units. However, the number of patients and the scope of the data are the strengths of our study.In addition, studies on poisoning in children in previous years in our center demonstrated the change in the same region over the years, which provided the opportunity to compare the data.

CONCLUSION

As a result, admissions due to poisoning under the age of 6 were predominantly male, and all were accidental. Whereas poisonings above the age of 12 were seen mostly in girls and were generally due to suicide. Our study also showed that poisonings in children passed with milder symptoms, and most of the children were discharged after a short observation without theneed for hospitalization. A well-balanced clinical management may prevent unnecessary hospitalization and unnecessary medical interventions. Suicide and self-harm in adolescents have been increasingly significant health problems in recent years. A poison counseling center establishment for only pediatric patients may enable us to reveal the causes of poisoning in children of different age groups and take more effective measures.

Ethical approval

This study has been approved by the İstanbul Kartal Dr. Lütfi Kırdar City Hospital Clinical Research Ethics Committee (approval date 22/06/2021, number 2021/514/204/14).

Author contribution

Surgical and Medical Practices: MTK, GE, AE, SM, İK, FHE, YÇ, YA; Concept: MTK, GE, AE, SM, İK, KP, HG, YÇ, YA; Design: MTK, AE, SM, İK, KP, HG, FHE, YÇ, YA; Data Collection or Processing: MTK, GE, SM, İK, KP, HG, FHE, YÇ, YA; Analysis or Interpretation: MTK, GE, AE, SM, İK, KP, HG, FHE, YÇ, YA; Literature Search: MTK, AE, İK, YÇ, YA; Writing: MTK, GE, SM, İK, KP, HG, FHE, YÇ, YA. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Case Report

Four cases with ectrodactyly, ectodermal dysplasia, cleft lip/palate syndrome: Clinical evaluation and management and literature review

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ABSTRACT

A rare syndrome is ectrodactyly-ectodermal dysplasia-cleft lip/palate (EEC) syndrome, which may present with lobster claw deformity. The main clinical characteristics indicate involvement of ectodermal and mesodermal tissues, including mesoaxial and longitudinal defect of distal extremity, cleft lip and palate, and developmental defects of ectoderm derives. Renal anomalies and hormonal disorders may be seen in EEC patients. This article discusses endocrine problems in 4 EEC patients diagnosed based on clinical characteristics.

Keywords: Ectrodactyly, ectodermal dysplasia cleft lip, lobstarclow, adipsic hypernatremia

INTRODUCTION

Ectrodactyly-ectodermal dysplasia-cleft lip/palate (EEC) syndrome is a rare autosomal dominant disorder that also develops de novo in most cases. It displays decreased genetic makeup penetrance and variability.[1-3] The syndrome has 2 types: Ectrodactyly, ectodermal dysplasia, and cleft lip/palate syndrome 1 (EEC1, OMIM **%** 129900); Ectrodactyly, ectodermal dysplasia, and cleft lip/palate syndrome 3 (EEC3). The EEC3 is the most common (90%), and the EEC1 (10% of cases). EEC syndrome-3 (EEC3) is caused by a heterozygous mutation in the gene encoding p63 (TP63) (OMIM; *603273) on chromosome 3q28. EEC1 has been linked to chromosome 7q11.2-q21.3(OMIM **%** 129900). It is part of "split hand foot malformation", a group of disorders including distal extremities in varying degrees.[1,3] Although symptoms may vary widely between patients, it most commonly presents with an absence of digits or anomaly in hand and foot (ectrodactyly, split hand/foot), cleft lip/palate, ectodermal dysplasia, anomalies of hair and sweat glands, as well as distinctive facial characteristics, ocular and urinary anomalies.[1,3]

Here, we presented 4 EEC patients diagnosed with clinical characteristics for their rarity and comorbid endocrine anomalies.

