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Original Article

Comparison of Parenteral Maintenance Isotonic and Hypotonic Fluid Therapies administered to Hospitalized Children In Terms of Hyponatremia Risk

Hastenede Yatan Çocuklarda Parenteral İdame İzotonik ve Hipotonik Sıvıların Hiponatremi Riski Açısından Karşılaştırılması

Nur Çalışkan, Esma Altınel Açoğlu, Fatma Zehra Öztek Çelebi, Melahat Melek Oğuz

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ABSTRACT

Objective: Isotonic fluids are recommended for parenteral maintenance fluid therapy because they reduce morbidity and mortality due to iatrogenic hyponatremia in children. However, there is still an ongoing debate regarding the ideal fluid therapy to be used in children. This study aims to provide insight into the development of hyponatremia in patients using hypotonic and isotonic fluids for maintenance and the comparative effects of these fluid regimens.

Method: The study included hospitalized patients aged 1 to 83 months between January 2021 and June 2022, with normal serum sodium levels and given maintenance fluid therapy. Patients were categorized into three maintenance fluid groups: 0.3% saline (0.3% saline in 3.3% dextrose), 0.45% saline (0.45% saline in 5% dextrose), and normal saline (0.9% saline in 5% dextrose). The groups were further stratified based on control sodium level measurement times (8-16 hours, 17-32 hours, and 33-48 hours), and data were compared with baseline sodium levels.

Results: The study involved 215 patients aged 1-83 months. There was no significant difference between the groups in terms of initial serum sodium levels. However, comparing control sodium levels revealed significant distinctions between each group (respectively, 0.3% saline and 0.45% saline groups (p=0.009), 0.45% saline and normal saline (p=0.003), 0.3% saline and normal saline groups (p<0,001). Significantly, the difference between baseline and control sodium values varied across fluid groups (p<0.001). Treatment duration did not impact the sodium level change.

Conclusion: Using hypotonic fluids in pediatric maintenance fluid therapy elevates the risk of hospital-acquired hyponatremia. Opting for isotonic fluids in parenteral maintenance therapy is safer.

Keywords: Child, hyponatremia, maintenance fluid, isotonic, hypotonic

ÖZ

Amaç: Çocuklarda izotonik sıvıların daha yaygın kullanımının iyatrojenik hiponatremiye bağlı morbidite ve mortaliteyi azaltacağı düşünülmektedir. Ancak çocuklarda kullanılacak ideal sıvı tedavisine ilişkin tartışmalar halen devam etmektedir. Bu çalışmada idame tedavide kullanılan hipotonik ve izotonik sıvıların hiponatremi riski açısından karşılaştırılması amaçlanmıştır.

Yöntem: Çalışmaya Ocak 2021 ve Haziran 2022 tarihleri arasında hastanede yatırılarak izlenen ve yatışı sırasında serum Sodyum düzeyi normal saptanan, 1 ay-83 ay arası hastalar dahil edildi. Hastalar idame sıvı içeriğine göre, %0,3 salin (%3,3 dekstrozda %0,3 salin), %0,45 salin (%5 dekstrozda %0,45 salin) ve normal salin (%5 dekstrozda %0,9 salin) olmak üzere üç gruba ayrıldı. Gruplar, kontrol sodyum seviyesi ölçüm sürelerine göre (8-16 saat, 17-32 saat ve 33-48 saat) gruplandırıldı ve veriler başlangıçtaki sodyum seviyeleriyle karşılaştırıldı.

Bulgular: Çalışmaya 1-83 ay arası 215 hasta dahil edildi. Hastalar aldıkları mayilere göre başlangıç sodyum düzeyi açısından karşılaştırılmış ve gruplar arasında anlamlı fark saptanmamıştır. Ancak kontrol sodyum düzeyleri karşılaştırıldığında her grup arasında anlamlı fark saptanmıştır. Sırasıyla; %0,3 salin ve %0,45 salin grupları (p=0,009), %0,45 salin ve normal salin grupları (p=0,003), %0,3 salin ve normal salin grupları (p<0,001). Hastalar, aldıkları mayilere göre başlangıç ve kontrol sodyum değerleri arasındaki fark açısından karşılaştırıldığında üç grup arasında anlamlı fark olduğu görülmüştür (p<0,001). Kontrol sodyum alınma saatinin sodyum düzeyindeki değişimi etkilemediği görülmüştür.

Sonuç: Çocuk hastalarda idame sıvı tedavisinde hipotonik sıvılar kullanıldığında hastane kaynaklı hiponatremi riski artmaktadır. Parenteral idame sıvı tedavisinde izotonik sıvıların kullanımı hiponatremi riski açısından daha güvenlidir.

Anahtar kelimeler: Çocuk, hiponatremi, idame sıvı, izotonik, hipotonik

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INTRODUCTION

Children's daily dietary, hydration, and electrolyte requirements change. Due to increased fluid loss and decreased nutrition and fluid intake, infants are more susceptible to developing dehydration quickly. However, because of age-related increases in the efficiency of compensatory systems such as water and electrolyte absorption and excretion, signs of fluid loss in older children may become manifest 12-18 hours after onset of severe dehydration[1]. Parenteral replacement of fluids and electrolytes becomes a crucial component of treatment when infections, surgical complications, or risks associated with oral intake prevent enteral feeding[2]. The most frequent electrolyte imbalance among these individuals is hyponatremia[3-5]. Hyponatremia may develop due to increased water retention with antidiuretic hormone (ADH) release, which may also be triggered by conditions such as pain and stress. It is recommended to avoid hypotonic solutions to prevent development of neurologic complications that may occur in these patient groups who should be especially careful in terms of the risk of hyponatremia[6,7]. Until recently, hypotonic fluids such as 0.3% and 0.45% saline solutions were frequently used as maintenance fluids in children. In recent years, many studies have been published showing that the use of hypotonic solutions as maintenance fluids in children increases the risk of hyponatremia, which decreases with the use of isotonic fluids. In 2018, the American Academy of Pediatrics (AAP) published a guideline with evidence-based recommendations for the treatment of pediatric patients who need maintenance fluid therapy[2]. Isotonic fluids containing 5% dextrose and 0.9% sodium chloride are recommended as daily maintenance fluid therapy in children between 28 days and 18 years of age, except for patients with congenital or acquired heart disease, renal disease, liver disease, central nervous system disease, diabetes insipidus, cancer, and severe burns[1,2]. Increased usage of isotonic fluids for maintenance is advised by recent studies. However, few clinical studies in our country have examined the effects of maintenance fluid therapies on blood sodium (Na) levels, which may be associated with the continued use of hypotonic solutions in many centers. This study aims to evaluate the impact of maintenance fluid therapies using hypotonic and isotonic solutions on the incidence of hyponatremia in hospitalized children.

MATERIALS and METHODS

This prospective, single-blind, randomized, controlled clinical study, which included 215 patients aged 1 to 83 months hospitalized in pediatric inpatient wards between January 2021 and June 2022, was conducted in our tertiary referral center after obtaining approval from the Clinical Research Ethics Committee of University of Health Sciences Turkey, Ankara Dr. Sami Ulus Maternity, Child Health and Diseases Training and Research Hospital (approval number: 2020-021, dated: 02.12.2020). Patients with symptoms such as diarrhea and vomiting that may affect fluid-electrolyte balance, patients with serum Na levels outside the normal limits during hospitalization, patients requiring deficit fluid therapy due to dehydration, and patients with chronic diseases that may progress to Na and water balance disorders were excluded from the study. A wide range of patients including those with drug intoxication, lower respiratory tract infection, abdominal pain, urinary tract infection, aphthous stomatitis, gastrointestinal bleeding, immune thrombocytopenic purpura, and anemia were enrolled in the study. Daily parenteral maintenance fluid requirements were calculated according to the Holliday Segar formula[1]. A total of 215 patients included in the study were divided into three groups according to maintenance fluid therapy they received as follows: 0.3% saline (0.3% saline in 3.3% dextrose) (n=69); 0.45% saline (0.45% saline in 5% dextrose) (n=72) and normal saline (0.9% saline in 5% dextrose) (n=74) (Table 1). The majority of the patients were those who were unable to consume sufficient oral nutrition during the first days of hospitalization or had their oral intake restricted due to potential complications. Serum Na levels <135 mmol/L and >145 mmol/L were accepted as criteria for hypo-and hypernatremia, respectively[5]. Based on serum Na levels, hyponatremia was defined as mild (135-130 mEq/L), moderate (130-125 mEq/L), and

Table 1. Distribution of fluid treatment contents by age groups

Age groups (months)	0.3% saline (n)	0.45% saline (n)	Normal saline (n)	Total (n)
1-24	**44**	25	38	107
25-60	20	40	34	94
61-83	5	7	2	14
Total	**69**	**72**	**74**	215

severe (<125 mEq/L) hyponatremia[5]. Serum Na levels of the patients were checked at 8-16, 17-32, and 33-48 hours after administration of different concentrations of maintenance fluids to evaluate their effects on serum Na levels. In the study the first control serum Na level of each patient measured after the initiation of maintenance fluid therapy was compared with the baseline Na level. The patients were divided into three age groups as follows: 1-24 months (n=107), 25-60 months (n=94), and 61-83 months (n=14). Table 1 shows the fluid contents received by the patients in these three age groups. In each patient group, initial and control serum Na levels were compared. Informed consent forms were obtained from the parents of the patients, and principles of confidentiality were maintained by the investigators. Age, gender, clinical findings, and serum Na levels of the patients were recorded. Serum Na levels were quantified by the ion-selective analyzer method using a Beckman Coulter brand AU5800 model biochemistry autoanalyzer and Beckman Coulter brand kits after blood samples were centrifuged at 4000 rpm for 10 minutes.

Statistical Analysis

The research data were evaluated using the SPSS, version 22.0. Descriptive statistics were expressed as standard deviation, numbers, percentages, ratios, median, and mean values. Mean ± standard deviation and median (minimum-maximum) values were used for quantitative variables, and numbers (percentages) for qualitative variables. Whether there was a statistically significant difference between the categories of the qualitative variable with two categories for the quantitative variable was examined using the Student's t-test, independent sample t-test, and dependent sample t-test if the assumptions of normal distribution were met. For the quantitative variables, if the assumptions of normal distribution were met, the One-Way ANOVA test was used to determine whether there was a statistically significant difference between the categories of the qualitative variable with more than two categories. A post-hoc test was used to check whether there was a significant difference between the two categories. The chi-square test was used to examine the relationship between two qualitative variables. The statistical significance level of the p-value was considered to be below 0.05.

RESULTS

The study included a total of 215 patients aged between 1 and 83 months (median age:25 months), and 58.1% of them were male. Patients were divided into 0.3% saline (n=69:32.1%), 0.45% saline (n=72:33.5%), and normal saline (n=74:34.4%) according to the concentration of Na they received for their fluid therapies The incidence of hyponatremia among patients receiving three fluid therapies with 0.3% saline, 0.45% saline, or normal saline was 37%, 16%, and 1%, respectively. In the study, two of the 42 patients with hyponatremia had moderate, and 40 cases had mild hyponatremia. No patient had severe hyponatremia. The data obtained by comparing the baseline and control Na values of all patients according to the fluid therapies they received are shown in Table 2. No significant difference was found between the groups when patients were compared in terms of the baseline Na levels. While control Na levels were significantly different between groups in the (0.3% saline vs 0.45% saline groups (p=0.009), 0.45% saline vs normal saline (p=0.003), 0.3% saline vs normal saline groups (p<0,001) (Figure 1, Table 3). The timing of measurements of control Na levels varied due to several factors, including the fact that all control blood samples were collected by our team, the clinical condition of the patient influencing the timing of sample collection, patient density in the clinic, and early termination of fluid replacement therapies before 24 hours. The serum Na level was measured at an average of 21 hours after admission. The median time for control blood collection was 22.4 hours, ranging from a minimum of 8 hours to a maximum of 48 hours after patient's referral. Control Na levels were measured between 8-16 (n=73:33%), 17-32 [n=124: (57%) 33-48 (n=17:7%] hours after their admission to the clinic. It was observed that the timing of control Na sampling did not significantly affect changes in Na levels. The patients

Table 2. Baseline and control Na^{++} values of the patients according to the fluid they received

Fluid contents	Mean baseline Na^{++} level (meq/L)*	p-value**	Mean control Na^{++} level (meq/L)*	p-value**
0.3% saline (n=69)	137.38±2.08	0.769	135.36±2.42	**0.03001**
0.45% saline (n=72)	137.21±1.92		136.5±2.27	
Normal saline (n=74)	137.1±1.50		137.74±2.13	