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CASE 1

A 6-years and 10 months old girl was the second live birth in the third pregnancy of a 31-years old mother. The birth weight was 3140 g. There was no consanguinity between parents. In the first examination at 13 months of age, weight was 4850 g (-5.3 SDS), and height was 67 cm (-3.3 SDS). In addition, there was a cleft lip and palate, low-set ear, flat nasal bridge, prominent frontal process, agenesis in the middle finger and metacarpal bone of the right hand, syndactyly between the fourth and fifth digits in the left hand, and bilateral total hearing loss. Pituitary hormone screening was performed due to the midline defect, T4 was 0.7 ng/dl (N:0,86-1,4), TSH was 0.4 µIU/mL (N:0,6-5,5 µIU/mL), revealing central hypothyroidism. MR imaging of the pituitary was as expected. In addition, echocardiography and abdominal sonography were also found to be as expected. The patient was diagnosed with EEC syndrome by phenotypic characteristics and was scheduled for a follow-up. In control visits at 2 years and 8 months of age, genital hair growth was observed in the physical examination. Bodyweight and height were 10 kg (-2.3 SDS) and 83 cm (-2.49 SDS), respectively. Thelarche and pubarche were rated as Tanner stages 1 and 2, respectively. The hormonal evaluation revealed the following results: ACTH, 20.3 pg/mL (normal range 10-60 pg/mL) and 17-hydroxyprogesterone, 14.1ng/mL (reference <2 ng/mL), cortisol was 15.5 µg/dl. Bone age was compatible with calendar age. The patient was diagnosed with non-classical congenital adrenal hyperplasia and prescribed hydrocortisone after genetic testing revealed Val281L homozygous mutation in exon 7 on CYP21A1. Informed consent was obtained from the patient's parents.

CASE 2

A 10-years and 5-month-old boy presented to the pediatrics outpatient clinic with micro-penis. He was referred to our clinic due to hypernatremia. In his medical history, it was found that his birth weight was 3000 and that he underwent surgery for cleft lip/palate at 8 months of age and bilateral cryptorchidism at one year of age. In addition, it was found out that he underwent columella and dentoalveolar surgery at 1 year of age. There was no consanguinity between parents. In physical examination, weight and height were 35.6 kg (50-70p) and 140.2 cm (50-75p), and mental development was normal. There were bilateral split hand deformity and syndactyly in two fingers on the right and two fingers and the fourth and fifth accessory fingers on the left. There was a scar from cleft lip/palate surgery on the face and a scar from cryptorchidism surgery on the bilateral inguinal regions. Penis length was within normal limits according to age (stretched penile length: 4.9 cm, normal was: >4.83 cm according to his age group), and testicles were within the scrotum but found to be atrophic (TV:<1 ml, normal was 2.67±0,98 ml according to his age) then verified with USG. Repeated sodium measurement was 153 mmol/L, whereas urine density was 1035, and urine output was calculated as 0.71 cc/kg/hour. The findings were consistent with adipsic hypernatremia, thus orally replacing the free fluid gap. The sodium level and urine density were normalized with increased urine output (the urine osmolarity device was faulty). In the hormonal assessment for pituitary causes, the patient was diagnosed with central adrenal insufficiency (ACTH was <15 pg/ml, cortisol was 2 µg/dl, and cortisol peak was 7 µg/dl in the IV ACTH test); thus, hydrocortisone was prescribed. The remaining

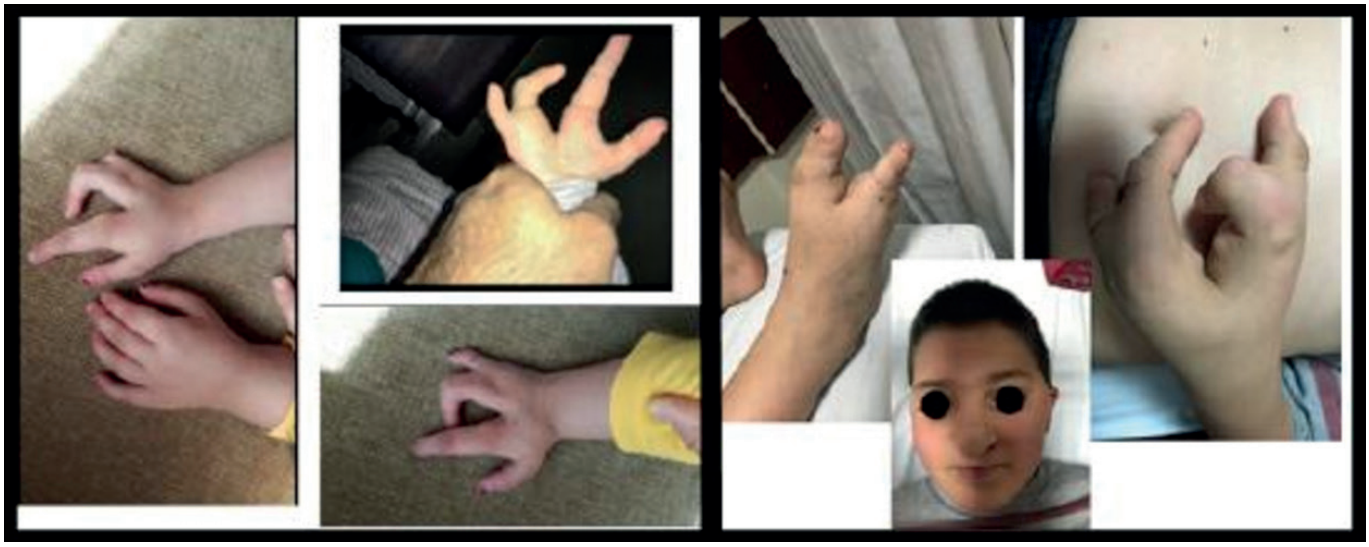

Figure 1. The photograph of case 1 is presented in the left box, and of case 2 is in the right box

pituitary hormones were found to be expected. The patient underwent a brain MRI due to central adrenal insufficiency and adipsic hypernatremia, revealing lobar holoprosencephaly. The consent form was obtained from the patient parents.

CASE 3

A 20-days old boy was referred to our clinic for further assessment of a midline defect. In his medical history, he was born from the first pregnancy of a 28-years old mother (birth weight: 2920 g) and admitted to the neonatal intensive care unit due to multiple malformations. In physical examination, his body weight and height were 2902 g (1.67 SDS) and 51 cm (-0.24 SDS), and his head circumference was 36 cm (-0.06 SDS). In addition, there was a cleft lip/palate, a split hand/foot anomaly, syndactyly at the fourth and fifth accessory fingers in both feet, a low-set ear, and a 1/6 systolic murmur along the left side of the sternum. No intracranial abnormality was detected on transfontanelle sonography, ostium secundum atrial septal defect (ASD) on echocardiography, and grade 1-to-2 pelvicalyceal ectasia in the left kidney on renal sonography. In the hormonal assessment of the hypothalamic-pituitary axis, the growth hormone level was 5.6 ng/ml(N:>7 ng/ml (4), indicating a low level for the neonatal period. No hypoglycemia, a finding of GH deficiency, was observed. A follow-up was scheduled for GH deficiency. Informed consent was obtained from the patient's parents.