*: Mean ± standard deviation, **: ANOVA, Na: Sodium

were divided into three groups according to age: 1-24 months (n=107), 25-60 months (n=94), and 61-83 months (n=14). Since the majority of cases in the study were in the 1-24 month age group, the data for this group were analyzed in greater detail. No significant difference was found between hospitalization and control serum Na levels according to age groups. When the patient group aged 1-24 months was compared in terms of baseline and control Na levels, no difference was found between the groups receiving 0.3% saline and 0.45% saline treatments (p=0.422), and the control Na level of the group receiving normal saline was significantly higher than the other two groups (p=0.018, p<0.001, respectively). Patients aged between 1 and 24 months were also compared by dividing them into 2 groups as patients who did and did not receive normal saline concentration. There was no significant difference between the baseline Na values of both groups. The control Na values of the group that did not receive normal saline concentration were found to be significantly lower than the group that did (p<0.001). In the comparison of the difference between the baseline and control Na values of the patients aged 1-24 months according to the fluid therapy groups, a significant difference was observed between these three groups (p<0.001). In the post hoc analysis, it was observed that the difference between the baseline and control Na values of the group receiving 0.3% saline solution was higher than those of the groups receiving 0.45% saline or normal saline (p=0.007, p<0.001, respectively) (Table 4). Patients between the ages of 25 and 60 months were divided into normal saline, 0.45% saline and 0.3% saline groups. Baseline Na concentrations of the groups' were similar. Albeit the presence of a borderline intergroup significance (p=0.052) mean control Na levels did not differ significantly between groups of patients receiving 0.45% saline vs isotonic fluid therapy. Also

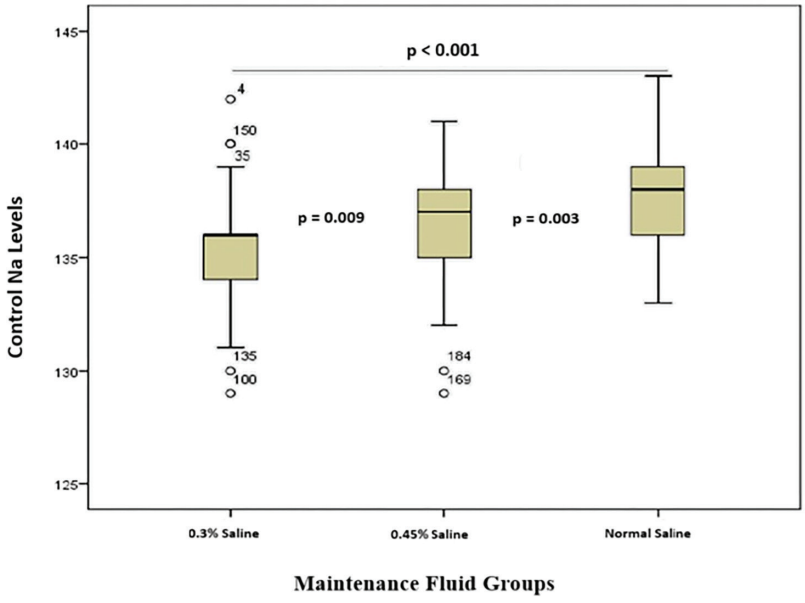

Figure 1. Comparison of baseline and control sodium levels according to fluid contents

Table 3. Comparison of baseline and control sodium values according to fluid therapies used

Fluid contents	Mean baseline Na level (meq/L)*		p-value**	Mean control Na level (meq/L)*		p-value**
0.3% saline-0.45% saline	137.38±2.08	137.21±1.92	0.851	135.36±2.4	136.5±2.27	**0.009**
0.45% saline-normal saline	137.21±1.92	137.1±1.50	0.988	136.5±2.27	137.74±2.13	**0.003**
0.3% saline-normal saline	137.1±1.50	137.38±2.08	0.768	137.74±2.13	135.36±2.42	**<0.001**

*: Mean ± standard deviation, **: ANOVA post-hoc analysis, Na: Sodium

Table 4. Comparison of control sodium levels in patients aged 1 to 24 months according to fluid therapy groups				
Fluid contents	**Baseline Na[44] level* (mg/dL)**	**Control Na level* (mg/dL)**	**Difference between baseline and control Na values**	**p-value**
0.3% saline (n=44)	137.66±2.3	135.55±2.5	-2.1136	**<0.001**
0.45% saline (n=25	136.4±1.0	136.24±1.6	-0.1600	
Normal saline (n=38)	137.05±1.5	137.82±2.0	-0.7632	
*: Mean ± standard deviation, **: Post-hoc analysis, Na: Sodium				

no discernible difference was noted in baseline serum Na concentrations of patients receiving 0.3% vs 0.45% saline solutions. Significantly lower control Na values were noted in other groups compared to the isotonic group (p=0.000).

DISCUSSION

In the literature the incidence of hospital-acquired hyponatremia varies between 15% and 42%[2,9,11]. Numerous factors, such as pulmonary system pathologies, central nervous system infections, and surgical procedures trigger non-osmotic ADH release in pediatric patients, resulting in increased water retention and hyponatremia. Due to the relatively larger brain tissue occupied in the cranial cavity of the children compared to adults, the risk of symptomatic hyponatremia and the neurological complications like seizures and cerebral edema is elevated. Thus, the authors recommend using isotonic fluids as a crucial measure to prevent hospital-acquired hyponatremia[13]. Holiday and Segar noted that hypotonic fluid treatments, used for acutely ill children, could cause hyponatremia, particularly with potential risk of overhydration, and suggested use of protocols involving isotonic fluids. However, they also acknowledged that isotonic fluids might raise the risk of hypernatremia[14].

Many recent studies have shown that hypotonic fluids administered as daily maintenance fluid therapy may cause iatrogenic hyponatremia and the use of isotonic fluids is effective in preventing the development of mild or moderate hyponatremia[5,8,9-12] in their study conducted in 2003, Moritz and Ayus[13] examined more than 50 cases of hospital-acquired hyponatremia resulting in morbidity and mortality, especially related to the neurological system.

The present study has clearly shown that the patients in the 1/3 saline group had noticeably lower control Na levels than the normal saline group. The study has also demonstrated that the incidence of hyponatremia considerably increased when three fluid therapies with lower Na concentrations were used Choong et al.[9] followed up their patients postoperatively after their discharge from intensive care unit, and detected the incidence rate of 42%, for the hospital-acquired hyponatremia while Carandang et al.[11] reported its incidence as 34.7%. In our study, the frequency of hyponatremia was determined to be 19%. The group that received 1/3 saline treatment had the highest frequency of hyponatremia (37%), whereas the group receiving normal saline with 5% dextrose had a significantly lower rate of hyponatremia (1%). We have observed that as the Na content of the three fluids used decreases, the incidence of hyponatremia significantly increases. A Finland study conducted in 2021 assessed severe cases f hospital-acquired hyponatremia in children. They evaluated 46.518 children under 15 years of age who presented to the emergency departments over a decade. Findings revealed that 7 out of 6.984 patients receiving maintenance fluid therapy developed severe hyponatremia, with two of them displaying neurological symptoms, suggesting that the severe hyponatremia was present in approximately one in every 998 acute pediatric patients receiving moderately hypotonic fluid therapy. Excluding high-risk patient groups in the study may have lowered the complication rates, and larger patient groups could pose a higher risk of complications and severe hyponatremia[15]. When reviewing relevant studies in the literature, it was observed that the sample size, the number of control groups, the characteristics of the patient population, and the duration of treatment vary among studies. In our study, a significant portion of the patient population consisted of those admitted to the general pediatric service with conditions such as pneumonia, bronchiolitis, seizures, and suspected drug ingestion. The study excluded children with congenital or acquired heart diseases, malnutrition, malabsorption,

diarrhea, vomiting, chronic kidney or liver disease, diabetes mellitus, diabetes insipidus, and diuretic users. Consequently, the frequency of hyponatremia may be lower in our study compared to other publications. The baseline serum Na levels in the three fluid therapy groups were similar, with an approximate mean value of 137 mEq/L. However, the post-fluid treatment control Na levels were notably different, with 135.36 mEq/L in the 1/3 saline, 136.5 mEq/L in the 1/2 saline, and 137.74 mEq/L in the normal saline groups with statistically significant differences among groups ($p<0.001$). The timing of control sample collection did not significantly affect fluctuations in serum Na levels. Although the difference in post-treatment serum Na levels among three groups was statistically but not clinically significant, The mean Na levels in all groups remained within their normal physiological ranges, and patients did not exhibit symptoms of hyponatremia or hypernatremia. Therefore, while the results support the preference for isotonic fluids in preventing hyponatremia, the clinical impact of these differences on serum Na levels remains minimal. However, it should be noted that the difference in sodium levels may be more pronounced and clinically significant in patients who require parenteral fluid therapy for longer durations. Carandanget al.[11] conducted the longest serum Na monitoring study in the literature, extending to 7 days, and reported a 34.7% incidence for hospital-acquired hyponatremia. In a Mexican study comparing fluid therapies in patients aged 3 months to 15 years, control serum Na levels were measured at the postprocedural 8th hour. Results showed that patients receiving hypotonic fluids had lower serum Na levels, with values of 134.65 mEq/L in the 1/3 saline and 134.90 mEq/L in the 1/2 saline groups, while those in the isotonic saline group had serum Na levels of 137.98 mEq/L[16]. In a study published in The Lancet in 2015 by McNab et al.[17], similar to our study, the use of isotonic saline was found to reduce the risk of hyponatremia. According to a study conducted by Bagri et al.[18] in India in 2019, 75 patients who received 1/2 normal saline were compared with 75 patients who received isotonic saline solutions. The 24-hour control Na levels in the isotonic saline group were significantly higher than those in the hypotonic saline group (mean values: 135.1 mEq/L, vs. 138.3 mEq/L)[18]. In a 2019 study conducted by Torres et al.[19] in Argentina, 294 patients aged 29 days to 15 years were divided into two groups as those receiving 1/2 normal saline vs. isotonic saline treatment. After 24 hours, the isotonic saline group had significantly higher serum Na levels (139.3±3.1 mEq/L) compared to the hypotonic saline group (134.4±5.6 mEq/L). This research highlighted the fact that children under one year of age receiving hypotonic fluid therapy are at higher risk for hyponatremia due to various factors such as body surface area-to-weight ratio and fluid requirements[19]. Therefore, our study separately assessed patients under two years regarding hyponatremia, and comparable data were obtained when our study group was compared with the other study groups in terms of risk of hypothermia. In a study comparing hypotonic and isotonic solutions used for fluid therapy in patients with gastroenteritis, Neville et al.[20] reported that hyponatremia was more prevalent in the hypotonic saline group after a four-hour follow-up. In another study by the same researchers, dehydration, vomiting, and stress were identified as major stimulants of ADH release. It was also reported that patients receiving hypotonic saline for four hours or longer had 29% higher plasma ADH levels. All of these factors can contribute to dilutional hyponatremia[21]. More comprehensive research is needed on this subject. In a study led by Kumar et al.[22], 168 patients aged 3 months to 5 years admitted to the general pediatric service were equally distributed into two groups as those receiving 1/2 normal or isotonic saline), and their serum Na levels were monitored at 12 and 24 hours. After 12 hours, no significant difference was found between the fluid therapy groups. Regarding incidence of hyponatremia. However, at 24 hours, patients in the isotonic saline group had significantly higher serum Na levels. The study noted a lack of data on simultaneous oral fluid intake and excessive hydration in patients[22]. It should be noted that factors like these can lead to different results in studies. In our study, hypernatremia was examined as a secondary variable,and levels above 145 mg/dL were considered evidence of hypernatremia. One of the concerns in the use of isotonic parenteral maintenance fluid therapy in children is the possibility of developing hypernatremia. In another study, patients who received 0.45% saline and normal saline were compared based on their serum Na values measured at 24 and 48 hours[23]. In this study, no patients experienced hypernatremia[13]. In the current study, remarkably, none of the patients developed hypernatremia, including the group with serum Na controls at 33-48 hours after receiving fluid therapy. It's essential to acknowledge that longer- term or larger-scale studies may yield different findings regarding hypernatremia. To obtain reliable information on how many days after maintenance fluid therapy there is a risk of developing hypernatremia, serum Na levels should be examined in a larger number of patients that require maintenance fluid therapy for a longer time

period. Although the recommendations in the current literature and AAP recommendations are very clear, pediatricians may not always prefer isotonic fluids. In a survey study in 2020, it was reported that the rate of using isotonic fluid increased as the age of the patient increased[24]. According to a study conducted in the United States, after the training given to clinicians in line with the recommendations of the AAP, the rate of isotonic fluid use increased from 63% to 95% within 9 months[25]. This highlights the importance of training in raising awareness among pediatricians.