CASE 4

The patient consulted our department for hypocalcemia, hypomagnesemia, decreased parathyroid hormone, and extremity anomalies on postnatal day 8. In the medical history, the patient was born from the fourth pregnancy of a 32-years old mother. The gestational age was 37 weeks at birth and the birth weight was 3630 g. The patient was admitted to the neonatal care unit due to multiple malformations. It was found that there was cerebellar hypoplasia in intracranial assessment, ureteropelvic stricture at left in renal assessment, and in cardiac evaluation double-outlet right ventricle and findings compatible with transposition of great vessels during the antenatal examination. In physical examination at presentation, weight was 3630 g (0.37 SDS), height was 46 cm (-1.86 SDS), and head circumference was 37 cm (1.43 SDS). There was a low-set ear, flat nasal bridge, split hand and foot deformity, 6 fingers in the right foot with syndactyly in the second and third fingers, syndactyly in the first and second fingers at the left foot, and pectus excavatum deformity. A clamp at the umbilicus and a single umbilical artery were observed in the umbilicus. In the cardiac examination, a marked 2/6 systolic murmur was recorded at the aortic region. In the genital examination, bilateral scrotal hypoplasia was observed and stretched penile length was measured to be 1.8 cm (normal was: 3.64±0.36 cm according to his age group). No gonad was detected in the right inguinal canal, and gonad-like tissue was detected in the left inguinal canal during palpation. There was facial asymmetry on the left side during crying. On transfontanelle assessment, the lateral ventricles were bilateral asymmetric and dilated, while the corpus callosum was thinner than expected. A subependymal cyst was observed at the level of the caudothalamic sulcus on the right. Based on a prenatal cardiac examination, findings compatible with double-aortic arch anomaly were detected on CT angiography. This finding was confirmed by a postnatal echocardiogram. The hepatic

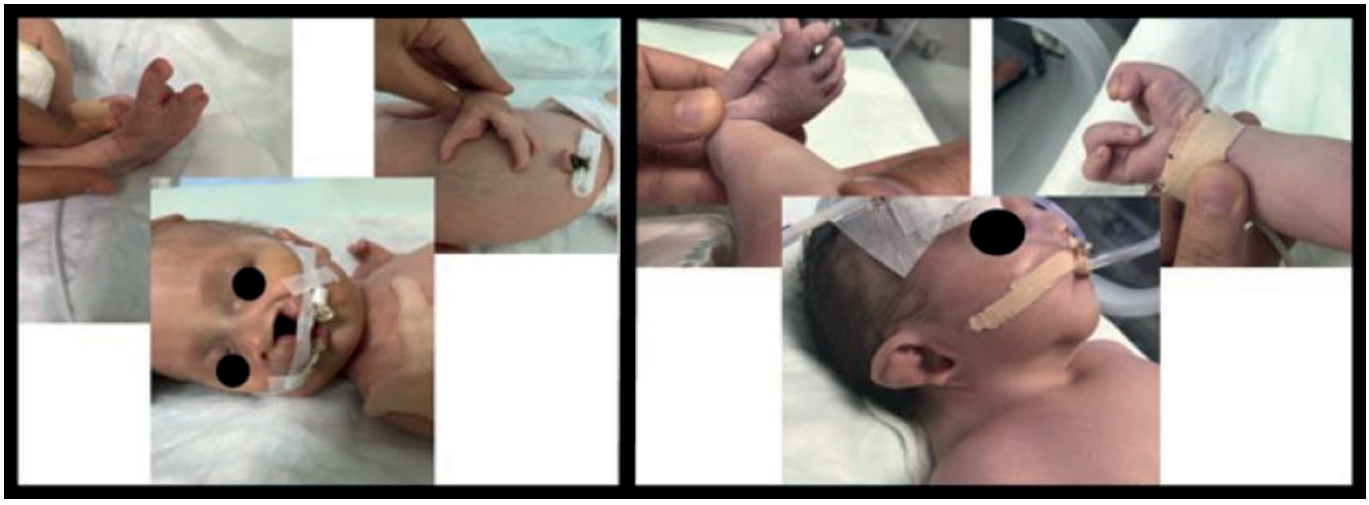

Figure 2. The photograph of case 3 is presented in the left box, and of case 4 is in the right box

artery branches were dilated and tortuous on abdominal sonography, while the renal assessment was regular. In the hormonal assessment for the hypothalamic-pituitary axis on day 15 of life, GH was 15 ng/ml. At the same time, LH, FSH, and total testosterone were <0.1 mIU/L(N:>0.3 mIU/L for mini puberty), 0.3mIU/L, and 31 ng/dL(N:70-400 ng/dL), respectively. It was found that mini puberty failed in the patient; thus, a follow-up was scheduled for hypogonadotropic hypogonadism. Informed consent was obtained from the patient's parents.

Table 1. Clinical features of cases

Features	Case 1	Case 2	Case 3	Case 4
Cleft lip	+	+	+	-
Cleft palate	+	+	+	-
Ectrodactyly	+	+	+	+
Syndactyly	+	+	+	+
Nail hypoplasia	-	-	-	+
Teeth defects	-	+	-	-
Genitourinary defects	-	+	+	+
Malformed auricles	-	+	-	+
Flat nasal tip	-	+	-	+
Micropenis	-	-	-	+
Cryptorchidism	-	+	-	+
Sparse eyebrows	+	-	+	+
Mental retardation	+	+	-	-
Semilobar holoprosencephaly	-	+	-	-
Growth hormone deficiency	-	-	+	-
Hypogonadotropic hypogonadism	-	-	-	+
Adipsic hypernatremia	-	+	-	-

DISCUSSION

The EEC is the most common split hand and foot deformity syndrome. Rudiger first described a girl with ectrodactyly in both hands and one foot, severe keratitis, ectodermal dysplasia, and cleft lip and palate deformity in 1970. Rudiger was also the first author to propose the acronym EEC. Similar findings were reported in a case by Cokayne in 1936. Although several studies have been carried out to elucidate EEC's genetic and clinical characteristics, it remains one of the rare syndromes. Findings related to the renal, cardiac, and other systems have been well-defined; however, the number of cases assessed by endocrine findings is relatively limited. Phenotypic characteristics were compatible with EEC syndrome in all cases presented here, and a detailed assessment was performed regarding endocrine disorders.

Ectrodactyly, also known as split hand-foot deformity, involves the hand and feet midline. Cleft lip, which is variably associated with cleft palate, is one of the fundamental findings seen in 68-100% of cases. Ectodermal dysplasia affects structures derived from embryonic ectoderms such as the epidermis, pituitary gland, hypothalamus, sweat glands, enamel, nail, lens, and ear, resulting in developmental defects. In addition, neuroectodermal and meso-ectodermal development defects are also common. The association of cleft lip/palate with ectrodactyly distinguishes EEC syndrome from other split hand and foot malformations.[2,3] Ectodermal dysplasia findings such as malformations of the ear and hair, dystrophic nails, and tooth anomalies are also present in 77% of patients with EEC syndrome.[4-6] Microcephaly and mental retardation were reported in 5-10% of EEC patients.[7,8] In addition to the classic triad of EEC, there was a dentoalveolar defect, prominent ear, and lobar holoprosencephaly detected by MRI in case 2, a low-set ear, and ear rotation anomaly in case 4. There was mental retardation in cases 1 and 2. However, there was no hair and nail defect in our patients.

Renal anomalies are also common structural changes in patients with EEC syndrome. Although it was previously considered a minor component, subsequent studies have shown that its incidence is underestimated. In 24 patients with EEC, Buss et al. found urinary anomalies such as glandular hypospadias, ureteral reflux, hydronephrosis, and decreased bladder volume in one-fourth of patients.[5,9-11] In addition, voiding problems such as dysuria or pain were present in family members of a patient with EEC, and abnormal bladder epithelization was detected in this family.[12] Among our cases, grade 1-to-2 pelvicalyceal ectasia was present in the left kidney in case 3. No other urinary problems were detected, but the parents were warned about voiding problems.