Study Limitations

Among the limitations of our study is the lack of data on patients' serum ADH levels, urine osmolality, body weights before, and after fluid therapy. Although these data could have been useful in excluding overhydration, these risks could be observed equally in all groups. Due to the principles of the minimally invasive approach in pediatric patients, unnecessary tests are avoided, and detailed analysis cannot always be conducted. In addition, our study was conducted in a single center. Serum Na levels were mostly measured within the first 24 hours after initiation of fluid therapy. However the incidence of hyponatremia when hypotonic fluids were used was statistically, but not clinically significant. A more comprehensive risk assessment for hyponatremia can be conducted in multicenter studies with larger sample sizes and with patients receiving long-term maintenance fluid therapy.

CONCLUSION

In our country, there are not enough clinical studies on the effect of maintenance fluid content on serum Na levels, and hypotonic fluids continue to be used in many centers. This study highlights any potential risks connected to using hypotonic fluids. It promotes a switch to isotonic solutions to reduce the risk of hyponatremia, emphasizing the need for additional research and physician education.

Ethics

Ethics Committee Approval: This prospective study was conducted in our tertiary referral center after obtaining approval from the Clinical Research Ethics Committee of University of Health Sciences Turkey Ankara Dr. Sami Ulus Maternity, Child Health and Diseases Training and Research Hospital (approval number: 2020-021, date: 02.12.2020).

Informed Consent: Informed consent forms were obtained from the parents of the patients, and principles of confidentiality were maintained by the investigators.

Footnotes

Author Contributions

Surgical and Medical Practices: N.Ç., E.A.A., F.Z.Ö.Ç., M.M.O., Concept: N.Ç., E.A.A., Design: N.Ç., E.A.A., Data Collection or Processing: N.Ç., E.A.A., F.Z.Ö.Ç., M.M.O., Analysis or Interpretation: N.Ç., E.A.A., F.Z.Ö.Ç., M.M.O, Literature Search: N.Ç, E.A.A., Writing: N.Ç., E.A.A.

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Original Article

Evaluation of Oral and Dental Health Findings in Children with Hemophilia

Hemofili Hastası Çocuklarda Ağız ve Diş Sağlığı Bulgularının Değerlendirilmesi

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ABSTRACT

Objective: This study aims to compare the dental caries, plaque accumulation, gingival health, and oral hygiene habits of children with hemophilia to those of systemically healthy children of the same age group.

Method: Our study consists of a study group of 54 male children with hemophilia, with a mean age of 7.80±3.18 years, and a control group of 55 healthy male children, with a mean age of 8.20±2.63 years. A case report form was used to assess patients' demographics, medical and dental history, and oral hygiene habits. In addition to an intraoral examination, data related to oral hygiene, including caries indices [decayed, missing, filled teeth (DMFT/dmft) gingival index (GI), and plaque index (PI), were recorded in the case report form.

Results: The dmft score of the control group was found to be significantly higher than that of the study group. However, the DMFT score did not show a significant difference between the groups. The GI score did not exhibit a significant difference between the groups either. The PI score of the control group was found to be significantly higher than that of the study group. No significant difference was observed between the two groups in terms of oral hygiene habits.

Conclusion: Children with hemophilia are a special patient group at risk in terms of oral and dental health. Awareness should be raised among patients and their parents to ensure preventive dental treatments and regular dental check-ups from an early age.

Keywords: Hemophilia, oral hygiene, DMFT/dmft index, gingival index, plaque index

ÖZ

Amaç: Bu çalışmada, hemofili hastası çocukların diş çürüğü, plak birikimi, diş eti sağlığı ve oral hijyen alışkanlıklarının yaş grubu ile uyumlu sistemik olarak sağlıklı çocuklarla karşılaştırılması hedeflenmiştir.

Yöntem: Çalışmamız, yaş ortalaması 7,80±3,18 olan 54 hemofili hastası erkek çocuk hastadan oluşan çalışma grubu ve yaş ortalaması 8,20±2,63 olan sağlıklı 55 erkek çocuktan oluşan kontrol grubundan oluşmaktadır. Hastaların demografik özelliklerini, tıbbi ve dental geçmişlerini ve ağız hijyeni alışkanlıklarını değerlendirmek için bir olgu rapor formu kullanılmıştır. Ağız içi muayene ile birlikte olgu rapor formunda yer alan ağız hijyeni ile ilişkili çürük indeksleri [daimi dişlerde çürük, eksik ve dolgulu diş sayısı (DMFT/dmft)], dişeti indeksi (GI) ve plak indeksi (PI) verileri kaydedilmiştir.

Bulgular: Kontrol grubu dmft skoru, çalışma grubuna göre anlamlı düzeyde yüksek bulunmuştur. DMFT skorunun ise gruplara göre anlamlı farklılık göstermediği tespit edilmiştir. GI skoru gruplara göre istatistiksel olarak anlamlı farklılık göstermemiştir. Kontrol grubu PI skoru, çalışma grubu PI skoruna göre anlamlı düzeyde daha yüksek tespit edilmiştir. Oral hijyen alışkanlıkları açısından iki grup arasında anlamlı bir fark bulunmamıştır.

Sonuç: Hemofili hastalığına sahip çocuklar ağız ve diş sağlığı açısından risk altında olan özel hasta grubundadır. Erken yaşlardan itibaren koruyucu diş tedavileri ve düzenli diş hekimi kontrollerinin sağlanması amacıyla hastalar ve ebeveynlerinde farkındalık oluşturulmalıdır.

Anahtar kelimeler: Hemofili, oral hijyen, DMFT/dmft indeksi, gingival indeks, plak indeksi

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INTRODUCTION

Hemophilia is a congenital bleeding disorder caused by a deficiency of coagulation Factor VIII or Factor IX, and follows an X-linked recessive inheritance pattern. The deficiency results from mutations in the genes encoding the respective coagulation factors[1]. Individuals affected by hemophilia exhibit a lifelong predisposition to bleeding due to the failure of secondary hemostasis, with the severity of the disorder correlating with the extent of deficiency in the specific coagulation factor[2]. A family history of bleeding is identified in approximately two-thirds of all patients. Hemophilia A is significantly more common than hemophilia B, with estimates suggesting that hemophilia A accounts for 80-85%, while hemophilia B constitutes approximately 15-20% of all hemophilia cases[3].

Oral and dental health constitute integral part of overall health. Throughout both childhood and adulthood, oral and dental health can be directly affected by various systemic diseases that impact other bodily systems and may also negatively influence general health state[4]. Since the oral cavity is one of the highly vascularized regions prone to frequent bleeding in individuals with hemophilia, it is crucial for dentists to have adequate knowledge in oral and dental care in order to play a role in early diagnosis, administer appropriate dental treatments, and prevent potential complications [5,6]. Patients with bleeding disorders may neglect oral and dental care due to their low levels of education, difficulties in affording for factor concentrates or fear of bleeding during dental procedures or tooth brushing[7].

Although individuals with hemophilia do not constitute a large proportion of the population, their dental treatments are often challenging, very risky, and costly, as they may require factor supplementation prior to procedures[8]. Therefore, after the diagnosis of hemophilia is established, it is crucial to educate families about regular dental check-ups, oral hygiene practices, and preventive dental treatments. Early-stage awareness and preventive approaches play a critical role in reducing the need for more invasive and complex treatments in the future, thereby enhancing the patients' quality of life and preventing high treatment costs[1,9-11].

The aim of our study is to compare the oral health findings of children with hemophilia to those of systemically healthy children of the same age group. Additionally, the study aims to raise an awareness about the importance of establishing the foundations of healthy and proper oral hygiene at an early age for children with hemophilia, as is the case for all children with special medical conditions.

MATERIALS and METHODS

The study group of our research consisted of children aged 2-13 years diagnosed,and followed up with hemophilia at the Ege University Department of Pediatrics, Division of Pediatric Hematology and Oncology, Faculty of Medicine, as well as children with hemophilia aged 2-13 years who applied for a general examination at the Ege University Department of Pedodontics, Faculty of Dentistry, located in İzmir and surrounding provinces. The control group consisted of healthy children aged 2-13 years without any systemic disease who applied to the Ege University Department of Pedodontics, Faculty of Dentistry for a general dental examination.

Our study was ethically approved by the Ege University Medical Research Ethics Committee with the decision dated April 25, 2024, and numbered 24-4.1T/62.

Selection Criteria of the Subjects

Patients aged between 2-13 years with the established diagnosis of hemophilia, whose caregivers had given their consent for the participation of the children in the study constituted the study group. Patients older than 13 years, without proven diagnosis of hemophilia, and refused to participate were excluded from the study. The control group included children aged 2-13 years who were healthy without any systemic disease, physical or mental disabilities, and applied for a routine examination to the Department of Pedodontics, and Faculty of Dentistry of Ege University.

Study Design and Procedures

In this study, a case report form was used as a data collection tool. The form contained various questions to assess the patient's demographic characteristics, medical and dental history, and oral hygiene habits. In the study group, information acquired from the parents about the child's age, gender, type of hemophilia, any accompanying systemic diseases, medication use, and the presence of any physical/mental disabilities were recorded. To evaluate oral hygiene habits, questions about the presence and frequency of tooth brushing, type of toothbrush, whether bleeding occurs while brushing, interproximal tooth care and its frequency, presence of foul breath, frequency of dental visits, and the timing of the last dental visit were inquired. The form also inquired about whether bleeding problems

occurred during or after dental treatment, and whether premedication and consultation requests were made before dental procedures. In the control group, the parents provided information about the child's age, gender, tooth brushing habits and its frequency, type of toothbrush used, presence of bleeding during brushing, interproximal tooth care and frequency, presence of foul breath, frequency of dental visits, and the timing of the last visit.

Both groups of patients underwent dental examinations using a mirror and probe under a reflected light during the appointment. The caries status of the patients was recorded according to the decayed, missing, filled teeth (DMFT/dmft) index. The DMFT index is calculated by summing the number of decayed, missing, and filled permanent teeth, while the dmft index is determined by the total number of decayed and filled primary teeth. This index was first introduced by Klein and Palmer in 1938 and is considered a key measure in dental epidemiology for assessing the oral health status of populations[12].

Dental surfaces were examined using a mirror and a blunt-ended probe under reflector light. A single score was assigned for each tooth, and the total score was used to determine the index value. In the calculation of the DMFT or dmft indices, congenitally missing teeth, unerupted teeth, supernumerary teeth, teeth lost or restored due to reasons other than caries, and physiologically exfoliated primary teeth were excluded from the evaluation. Information about the type of dentition (primary, permanent, or mixed dentition) was also recorded during the intraoral examination. The gingival health status was assessed using the gingival index (GI) proposed by Silness and Loe[13] (1963) during the oral examination. The GI is a scoring system that grades different stages of gingival inflammation based on clinical features. Six representative teeth, reflecting the entire mouth, are examined for the severity of inflammatory changes in the gingiva, and each site is assigned a score ranging from 0 to 3 points. The scores for each tooth are summed and divided by four to obtain the GI value for that tooth. The indices of the teeth representing each region are then summed and divided by six to calculate the patient's overall GI. The GI value represents an average GI score of the examined gingival areas of the patient[13].

Plaque presence and amount on the dental surfaces were recorded according to the Plaque Index (PI) proposed by Silness and Loe[13] (1964). The PI is an index used to determine the amount of dental plaque in contact with the gingiva. Six teeth representing the entire mouth are selected for examination. Each of the four surfaces of the selected teeth—buccal, lingual, mesial, and distal—is scored on a scale from 0 to 3 points. The scores for each tooth are summed and divided by four to obtain the PI value for that tooth. The indices of the teeth representing each region are then summed and divided by six to calculate the patient's overall PI. The PI value represents the average score of the examined gingival sites for the patient[14].

To ensure standardization, all oral examinations and evaluations of patients in both the study and control groups were performed by a single researcher (M.D.).