In patients with EEC, hormonal alterations may be present, mainly due to the involvement of the hypothalamic-pituitary axis. Firstly, Van Maldergem et al. reported a boy with hypogonadism. In subsequent reports, hypothalamic-pituitary disorders such as hypogonadotropic hypogonadism, pituitary hypoplasia, GH deficiency, and diabetes insipidus were reported.[11-16] Adipsic hypernatremia was reported as a hypothalamic pathology in only one case with EEC.[17] Among our cases, central hypothyroidism was detected in case 1, while

Table 2. The detailed clinical features of our study patients and review of the literature

	Buss et al. (1995) (n=24)	Bigatà et al. (2003) (n=5)	Maclean et al. (2007) (n=6)	Hatipoğlu et al. (2009) (n=2)	Alves et al. (2015) (n=2)	Augello et al. (2015) (n=2)	This Study (n=4)
Cleft lip	13	1	-	2	1	2	3
Cleft palate	11	3	1	2	1	2	3
Ectrodactyly	20	3	1	2	2	2	4
Syndactyly	7	2	1	1	-	1	4
Nail hypoplasia	19	3	1	1	2	1	1
Teeth defects	24	5	4	-	1	-	1
Genitourinary defects	6	1	5	2	-	-	3
Malformed auricles	-	1	3	1	-	-	2
Flat nasal tip	-	-	2	-	2	2	2
Micropenis	-	-	-	2	-	-	1
Cryptorchidism	-	1	-	2	-	-	2
Sparse eyebrows	-	-	1	-	2	-	3
Mental retardation	-	-	-	-	-	-	2
Semilobar holoprosencephaly	-	-	-	-	-	-	1
Growth hormone deficiency	-	-	1	1	-	-	1
Hypogonadotropic hypogonadism	-	-	-	2	-	-	1
Adipsic hypernatremia	-	-	-	1	-	-	1

central adrenal insufficiency and adipsic hypernatremia were detected in case 2. Moreover, GH deficiency was detected in case 3, while a follow-up for hypogonadism was scheduled in case 4. The central hypothyroidism in case 1 and the central adrenal insufficiency in case 2 were secondary to the brain abnormality and are expected but rare hormonal disorders.

Interestingly, congenital adrenal hyperplasia was detected during evaluations for premature pubarche at 3 years of age in case 1. To the best of our knowledge, there is no case report on the association of EEC and congenital adrenal hyperplasia. There are 2 forms of congenital adrenal hyperplasia inherited in an autosomal recessive manner: classical and non-classical. The classical form includes a life-threatening salt-wasting type and a simple-virilizing type causing ambiguous genitalia. This form shows a delayed onset of symptoms and is seen in 1: 13,000-1: 15,000 live births. The non-classical form is more prevalent than the other.[18,19] The non-classical form can either be asymptomatic or present with premature pubarche, hirsutism, menstrual disorders, and infertility. Although the actual frequency is unknown, it is not surprising that non-classical congenital adrenal hyperplasia is more common than expected in our Turkish community due to the frequency of consanguinity.[20] The non-classical congenital adrenal hyperplasia detected as an endocrine pathology in our EEC patient was considered a co-incidence due to its higher prevalence in the population since there seems to be no genetic association between these entities.

As our cases show, EEC syndrome involving many symptoms can present with a broad spectrum of clinical manifestations. The EEC syndrome should be kept in mind in cases with ectrodactyly and cleft lip/palate, and comprehensive evaluations, including water metabolism, should be undertaken regarding the hypothalamic-pituitary in particular. Diagnosing secondary adrenal insufficiency, which can be life-threatening, water metabolism disorders, and GH deficiency is essential. Moreover, other congenital endocrine problems, such as congenital adrenal hyperplasia, should be considered in these patients.

Ethical approval

Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: GT, ÜGŞ, ZUT, MNH, LA, NH, TG; Concept: GT, ÜGŞ, ZUT, MNH, LA, NH; Design: GT, ÜGŞ, ZUT, MNH, LA, NH; Data Collection or Processing: GT, ÜGŞ, ZUT, MNH, LA, NH, TG; Analysis or Interpretation: GT, ÜGŞ, ZUT, MNH, LA, NH, TG; Literature Search: GT, ÜGŞ, ZUT, MNH, LA, NH, TG; Writing: GT, ÜGŞ, ZUT, MNH, LA, NH, TG. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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