Statistical Analysis

The data were analyzed using the SPSS 21.0 software. The frequency and percentage tables of the evaluation questions in the case report form were compared between groups using the chi-square test. Since our groups did not show a normal distribution, the comparison of the DMFT, GI, and PI scores between two groups was performed using the Mann-Whitney U test, while for comparisons involving more than two groups, the Kruskal-Wallis H test was used. To analyze the correlation between DMFT, GI, and PI scores, the Spearman's Rho correlation test was applied. The confidence interval was set at 95%, and the significance level was determined as $p<0.05$.

RESULTS

The study group consisted of 54 male hemophiliac children with a mean age of 7.80±3.18 years and a control group of 55 healthy male children with a mean age of 8.20±2.63 years. Among the cases in the study group, 83.3% (n=45) were diagnosed with hemophilia A, and 16.7% (n=9) of them with hemophilia B (Table 1). Fifty-four hemophiliac patients in the study group, had either mild (n=14: 25.9%), moderate (n=9: 16.6%) or severe (n=31: 57.4%) hemophilia.

In the study group, 87% and in the control group, 85.5% of the cases were found to have the habit of tooth brushing. There was no statistically significant difference

Table 1. Distribution of the study group according to hemophilia type

Hemophilia type	n	%
A	45	83.3
B	9	16.7

between groups in terms of the daily frequency of tooth brushing. In the patient group, 23.4% and in the control group, 12.8% of the cases brushed their teeth twice a day. Teeth brushing frequency appeared consistent across the groups, without any significant differences between both groups. Gum bleeding during tooth brushing was observed in 14.8% of the cases in the study and 16.4% of the cases in the control group. Frequency of gum bleeding during tooth brushing did not differ significantly between both groups. Foul breath was reported in 27.8% of the cases in the study and 47.3% of the cases in the control group. The control group demonstrated a significantly higher frequency of foul breath compared to the study group (Table 2).

It was revealed that more than half of the cases in the study (55.6%) and in the control group (60%) applied to their dentists regularly. The groups did not differ significantly in terms of their regular dental visit patterns.Some (35.2%) cases in the study, and control (38.2%) groups visited their dentists more than two years previously. The frequency of dental visits did not differ statistically significantly between both groups. The most recent dental visits in the study, and control groups were made by 44.4% of the cases 6 months-2 years previously, and realized by 47.3% of the cases in the control group 6 months previously. The study group significantly delayed their dental visits compared to the control group (p=0.007) (Table 3).

The dmft values of the cases in the study, and control groups were 4.06±4.29, and 5.79±2.87, respectively. The control group exhibited a significantly greater dmft score compared to the study group (p=0.006) (Table 4). The DMFT values in the study, and control groups were 1.46±2.16, and 2.46±3.05, respectively. The DMFT index appeared greater in the control group; without any statistically significant intergroup difference. The GI values in the study and the control groups were 1.44±0.54, and 1.54±0.54, respectively. Both groups exhibited similar GI values, without any statistically significant intergroup difference. The PI values in the study, and the control groups were 1.80±0.79, and 2.20±0.75, respectively. The PI was significantly elevated in the control group relative to the study group (p=0.006) (Table 4).

Table 2. Distribution of oral and dental care behaviors according to groups

	Study group		**Control group**			
	n	**%**	**n**	**%**	**X^2**	**p**
Tooth brushing					0.057	0.810
Yes	47	87.0	47	85.5		
No	7	13.0	8	14.5		
Tooth brushing frequency					2.146	0.342
Rarely	20	42.6	20	42.6		
Once a day	16	34.0	21	44.7		
Twice a day	11	23.4	6	12.8		
Toothbrush type					2.063	0.356
Manual	40	74.1	45	81.8		
Electric	4	7.4	5	9.1		
Manual ve electric	10	18.5	5	9.1		
Gum bleeding while brushing teeth					0.050	0.824
Yes	8	14.8	9	16.4		
No	46	85.2	46	83.6		
Interdental care					1.945	0.163
Yes (irregular)	4	7.4	1	1.8		
No	50	92.6	54	98.2		
Oral malodor					4.413	**0.036***
Yes	15	27.8	26	47.3		
No	39	72.2	29	52.7		

*: p<0.05

Table 3. Distribution and comparison of behaviors related to dental check-ups and examinations according to groups						
	Study group		Control group			
	n	%	n	%	X^2	p
Regular dental visit					0.221	0.639
Yes	30	55.6	33	60.0		
No	24	44.4	22	40.0		
Frequency of dental visits					1.025	0.795
Every 6 months	6	11.1	9	16.4		
Once a year	17	31.5	14	25.5		
Once every two years	12	22.2	11	20.0		
Less than once every two years	19	35.2	21	38.2		
Last dental visit					12.214	**0.007***
0-6 months	9	16.7	26	47.3		
6 months-2 years	24	44.4	14	25.5		
More than 2 years	6	11.1	3	5.5		
Never	15	27.8	12	21.8		
*: p<0.05						

Table 4. Comparison of DMFT, dmft, gingival index, and plaque index values according to groups				
	Study group	Control group	Total	
Variable	$\overline{X}$±SD	$\overline{X}$±SD	$\overline{X}$±SD	p
dmft	4.06±4.29	5.79±2.87	4.90±3.75	**0.006***
DMFT	1.46±2.16	2.46±3.05	1.90±2.69	0.124
GI	1.44±0.54	1.54±0.54	1.49±0.54	0.305
PI	1.80±0.79	2.20±0.75	2.00±0.79	**0.006***
*: p<0.05, DMFT/dmft: Decayed, missing, filled teeth, SD: Standard deviation				

DISCUSSION

The results of studies on the oral and dental health of children with hemophilia show differences between countries. Some studies have found that the oral and dental health status of hemophiliac patients are better compared to healthy patients[10,15-19], while others have reported poorer results[8,20-24]. There are also studies that report no difference between the groups[7,25].

In our study, the number of hemophilia A patients (45 patients, 83.3%) was five times higher than the number of hemophilia B patients (9 patients, 16.7%). When similar studies and literature on hemophilia were reviewed, it was reported that the prevalence of hemophilia A is higher than that of hemophilia B, which is consistent with the findings of our study[8,11,22,26-28].

Dental caries is recognized as one of the most prevalent chronic health problems affecting children worldwide[29]. In the study by Nagaveni et al.[18] compared to the control group, the study group exhibited decreased levels in both DMFT and dmft scores. When oral hygiene was compared, it was observed that children with hemophilia had better oral hygiene, which was in line with the decay status. In the studies by Sonbol et al.[16] the frequency of tooth decay was significantly lower in the hemophilia group. In a study conducted in Iran, the DMFT/S values were significantly lower in the hemophilia group[10]. In the studies by Zaliuniene et al.[30] better oral health, fewer number of primary tooth caries and lower need for dental treatment were observed in hemophilia patients. However, when permanent teeth were compared, no significant difference was found. In our research, consistent with previous findings, the study group exhibited a significantly lower dmft score compared to the control group. Although the control group showed a higher DMFT value, the difference between the groups did not reach statistical significance. In light of the data obtained in this study, it is thought that parents of children with hemophilia pay more

attention to their children's oral health care, as they are aware of the potential risks that may arise during dental treatment. Unlike our study, in the studies by Kabil et al.[20] the DMFT and dmft values were found to be significantly higher in hemophilia patients compared to the control group. In another study, the DMFT/dmft values were higher among children with hemophilia. They suggested that the higher rates of dental caries in hemophilic children could be due to high sugar consumption and inadequate oral hygiene habits[21].

In many studies, no meaningful differences between the groups with and without hemophilia regarding gum health has been found, similar to our study[16,19,31]. Our findings showed elevated GI values in the control group, though the difference was not statistically meaningful. In contrast to the present study, in the study by Alpkılıç et al.[32] the GI values of hemophilic patients were found to be statistically significantly greater than those of the control group.

Some previous research studies have indicated that the PI values did not differ significantly between groups[19,31,33]. However, our results showed a significantly increased PI value in the control group relative to the study group. In the study by Sonbol et al.[16] which included 38 hemophilic patients and 30 healthy children, similar to our study, the PI for permanent dentition was found to be significantly higher in the control group. There was no notable intergroup variation regarding gingivitis. Unlike our study, the study by Salem et al.[34] found that PI values were significantly higher in the hemophilia group. In the study by Babu et al.[21] statistical analysis revealed higher GI values in hemophilic children. No difference was found in PI values between both groups. Another study reported significantly elevated index scores for dental debris, calculus, and gingival inflammation in hemophilic patients. The same study also found that the oral hygiene status of hemophilia patients was lower compared to healthy individuals[35].

In a study conducted in India, it was found that only 23% of patients in the hemophilia group, whereas 46% of the cases in the healthy group had the habit of brushing their teeth "twice a day," with a statistically significant difference between both groups[22]. In Güler's[36] study, where brushing habits were evaluated, 72% of the children with hemophilia, whereas only 42% of healthy children responded that they had brushed their teeth "more than once a day" or "once a day". It was concluded that children with hemophilia and their families paid more attention to brushing their teeth compared to the healthy group. In our study, 23.4% of patients in the hemophilia group whereas 12.8% of the cases in the control group brushed their teeth "twice a day". There was no statistically significant difference in terms of brushing frequencies between both groups. It has been reported that patients with bleeding disorders tend to avoid brushing their teeth due to the fear of gum bleeding[34]. Consistent with our findings, Czajkowska et al.[24] reported the incidence of bleeding while brushing teeth was greater among hemophilic patients, yet this difference was not statistically significant. Consistent with this data, our study observed no significant intergroup difference in frequencies of bleeding during brushing. Children with hemophilia and their parents should be educated that, with proper treatment tailored to the patient and in cooperation with medical professionals, the risk of bleeding can be minimized. In a study conducted in Italy, dental treatment data from three hemophilia centers over 10 years were examined, and it was found that bleeding complications were very low. The study concluded that dental treatments, under proper conditions, are highly effective and safe[37].

Study Limitations

Our study was conducted with a limited number of hemophiliac patients in a specific age group. Subsequent researches should aim to expand the sample size, investigate different age groups, and evaluate oral and dental health findings by reaching a larger population of children with hemophilia. Oral and dental health assessments in this study were conducted through a single clinical examination and did not include follow-up evaluations. This is another limitation of our study in terms of assessing changes in the children's oral health over time or the effectiveness of oral hygiene education provided. Future research conducted over longer time periods and supported by periodic follow-up examinations would provide better insight into the improvement of the oral and dental health of children with hemophilia over time and allow for more comprehensive comparisons with healthy control groups.

CONCLUSION

Our study population consisted of a study group of children with hemophilia and a control group of healthy children. In our study, the primary dentition dmft scores and PI values were found to be significantly higher in the control group compared to the study group. There was no notable difference in oral hygiene practices between the groups.

The preservation of dental health in patients with hemophilia is important, especially to prevent the risk of complications that may arise during comprehensive dental treatments and to avoid the costs of premedication taken before treatment. This approach should be our primary goal.

Studies can be conducted to increase the knowledge of dentists regarding the approach to patients with hemophilia. Additionally, pre-treatment consultations should be made in collaboration with hematology specialists, and patient management should be planned using a multidisciplinary approach.

Providing hemophiliac children and their families trustworthy information can help raise awareness about proper oral health practices, the necessity of regular dental check-ups, and the value of preventive treatments.

In conclusion, the management of oral and dental health in patients with hemophilia should be initiated at an early age and continued with regular follow-ups. This approach will help minimize the need for advanced dental interventions in individuals with hemophilia.

Ethics

Ethics Committee Approval: Our study was ethically approved by the Ege University Medical Research Ethics Committee with the decision dated April 25, 2024, and numbered 24-4.1T/62.

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

Footnotes

Author Contributions

Surgical and Medical Practices: M.D., F.E., Concept: M.D., F.E., M.C.U., K.K., Design: M.D., F.E., M.C.U., K.K., Data Collection or Processing: M.D., M.C.U., K.K., Analysis or Interpretation: M.D., F.E., M.C.U., K.K., Literature Search: M.D., Writing: M.D., F.E.

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Original Article

Evaluation of Epicardial Adipose Tissue in Pediatric Patients with Chronic Kidney Diseases

Kronik Böbrek Hastalıkları Olan Pediatrik Hastalarda Epikardiyal Yağ Dokusunun Değerlendirilmesi

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ABSTRACT

Objective: Since with chronic kidney disease (CKD) is an inflammatory process, and disorders of uremia, calcium, and phosphorus metabolism are associated with cardiovascular disease (CVD), patients CKD are at high risk for developing CVDs. This study aims to evaluate epicardial adipose tissue (EAT) parameters which play an active role in the development of CVD and atherosclerosis in patients with CKD.

Method: Twenty-seven CKD patients aged 0-18 and their age -matched 15 control patients were compared. Physical examination and laboratory findings of the patient group were recorded. Both groups evaluated EAT with M-mode echocardiographic measurements.

Results: There was no difference between the 2 groups in terms of age, gender, and body mass index. EAT1, and EAT2 values were higher in the patient group, and these two measurements increased correlatedly as the CKD stage increased. Additionally, the correlation of EAT with blood phosphorus level and parathyroid hormone was evaluated.

Conclusion: Cardiovascular morbidity and mortality are high in CKD. Therefore, early diagnosis is important. Evaluations of EAT and follow-ups at certain intervals can give us information in this sense as a non-invasive parameter.

Keywords: Cardiovascular disease, chronic kidney disease, and epicardial adipose tissue

ÖZ

Amaç: Kronik böbrek hastalığı (KBH) hastaları kardiyovasküler hastalıklar (KVH) açısından yüksek risk altındadır. KBH bir enflamatuvar süreç olduğundan üremi, kalsiyum ve fosfor metabolizması bozuklukları da KVH ile ilişkilidir. Bu çalışma, KBH'li hastalarda KVH ve ateroskleroz gelişiminde aktif rol oynayan epikardiyal yağ dokusunu (EYD) değerlendirmeyi amaçlamaktadır.

Yöntem: 0-18 yaş aralığındaki 27 hasta ve 15 kontrol hastası karşılaştırıldı. Hasta grubunun fizik muayene ve laboratuvar bulguları kaydedildi. Her iki grup da EYD'yi M-mod ekokardiyografik ölçümlerle değerlendirdi.

Bulgular: Yaş, cinsiyet ve vücut kitle indeksi açısından 2 grup arasında fark yoktu. Hasta grubunda EYD1 ve EYD2 değerlerinin daha yüksek olduğu ve bu iki ölçümün KBH evresi arttıkça korele olarak arttığı görüldü. Ayrıca EYD'nin kan fosfor seviyesi ve paratiroid hormonu ile korelasyonu değerlendirildi.

Sonuç: KBH'de kardiyovasküler morbidite ve mortalite yüksektir. Bu nedenle erken tanı önemlidir. EYD değerlendirmeleri ve belirli aralıklarla takipler bize bu anlamda invaziv olmayan bir parametre olarak bilgi verebilir.

Anahtar kelimeler: Kardiyovasküler hastalık, kronik böbrek hastalığı, epikardiyal yağ doku

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INTRODUCTION

The prevalence of chronic kidney disease (CKD) is increasing worldwide due to the use of both improved diagnostic methods and easier access to physicians. Fluid and electrolyte disorders, uremia, mineral and bone disorders, anemia, hypertension (HT), dyslipidemia, cardiovascular disease (CVD), infection, inflammation, endocrine abnormalities, growth retardation, and neurodevelopmental disorders are seen in these patients[1]. There are many problems associated with CKD, the most important of which are CVD and related pathologies. British physician Richard Bright was the first to report the relationship between CKD and CVD[2]. The primary pathology in these patients is increased oxidative stress and inflammation. In patients with CKD, CVD mnifests itself in the form of cardiomyopathy, atherosclerosis, peripheral arterial disease, coronary artery disease (CAD), heart failure, ventricular dysfunction, HT, arrhythmias, and sudden cardiac death (Figure 1)[1]. Echocardiography (ECHO) is an essential noninvasive and diagnostic cardiac imaging modality. In addition to being diagnostic, ECHO is the most frequently used method in the follow-up of patients[3]. Patients with CKD should have regular cardiac evaluations, mainly including assessment of left ventricular (LV) function[3]. Epicardial adipose tissue (EAT) is located on the epicardium (Figure 2). EAT secretes antiatherogenic, proatherogenic, and proinflammatory cytokines. Therefore, it is defined as an endocrine and inflammatory organ. Although EAT is cardioprotective, its increased thickness is considered a risk factor for atherosclerosis and CVD[4]. Life expectancy in pediatric patients is long. Therefore, as EAT is both an early and non-invasive indicator of atherosclerosis and CVD, EAT should be monitored at regular intervals to prevent both morbidity and mortality in patients with CKD.

Many studies have proven that increased thickness of EAT is a risk factor for atherosclerosis and CVD in CKD patients. The study was conducted to demonstrate the validity of increase in EAT thickness in pediatric patients, to show that EAT emerges as a more significant risk factor as the CKD stage increases, and to investigate the relationship between EAT and metabolic parameters.

MATERIALS and METHODS

This study was approved by University of Health Sciences Türkiye, İzmir Tepecik Training and Research Hospital, Ethics Committee (approval number: 2021/11-30, dated: 15.11.2021). Informed consent forms were obtained from all participants. Pediatric patients under the age of 18 who were followed up for CKD in our Pediatric Nephrology Clinic of Health Sciences University, İzmir Tepecik Training and Research Hospital, between January 2008 and March 2022, were included in this retrospectively planned study. Children who applied to the pediatric cardiology clinic for control purposes and had not any health problems were included in the study as the control group. Age, sex, body mass index (BMI), BMI percentiles, systolic and diastolic blood pressure (BP), and BP percentiles of patients with CKD and the control group were evaluated. CKD stage, blood parathormone, calcium, phosphorus, and vitamin D levels were recorded in the patient group. All cases were assessed with ECHO. Physical examination and ECHO findings were compared in 2 groups. The correlation of biochemical parameters with EAT was evaluated in the patient group.

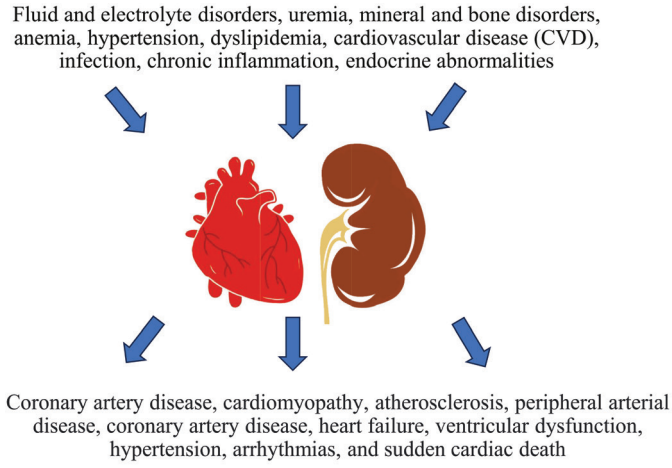

Figure 1. Effects related to chronic kidney disease

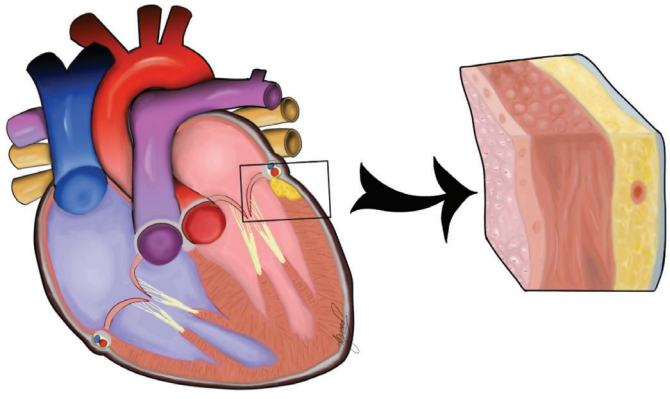

Figure 2. Location of epicardial adipose tissue in the heart

Echocardiographic Assessment and Evaluation of Epicardial Tissue

All patients underwent a complete ECHO examination, including EAT measurement. The same pediatric cardiologist performed the ECHO examinations using a Philips Affiniti 50 US device (Philips Healthcare, Andover, Netherlands) equipped with an S4-2 probe.

Conventional ECHO measurements including interventricular septal thickness (IVSd), LV dimensions, LV posterior wall thickness, and LV mass were made by M-mode ECHO. Ejection fraction (EF) and fractional shortening for etimation of EF were determined using standard methods[5]. In all patients. EAT was measured during ECHO. EAT of the right ventricular free wall at parasternal long- and short-axis was measured ECHO and EAT measurements were evaluated while the patient in the left decubitus position. EAT thickness was measured perpendicular to the free wall of the right ventricle at the end of diastole for three cardiac cycles. The EAT was visualized between the right ventricular free wall in the parasternal long (EAT 1) and short axis (EAT 2) views.

Statistical Analysis

The distribution characteristics of continuous numeric data were analysed by Kolmogrov-Smirnov test, presented as median values in hypertensive-healthy groups, and since critria of normal distribution were not met, they were compared using non-parametric Mann-Whitney U test. Pre- and post-treatment EAT1 and 2 and LVmass measurements were compared with the non-parametric Wilcoxon test. In imaging marker analysis, statistical significance of the receiver operating characteristic curve and area under the curve were evaluated. All statistical analyses were performed with SPSS 26.0 statistical software, $p<0.05$ was accepted as the limit of statistical significance.

RESULTS

The study population consisted of 27 children with CKD and a control group of 15 healthy children of the same age and gender. The average age of the patient and the control groups were 130.1±48.7 months and 142.4±43.2 months, respectively. The distribution of gender was equal in both groups. The average BMI was 19.2 kg/m^2 (13.75-24.4 kg/m^2) in the patient group and 20.8 kg/m^2 (15.94-28.3 kg/m^2) in the control group. IVSd, LVWd, LV mass, EAT1 and EAT2 measurements were statistically significantly increased in the patient group compared to the healthy group (p=0.019, 0.007, 0.000, 0.018, and 0.044, respectively) (Table 1).

The age at diagnosis of children with CKD was 24 (0-173) months, and the follow-up period was 73 (6-208) months. The patients were clasified in CKD stage I (n=10), II (n=1), III (n=8), and V (n=8). In the stage IV-V CKD group, one patient was on hemodialysis, five patients were on peritoneal dialysis, and two patients were preparing for renal replacement therapy. A statistically significant difference was found between CKD stages for LVmass, EAT1, and EAT2 (p=0.037, 0.028, and 0.021, respectively) (Table 2). Phosphorus, calcium, vitamin D, and parathyroid hormone levels according to the stages of CKD are given in Table 2 (p=0.043, 0.048, 0.021, and 0.004, respectively) (Table 2). PTH values of 27 pediatric patients were related to LVmass, EAT1, and EAT2 (r=0.986, 0.962, 0.876, respectively), and blood phosphorus values were associated with LVmass, EAT1, and EAT2 (r=0.989,

Table 1. Comparison of ECO parameters of the patient and control groups

ECHO findings	Patient group (n=27)	Control group (n=15)	p-value (p<0.05)
IVSd (mm), median (Q1-Q3)	0.60 (0.30-1.00)	0.50 (0.30-0.90)	**0.019**
LVIDd (mm), mean ± SD	4.05±0.71	3.91±0.51	0.245
LVIDs (mm), median (Q1-Q3)	2.20 (1.70-2.50)	2.10 (1.60-2.40)	0.437
LVWd (mm), median (Q1-Q3)	0.70 (0.40-1.30)	0.60 (0.4-0.80)	**0.007**
LVEF (%), mean ± SD	71.57±5.83	70.13±5.11	0.714
LVFS (%), mean ± SD	39.86±5.24	38.73±4.32	0.898
LVmass (g/m^2), median (Q1-Q3)	59.00 (40.00-121.00)	34.00 (20.20-45.30)	**0.000**
EAT 1 (mm), median (Q1-Q3)	2.00 (1.50-3.10)	1.90 (1.20-2.90)	**0.018**
EAT 2 (mm), median (Q1-Q3)	2.10 (1.40-3.50)	2.00 (1.00-3.10)	**0.044**

IVSd: Interventricular septum thickness in diastole (mm), LV: Left ventricular, LVIDs: Left ventricular internal dimension in systole, LVIDd: Left ventricular internal dimension in diastole, LVWd: Left ventricular posterior wall thickness in diastole (mm), ECO: Echocardiography, EAT: Epicardial adipose tissue

Table 2. Comparison of blood and cardiac parameters in groups			
	CKD stage 1-2	**CKD stage 3-4-5**	**p-value (p<0.05)**
LVmass (median) (min-max)	46 (40-72)	68 (56-121)	**0.037**
EAT1 (median) (min-max)	1.6 (1.2-1.9)	2.6 (1.6-3)	**0.028**
EAT2 (median) (min-max)	1.5 (1-1.8)	2.4 (2-3.5)	**0.021**
Phosphorus (median) (min-max) (mg/dL)	4.6 (3.8-5.7)	6.2 (5.2-8.6)	**0.043**
Calcium (median) (min-max) (mg/dL)	9.6 (9.1-10.4)	8.9 (8.6-9.5)	**0.048**
Parathyroid hormone (median) (min-max) (mg/dL)	79.4 (63.7-96.1)	362.1 (186-1924)	**0.004**
Vitamin D (median) (min-max) (ng/L)	30.4 (26.7-35.4)	22.6 (7.7-32.1)	**0.021**
LV: Left ventricular, CKD: Chronic kidney disease; EAT: Epicardial adipose tissue			

0.912, 0.876, respectively). LVmass, EAT1, and EAT2 measurements were negatively correlated with blood calcium levels and vitamin D levels (r=-0.752, -0.876, -0.865 for blood calcium; r=-0.732, -0.841, -0.897 for vitamin D, respectively). Cardiac involvement agravates, and symptoms became manifest in 16 (59%) patients with stage III and above. While 11 of 16 patients (69%) with stage III-IV-V had HT, 11 patients with stage I-II had not. The patient group was divided into stages I-II and advanced stages (stages III-IV-V). It was observed that LVmass, EAT1, EAT2, blood phosphorus, and PTH values significantly increased in the advanced stages of CKD. On the contrary, blood calcium and vitamin D levels significantly decreased in the advanced stages of CKD (Table 2).

DISCUSSION

Our retrospective study revealed significant increases in LVmass, EAT1, and EAT2 measurements in the CKD group. Our EAT measurements have not yet been validated in the literature. These parameters are affected by many factors, such as age, gender, BMI, and other concomitant diseases. Therefore, EAT is evaluated by comparing groups in studies. EAT is most frequently affected by HT, obesity, insulin resistance, dyslipidemia, oxidative stress, increased cytokine release, medication use, and non-adherence to treatment[6]. CKD is a state of increased inflammation, and patients have multiple risk factors. CAD is one of the most critical adverse outcomes of CKD. CVD in CKD has been associated with calcium, phosphorus metabolism, and uremia[7]. One of the first studies on this topic compared 80 CKD patients on dialysis with 27 controls. A significant association was found between EAT and coronary artery calcification (CAC)[8]. Another study evaluating 94 adults with stage III-V CKD found a correlation between EAT and CAC[9]. A study evaluating a total of 411 stage IV-V CKD patients, including those on hemodialysis (n=284) and peritoneal dialysis (n=70), determined that EAT was a risk factor for CAC and had effects on the myocardium related to perfusion damage[10]. Studies in the literature report that increased EAT in CKD is associated with left ventricular hypertrophy[11]. A meta-analysis of 17 studies of 1205 CKD patients and 756 healthy controls showed that EAT thickness was increased in the CKD group compared to healthy individuals[12]. In our research, LVmass, EAT1, and EAT2 measurements were significantly higher in the CKD group.

A study conducted on 277 adult patients with stage III-IV-V CKD who were not receiving dialysis treatment found that EAT increased as visceral adipose tissue increased. Increased EAT in CKD was associated with an increased risk of CVD independent of visceral adipose tissue and other factors[13]. A study comparing 59 chronic hemodialysis patients with healthy controls showed a significant increase in EAT and that this increase was associated with age, BMI, and CAC[14]. A study examining 109 hemodialysis patients showed a significant increase in EAT from the date of starting dialysis and that it was a predictor of mortality independent of all risk factors[15].

In a study examining 104 patients diagnosed with CKD, EAT thickness was shown to be negatively correlated with blood calcium levels and positively correlated with blood phosphorus levels[16]. Increased EAT is a hallmark of CAD, as is atherosclerosis[17]. EAT increases if blood phosphorus and parathyroid hormone levels are not well managed, as in CKD. EAT also increases when blood calcium levels are low[18]. In the examinations performed before and after parathyroidectomy in 34 CKD patients diagnosed with hyperparathyroidism, it was observed that EAT thickness decreased[19]. A significant negative correlation was found between vitamin D level and EAT thickness[19]. In our study, when CKD cases were grouped as stage I-II and stage III-IV-V, it was observed that EAT thickness showed a positive correlation with blood phosphorus and parathyroid hormone levels and a negative correlation with calcium and vitamin D levels in advanced CKD stages.

CONCLUSION

This study has again shown that EAT can be used as an imaging marker in the diagnosis and follow-up of patients because it is a non-invasive method. Because of this, it is crucial in childhood and CKD. Many studies are in the literature on both adults and dialysis patients. Our analysis is critical because it evaluates all stages related to childhood CKD. The number of patients is enough for childhood CKD. Future studies with larger samples will better confirm these results and explain the underlying mechanisms.

Ethics

Ethics Committee Approval: This study was approved by University of Health Sciences Türkiye, İzmir Tepecik Training and Research Hospital, Ethics Committee (approval number: 2021/11-30, dated: 15.11.2021).

Informed Consent: Retrospective study.

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Footnotes

Author Contributions

Surgical and Medical Practices: Ö.Ö.Ş., T.D., C.A., D.A., Concept: Ö.Ö.Ş., C.A., G.E., D.A., Design: Ö.Ö.Ş., T.D., C.A., S.A.Ç., D.A., Data Collection or Processing: T.D., B.E., G.E., C.A., S.A.Ç., F.M., B.K.D., Analysis or Interpretation: T.D., B.E., B.K.D., Literature Search: Ö.Ö.Ş., T.D., S.A.Ç., F.M., D.A., Writing: Ö.Ö.Ş., C.A.

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Original Article

Hemophilia and Obesity: Evaluating Prophylactic Dosing and Treatment Outcomes

Hemofili ve Obezite: Profilaktik Doz ve Tedavi Sonuçlarının Değerlendirilmesi

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ABSTRACT

Objective: Advancements in the treatment of hemophilia have extended life expectancy of the patients, while leading to the emergence of new comorbidities, including obesity, among them. This study aimed to evaluate the prevalence of obesity and overweight in patients with hemophilia while examining their associations with the clinical characteristics of the disease.

Method: Hemophilia patients were included in this single-center cross-sectional study. To assess joint health and functionality, the Functional Independence Score in Hemophilia and the Hemophilia Joint Health Score (HJHS) were applied. Patients were grouped according to their body mass indexes (BMIs). Differences in the number of bleeding episodes, prophylactic doses, and joint scores among BMI groups were evaluated.

Results: A total of 35 hemophilia patients aged between 4 and 20 years were included in the study. Based on their BMIs, 8 patients (22.9%) were obese, and 11 patients (31.4%) were obese/overweight. Patients in the obese/overweight group were significantly younger than those in the other group. No significant difference was found between the groups in terms of annual bleeding episodes and HJHS. Interestingly, although obese/overweight patients received significantly lower prophylaxis doses per kilogram of body weight, did not show any difference in clinical scores.

Conclusions: Our findings suggest that dose adjustments based on ideal body weight may lead to similar treatment outcomes. Additionally, younger age and parental protective behaviors may contribute to occurrence of fewer bleeding episodes in obese/overweight patients.

Keywords: Bleeding, hemophilia, obesity, overweight

ÖZ

Amaç: Hemofili tedavisindeki gelişmeler yaşam süresini uzatmış ve hastalar arasında obezite de dahil olmak üzere yeni komorbiditelerin ortaya çıkmasına neden olmuştur. Bu çalışmanın amacı hemofili hastalarında obezite ve fazla kilolu sıklığını tespit etmek ve bunun hemofilinin klinik özellikleriyle ilişkisini araştırmaktır.

Yöntem: Bu tek merkezli kesitsel çalışmaya hemofili hastaları dahil edildi. Eklem sağlığı ve işlevselliğini değerlendirmek amacıyla Hemofilide Fonksiyonel Bağımsızlık Skoru ve Hemofili Eklem Sağlığı Skoru uygulandı. Hastalar, vücut kitle indeksine göre gruplandırıldı. Vücut kitle indeksi grupları arasında kanama sayıları, profilaksi dozları ve eklem skorlamaları açısından fark olup olmadığı değerlendirildi.

Bulgular: Çalışmaya yaşları 4 ile 20 arasında değişen toplam 35 hemofili hastası dahil edildi. Vücut kitle indeksine göre 8 hasta (%22,9) obez, 11 hasta (%31,4) obez/fazla kilolu olarak sınıflandırıldı. Obez/fazla kilolu gruptaki hastalar, diğer gruptakilere göre anlamlı olarak daha küçük yaştaydı. Yıllık kanama sayıları ve Hemofili Eklem Sağlığı Skoru açısından gruplar arasında anlamlı bir fark bulunmadı. İlginç bir şekilde, vücut ağırlığının kilogramı başına anlamlı olarak daha düşük profilaksi dozları almalarına rağmen, obez/fazla kilolu hastalar klinik skorlarda herhangi bir farklılık göstermedi.

Sonuç: Bulgularımız, ideal vücut ağırlığına dayalı doz ayarlamalarının benzer tedavi sonuçlarına yol açabileceğini göstermektedir. Ayrıca, daha küçük yaşta olmak ve ebeveynlerin koruyucu tutumları, obez ya da fazla kilolu hastalarda daha az sayıda kanama epizodu görülmesine katkıda bulunmuş olabilir.

Anahtar kelimeler: Kanama, hemofili, obezite, fazla kilolu

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INTRODUCTION

Hemophilia is a bleeding disorder caused by inadequate synthesis of clotting factors. It is estimated to affect 400,000 people worldwide and is characterized by easy bleeding, delayed clotting, and intra-articular bleeding[1]. Patients may feel symptoms of joint bleeding such as swelling, pain, increased heat, and tingling on the affected site. With recurrent bleeding episodes, synovial damage develops and permanent damage occurs in the joint. Morbidity in hemophilia is often defined in terms of musculoskeletal dysfunction, while its severity is determined by clinical and radiological joint scores[2].

Based on their bleeding profile, patients with severe, and some with moderate hemophilia receive regular prophylaxis. Early initiation of primary prophylaxis is the most important tool in preserving joint function and preventing recurrent bleeding episodes[3]. Thanks to patients' access to factor concentrates and regular prophylactic treatment, the episodes of joint bleeding and the incidence of arthropathy have decreased dramatically[4].

Advancements in the management of hemophilia have increased life expectancy, however new morbidities have emerged among patients. In recent studies, the prevalence of obesity in hemophilia patients has increased up to the incidence rates observed in the general population, while some have reported obesity rates higher than those seen in the general population[5-8]. Some studies have found that hemophilic arthropathy is more common in obese hemophilia patients and that there is a correlation between increased body mass index (BMI) and decreased range of motion (ROM) of the joints[6,9,10]. In this context, obesity further increases the disease burden for patients whose movements are already restricted due to muscle dysfunction and joint inflammation. Additionally, some studies have shown that obesity is associated with an increased number of bleeding episodes[6,11]. However, consistent evidence has not yet been presented that weight gain in hemophilia patients creates a tendency to bleed, and there are studies that claim the opposite[12].

The objectives of this study were to determine the physical performance of hemophilia patients followed up in a tertiary care hospital in Turkey using objective criteria, to investigate the prevalence of obesity/overweight and its association with clinical features of hemophilia in these patients.

MATERIALS and METHODS

A single-center cross-sectional study was conducted at a tertiary care hospital, which is a referral center for the treatment of pediatric patients in the Aegean region of Turkey. Approval of the Local Research Ethics Committee of University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (approval number: 2021/03-09 dated: 11.02.2021) and written informed consent were obtained from the parents of the patients. Patients with hemophilia A and B between the ages of 4 and 20 years who applied to the Pediatric Hematology Clinic of Dr. Behçet Uz Children's Hospital for routine follow-up between February 2021 and March 2021 were included in this study. Patients who had bleeding episodes (joint, soft tissue, etc.) in the last two weeks or who were inhibitor-positive hemophilia were excluded from the study.

Age, type of hemophilia, clinical classification, the dose of prophylactic treatment (if any), the presence, and number of affected target joint(s), and extra-articular bleeding in the last six months/year were recorded on the case report form. The Functional Independence Score in Hemophilia (FISH) was applied to cases aged 7 years and older. The Hemophilia Joint Health Score (HJHS) v 2.1 was applied to all cases by a physical therapy and rehabilitation specialist. Body weights, and heights of the cases were measured, and their BMIs were calculated during outpatient clinic visits. For patients under 18 years of age, the BMI percentile reference values updated for Turkish children by Neyzi et al.[13] in 2015 were used. Patients over the age of 18 years were classified according to BMI without using percentiles and recorded in the case report form.

Definitions Used in the Study

Type of Hemophilia

Hemophilia patients with Factor (F) VIII deficiency are called hemophilia A, and those with FIX deficiency hemophilia B.

Clinical Classification of Hemophilia

Hemophilia patients with a basal factor level of <1% are classified as severe hemophilia, 1-5% as moderate hemophilia, and 5-40% as mild hemophilia.

Presence of Inhibitor

Inhibitor titer of >0.6 Bethesda Units (BU)/mL for FVIII; >0.3 BU/mL for FIX is considered inhibitor positive.

Prophylaxis

Even in the absence of acute bleeding episodes, factor concentrates are administered to patients regularly once, twice or three times a week to prevent complications of the disease.

Target Joint

The joint that demonstrates three or more episodes of intraarticular bleedings within 6 months is called a target joint.

BMI

Calculated by dividing body mass in kilograms by the square of height in meters.

Classification by BMI

When classifying BMI in the pediatric population, BMI percentiles are used according to the age and gender of the population. Accordingly; pediatric patients with BMIs under 5 percentile are classified as underweight, 5-85 percentile as normal, 85-95 percentile as overweight, 95 percentile and above as obese. Adult patients with BMIs below 18.5 are classified as underweight, 18.5-24.9 as normal, 25.0-29.9 as overweight, and 30 and above as obese.

Joint Health Scoring Systems Used in the Study

HJHS

The current version of the scale, HJHS v 2.1, allows the evaluation of six joints (right and left knee, elbow, and ankle) based on eight items[14]. These items are joint swelling (0-3 points), duration of swelling (0-1), muscle atrophy (0-2), crepitation with movement (0-2), loss of flexion (0-3), loss of extension (0-3), joint pain (0-2), and strength (0-4). The global gait score is evaluated between 0-4 points, with 1 point for each of the skills of walking, climbing stairs, running, and jumping on one leg. Each joint can receive a score between 0-20. The scores from each joint are summed, and the global gait score is added. The maximum score is 124, and the higher the score, the worse the joint health. Cases with a score of zero are considered healthy according to the HJHS. To achieve reliability and validity, it should be applied to pediatric patients aged 4 years and older[15].

FISH

FISH includes seven daily activities (eating, bathing, dressing, sitting in a chair, squatting, walking, and climbing uphill). Each activity is graded on a scale of 1 to 4 based on the degree of independence the patient has in performing the activity. The highest score is 28, in which case the patient can easily perform all activities without assistance. Patients should have no history of bleeding in the last two weeks and should be 7 years of age or older in order to perform the scoring properly[2].

Statistical Analysis

Statistical analyses were performed with SPSS, version 20.0 (SPSS Inc, Chicago, IL, USA). All numerical and categorical data were evaluated using descriptive statistics methods. Numerical continuous parametric variables of the patients were described using mean and standard deviation, and non-parametric numerical continuous variables with median and interquartile range (IQR). Categorical variables were presented as numbers (percentages).

Patients in the study were divided into two groups according to their BMIs as obese/overweight and normal/underweight patients. Student's t test was used to compare the means of parametric numerical data between two independent groups and Mann-Whitney U test to compare the median values of non-parametric numerical data. Chi-square test was applied to analyze categorical data. Results with a p-value <0.05 were considered statistically significant.

RESULTS

A total of 35 male patients with hemophilia A (n=29; 82.9%), and B (n=6; 17.1%) were included in our study. The mean age of the patients was 12.2±4.7 (4-20) years. According to factor levels, 30 patients (85.7%) had severe hemophilia, 4 patients (11.4%) had moderate hemophilia, and 1 patient (2.9%) had mild hemophilia. Table 1 shows the demographic and clinical characteristics of the patients.

Eighty percent (n=28) of the patients were receiving regular prophylaxis. Some patients (n=3; 10.0%) with severe, and moderate hemophilia (n=3: 75.0%), and the only patient with mild hemophilia did not receive prophylaxis. In our study, the mean prophylaxis dose was 20.5±5.3 IU/kg for hemophilia A patients and 25.1±10.8 IU/kg for hemophilia B patients.

The median number of bleeding episodes in the previous year was 1 (IQR: 0-10). No bleeding episodes were observed in 34.3% (n=12) of the patients in the previous year. Target joint development was observed in 14.3% (n=5) of the patients. The number of bleeding

episodes in the previous year was significantly higher in patients with severe hemophilia who did not receive regular prophylactic treatment compared to those who did (median [IQR]: 10 [10-20] vs. 1 [0-6], p=0.049).

FISH was applied to 30 patients, all of whom received a score of 28 points. According to the HJHS, 65.7% (n=23) of the patients were healthy, while 34.3% (n=12) of them had pathological scores. The number of hemorrhagic joints in the previous year was significantly higher in patients with pathological HJHS (HJHS: median [IQR]: 6.5 [0.8-32.5]) compared to those with HJHS within normal range (median [IQR]: 0 [0-3]) (p=0.022), whereas no significant difference was observed in the number of extra-articular hemorrhages between the two groups (median [IQR]: 0 [0-1.5] and 0 [0-0], respectively) (p>0.05). All patients with pathological HJHS (n=12) had severe hemophilia.

Hemophilia patients were obese (n=8: 22.9%) or overweight (n=3: 8.6%). Patients were classified as obese/overweight (n=11: 31.4%) or normal/underweight (n=24: 68.6%). Obese/overweight individuals were significantly younger than those in the other group (p=0.042). When obese/overweight group were compared with the other group, no difference was found in terms of the type of hemophilia, whether the disease was severe or not, the presence of target joints, whether or not they received prophylaxis, and the number of bleeding episodes (p>0.05). It was observed that obese/overweight hemophilia patients received statistically lower doses of prophylaxis per day and per week compared to other patients (p=0.042 and p=0.001). All obese/overweight patients who underwent FISH received a score of 28. There was no difference between being obese/overweight and being normal/underweight in terms of HJHS scoring (p>0.05). Table 2 shows joint health status and clinical differences between BMI groups.

Table 1. Demographic and clinical characteristics of the patients

Characteristics	**n (%)**
Age (years) mean ± sd (min-max)	12.2±4.7 (4-20)
Type of Hemophilia	
Hemophilia A	29 (82.9)
Hemophilia B	6 (17.1)
Clinical classification	
Severe hemophilia	30 (85.7)
Moderate hemophilia	4 (11.4)
Mild hemophilia	1 (2.9)
Classification by BMI	
Underweight	4 (11.4)
Normal	20 (57.1)
Overweight	3 (8.6)
Obese	8 (22.9)

BMI: Body mass index, sd: Standard deviation, min-max: Minimum-maximum

DISCUSSION

In recent years, advancements in the management of hemophilia-such as improved access to factor concentrates, personalized prophylaxis strategies, long-acting factor preparations, and a multidisciplinary treatment approach-have significantly extended life expectancy of the patients, bringing it on par with that of the general population. However, one emerging morbidity that poses a challenge, particularly in the context of preserving joint health, is obesity. In light of this information, we conducted an evaluation of the clinical characteristics of patients with hemophilia and explored the association between obesity and disease outcomes.

In our study, hemophilia patients were obese (22.9%) or obese/overweight. These incidence rates were significantly higher than the general population, where 8.2% of children aged 6-18 years are obese, and 22.5% are obese/overweight, according to the Turkey Nutrition and Health Survey 2010 report[16]. Additionally, a meta-analysis of 76 studies in Turkey found that the prevalence of obesity among male individuals aged 5-19 years was 7.4%[17]. These findings suggest that the rate of obesity in our hemophilia patients is notably higher than in the general Turkish population. In a 2019 study of 254 hemophilia patients with a median age of 13 years in Germany, the obesity/overweight rate was reported at 25.2%[8]. A similar rate of 25.6% was observed in a study conducted in Taiwan among hemophilia patients under 18 years of age[6]. Additionally, a 2018 meta-analysis of 28 studies from Europe and North America found an obesity/overweight rate of 31%, which aligns closely with our study findings[1].

In addition to the challenges posed by obesity in hemophilia patients, effective management of the disease remains crucial, particularly through primary prophylaxis. While a definitive cure for hemophilia remains elusive, primary prophylaxis stands as the cornerstone of treatment, aiming to maintain hemostasis and prevent bleeding episodes[18]. Hemophilia prophylaxis regimens in children vary globally, with high-dose regimens (25-40 IU/kg for hemophilia A, 40-60 IU/kg for hemophilia B), medium-dose regimens (15-

Table 2. Comparison of BMI groups in terms of clinical features and joint health status				
		Obese/overweight n: 11 (31.4%)	**Normal/underweight n: 24 (68.6%)**	**p-value**
Age (years) mean ± sd (min-max)		9.8±4.7 (5-18)	13.3±4.4 (4-20)	0.042
Type of hemophilia n (%)	A B	11 (38.0) 0 (0.0)	18 (62.0) 6 (100.0)	0.083
Clinical classification of hemophilia n (%)	Severe Moderate/mild	9 (30.0) 2 (40.0)	21 (70.0) 3 (60.0)	0.509
Prophylaxis n (%)	Yes No	8 (28.6) 3 (42.9)	20 (71.4) 4 (57.1)	0.381
Prophylaxis dose (IU/kg) daily mean ± sd (min-max)		17.3±3.5 (12.9-23.8)	23.1±7.2 (12.1-39.2)	0.042
Prophylaxis dose (IU/kg) weekly mean ± sd (min-max)		35.8±9.9 (23.8-53.9)	57.5±21.3 (20.0-97.4)	0.001
Number of bleedings in the last year median (IQR)		2 (0-10)	1 (0-9)	0.856
Target joint n (%)	Yes No	2 (40.0) 9 (30.0)	3 (60.0) 21 (70.0)	0.509
FISH n (%)	Healthy Patologic	8 (26.7) 0 (0.0)	22 (73.3) 0 (0.0)	
HJHS n (%)	Healthy Patologic	7 (30.4) 4 (33.3)	16 (69.6) 8 (66.7)	0.329

BMI: Body mass index, FISH: Functional Independence Score in Hemophilia, HJHS: Hemophilia Joint Health Score, IQR: Interquartile range, sd: Standard deviation, min-max: Minimum-maximum

25 IU/kg for hemophilia A, 20-40 IU/kg for hemophilia B), and low-dose regimens (10-15 IU/kg for both types) [19]. High- and medium-dose regimens initiated early in life have been shown to reduce annual bleeding rates by 90% while significantly preventing development of joint damage and degenerative disease[20,21]. In our study, the mean prophylactic dose was 20.5±5.3 IU/kg for hemophilia A and 25.1±10.8 IU/kg for hemophilia B, indicating that both groups received doses within the recommended ranges.

Today, the goal of treatment for hemophilia patients is to have no bleeding episodes at all[22,23]. Prophylactic treatment has been shown to be superior to on-demand treatment in preventing joint damage in hemophilia patients[20]. In our study, 34.3% (n=12) of patients with hemophilia, all of whom were receiving prophylaxis, had no bleeding episode within the previous year. Indeed, over the years, the number of target joints has declined, which can be attributed to the widespread use of prophylactic factor therapy. In our study, 14.3% (n=5) of patients with hemophilia developed a target joint. In a study conducted in our clinic in 2011 with 38 hemophilia patients, target joints were present in 39.5% (n=15) of the patients[24].

In this study, no significant differences were observed between the obese/overweight and the normal/underweight groups in terms of target joint involvement or bleeding frequency. Interestingly, despite receiving lower factor doses (IU/kg), the obese/overweight group achieved treatment outcomes, comparable to those with normal/underweight groups highlighting a noteworthy aspect of treatment efficacy in this population. This could be due to differences in how clotting factors are distributed and metabolized in the body. Various pharmacokinetic studies have indicated that overweight patients consume less FVIII per kilogram due to having a lower plasma volume in adipose tissue, and they are given more factor than they actually need[8]. Seaman et al.[25] suggested that patients with hemophilia may benefit from an individualized pharmacokinetic analysis using lean body mass and ideal body weight to determine the most accurate and potentially cost-effective method for achieving targeted FVIII recovery. On the other hand, another reason for the comparable outcome could be that overweight individuals may engage in less physically demanding activities, thereby reducing their risk of bleeding[26]. Obese/overweight hemophilia patients in our study were significantly younger than

normal/underweight patients (p=0.042), likely due to movement restrictions imposed by protective parental behaviors. Parents often limit their children's physical activities due to bleeding risks, which also reduces social interactions[27]. Such overprotective behaviors are common in families with chronically ill children, particularly in cultures where mothers are the primary caregivers[28]. In line with this, Kantarcıoğlu et al.[29] found that mothers of children with hemophilia were more protective than those of children with leukemia. The protective behaviors of parents of younger hemophilia patients may have reduced their physical activity, which, along with fewer bleeding episodes, could have contributed to their overweight status.

Monitoring joints with HJHS, a validated and reliable tool for assessing treatment effectiveness in patients with hemophilia, is crucial[14,30,31]. In our study, 34.3% (n=12) of patients had pathological joints according to HJHS, and all were diagnosed with severe hemophilia. These patients had a statistically higher number of bleedings in the previous year (p=0.008), confirming the strong correlation between recurrent bleeding episodes and joint damage. The patients with pathological joints were obese/overweight (n=4), and normal/underweight (n=8) according to HJHS which may also be related to the fact that obese/overweight patients are younger, with less time elapsed for joint damage, thanks to the protective behaviors of their parents.

Recurrent joint hemorrhages in patients with hemophilia may lead to musculoskeletal system changes, resulting in impaired functional capacity. FISH scoring developed for patients with hemophilia measures joint functions with daily activity parameters[32]. In our study, all 30 hemophilia patients whose ages were suitable for FISH scoring received 28 points, indicating that their joint functions were independent during daily activities. In a study reported by Liu et al.[33] from China in 2020, even low-dose prophylaxis (10-15 IU/kg, 2-3 days per week) was shown to improve FISH and other joint scores in hemophilia patients aged 4-18 years compared to on-demand treatment. In the same study, FISH scores of patients receiving low-dose prophylaxis ranged between 24-26 points. However, these patients received tertiary prophylaxis. In a study reported from India in 2020, FISH scores of the patients ranged between 13-28 points[34]. It can be said that our patients were able to maintain independence in their daily activities as also revealed by their FISH scores thanks to receiving prophylaxis at an effective dose before the development of joint damage. The contribution of the treatments to recovery is measured by repeating the FISH scoring at certain periods[33,35]. In a 2015 study conducted at our clinic with a similar patient group, FISH scores ranged from 22 to 28 points. Remarkably, all of our patients, irrespective of their obesity status, currently scored 28 points, underscoring the significant role of effective treatment in promoting recovery[36].

Study Limitations

The fact that the ROM of the patients was not measured in our study and that there was no scoring that measured the activities of the patients limited generalisability of our study findings. Additionally, as it is a single-center study, support from studies conducted at other centers is needed to validate our findings.

CONCLUSION

In conclusion, parameters such as annual counts of bleeding episodes, target joint formation, HJHS, and FISH help assess whether prophylaxis has been administered at an effective dose before development of joint damage. Our patients received prophylaxis within the recommended dose range, but obese/overweight patients had statistically lower weekly doses compared to normal/underweight patients. Despite this, there was no difference in annual counts of bleeding episodes or target joint formation between the groups. Furthermore, while HJHS results were similar, all obese/overweight patients were fully independent in their daily activities according to FISH. Our findings suggest that obese/overweight patients can receive adequate treatment with lower doses. However, personalized dosing would be the ideal approach. We believe that pharmacokinetic studies based on ideal or lean body weight could help determine the optimal dose for each patient, improving treatment accuracy.

Ethics

Ethics Committee Approval: Approval of the Local Research Ethics Committee of University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (approval number: 2021/03-09, dated: 11.02.2021)

Informed Consent: Written informed consent were obtained from the parents of the patients.

Footnotes

Author Contributions

Concept: H.Ö., Y.O., Design: H.Ö., Y.O., Data Collection or Processing: H.Ö., D.Ç., Analysis or Interpretation: H.Ö., D.Ç., Literature Search: H.Ö., Y.O., Writing: H.Ö., Y.O., D.Ç.

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Original Article

Differentiation of MIS-C Cases According to Disease Severity: Early Indicators and Clinical Approaches

MIS-C Şiddetinin Ayırımı: Erken Belirteçler ve Klinik Yaklaşımlar

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ABSTRACT

Objective: This study aims to identify key clinical and laboratory indicators that differentiate between severe and mild presentations of Multisystem Inflammatory Syndrome in Children (MIS-C), facilitating early recognition and application of targeted treatment strategies.

Method: A retrospective, single-center analysis was conducted, reviewing clinical data of patients with MIS-C to identify factors associated with disease severity. The study assessed demographic, clinical, laboratory, and echocardiographic parameters, comparing patients with severe MIS-C (requiring inotropic support or prolonged intensive care unit stay) to those with mild MIS-C. Statistical analyses were performed to determine significant intergroup differences.

Results: The group with severe MIS-C exhibited a longer duration of fever, presence of shock, tachycardia, and hypotension. Inflammatory markers such as lymphopenia, hypoalbuminemia, and elevated ferritin levels were significantly more pronounced in the severe MIS-C group. Elevated N-terminal pro-B-type natriuretic peptide and troponin levels were also significantly associated with severe MIS-C, indicating myocardial involvement. Echocardiographic findings of reduced ejection fraction and valve insufficiency were significant indicators of worsening clinical conditions. Coronavirus disease 2019 polymerase chain reaction and serological tests were not useful in differentiating between severe and mild forms of MIS-C.

Conclusion: Early recognition of clinical features of MIS-C and classification based on disease severity can guide clinicians in diagnosis and treatment of MIS-C. Prolonged fever, shock, elevation of specific inflammatory, and cardiac markers, and echocardiographic abnormalities should raise suspicion for severe disease, prompting rapid intervention and tailored treatment strategies to improve patient outcomes and reduce potential mortality and long-term sequelae.

Keywords: MIS-C, COVID-19, fever, myocarditis, valve insufficiency, hypotension

ÖZ

Amaç: Bu araştırmanın temel hedefi, Multisistem Enflamatuvar Sendromlu çocuklarda (MIS-C) hastalığın şiddetli ve hafif formlarını birbirinden ayırmayı sağlayacak önemli klinik ve laboratuvar göstergelerini belirleyerek erken teşhis ve kişiselleştirilmiş tedavi yaklaşımlarının uygulanmasını desteklemektir.

Yöntem: Bu retrospektif, tek merkezli analiz, MIS-C hastalarının klinik verilerini inceleyerek hastalık şiddetiyle ilişkili faktörleri belirlemek amacıyla yapılmıştır. Çalışmada demografik, klinik, laboratuvar ve ekokardiyografik parametreler değerlendirilmiş, şiddetli MIS-C (inotropik destek veya uzun süreli yoğun bakım ünitesi yatışı gerektiren) olan hastalar, hafif MIS-C'li olanlarla karşılaştırılmıştır. Gruplar arasındaki anlamlı farklılıkları belirlemek için istatistiksel analizler yapılmıştır.

Bulgular: Şiddetli MIS-C grubunda daha uzun süren ateş, şok varlığı, taşikardi ve hipotansiyon gözlendi. Lenfopeni, hipoalbüminemi ve yüksek ferritin düzeyleri gibi enflamatuvar belirteçler, şiddetli grupta anlamlı derecede daha belirgindi. Yüksek N-terminal pro-B tipi natriüretik peptid ve troponin düzeyleri de miyokardiyal tutulumu gösteren şiddetli MIS-C ile anlamlı derecede ilişkiliydi. Azalmış ejeksiyon fraksiyonu ve kapak yetersizliği olan ekokardiyografik bulgular, kötüleşen klinik durumların önemli göstergeleriydi. 2019 Koronavirüs hastalığı polimeraz zincir reaksiyonu ve serolojik testleri, şiddetli ve hafif hastalık arasında ayrım yapmak için yararlı değildi.

Sonuç: MIS-C klinik özelliklerinin erken tanınması ve şiddetine göre sınıflandırılması, klinisyenlere tanı ve tedavi süreçlerinde rehberlik edebilir. Uzamış ateş, şok, spesifik enflamatuvar belirteçler, yüksek kardiyak belirteçler ve ekokardiyografik anormallikler şiddetli hastalık şüphesini artırmalı, hızlı müdahale ve hastaların sonuçlarını iyileştirmek, potansiyel mortaliteyi ve uzun dönem sekelleri azaltmak için uyarlanmış tedavi stratejilerini teşvik etmelidir.

Anahtar kelimeler: MIS-C, COVID-19, ateş, miyokardit, kapak yetmezliği, hipotansiyon

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INTRODUCTION

The Coronavirus disease 2019 (COVID-19) pandemic, which emerged in December 2019, has brought with it a series of complications that have profoundly affected healthcare systems worldwide. One such complication is Multisystem Inflammatory Syndrome in Children (MIS-C), a rare but potentially serious condition. Although MIS-C occurs in less than 1% of children who have had COVID-19, the fact that 62% of these cases require intensive care and mortality rates less than 2% underscores the severity and urgency of this syndrome. MIS-C cases, first reported in the United Kingdom in April 2020, have been also reported in many countries in Europe, Canada, the United States, South Africa, and also China, making MIS-C a global health concern. MIS-C presents with a wide variety of clinical features. In some cases, symptoms of Kawasaki disease or incomplete Kawasaki disease are observed, while in the remag cases, it may mimic the clinical picture of toxic shock syndrome which complicates establishment of diagnosis and treatment of MIS-C[1-6].

Although the pathophysiology of MIS-C is not yet fully understood, it is thought that an excessive immune response developed against the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) forms the underlyung etiopathogenesis of this syndrome. MIS-C, which generally emerges between 2 and 6 weeks following a COVID-19 infection, shows similarities to Kawasaki disease, macrophage activation syndrome, and cytokine storm syndrome[3].

During the COVID-19 pandemic, cases of MIS-C have been frequently observed in pediatric emergency departments, where patients often receive their initial diagnosis. Despite negative polymerase chain reaction (PCR) test results, many MIS-C cases show positive antibodies in serology, suggesting a prior COVID-19 infection. Cardiac involvement is a significant finding in MIS-C, linked to systemic post-infectious inflammation, myocarditis, cardiomyopathy, or myocardial ischemia due to coronary aneurysms[1,2].

Even though the incidence of MIS-C cases has shown a downward trend, raising awareness about this potentially serious condition carries vital importance. In terms of establishing diagnosis and administering appropriate treatment modality. Early intervention can help improve outcomes and lower the risk of severe complications. The aim of this study is to evaluate the demographic characteristics, clinical findings, echocardiographic and laboratory findings of patients diagnosed as MIS-C who were referred to the emergency department, in order to differentiate between severe and mild forms of the disease. Evaluation at the time of initial diagnosis will allow for the classification of the disease as mild or severe, influencing the clinician's treatment and clinical approach. A more effective clinical approach has the potential to reduce the mortality and sequelae of MIS-C. In this context, we believe that determining the clinical characteristics and markers of disease severity in MIS-C is an important step in pediatric emergency medicine.

MATERIALS and METHODS

Data Collection

In this study archival files of the patients diagnosed with MIS-C at the Pediatric Emergency Department of Ege University Faculty of Medicine between October 2020 and July 2022 were reviewed retrospectively. After approval obtained from the Ege University Medical Research Ethics Committee, patient data were accessed retrospectively (approval number: 22-8.1T73, dated: 25.08.2022).

Cases included in the study were selected according to the diagnostic criteria of MIS-C defined by The Centers for Disease Control and Prevention (CDC)[6]. Patients with immunodeficiency, those with a history of malignancy, and cases with other serious infectious diseases were excluded from the study. Besides, demographic characteristics, vital signs, clinical symptoms, laboratory values, echocardiography findings, treatment processes, and outcomes were retrieved from electronic patient files.

The study included patients who met the following CDC criteria:

1. Younger than 21 years old.

2. Presence of fever ≥38 °C, positive inflammatory laboratory markers, ≥2 organ system involvement, and symptoms of severe illness requiring hospitalization.

3. Evidence of recent SARS-CoV-2 infection or contact history.

4. No alternative diagnosis.

5. Presence of at least two of the following indications: cardiac, mucocutaneous, hematologic, or gastrointestinal involvement, and shock.

MIS-C cases were divided into two groups based on clinical severity of the disease as "Severe MIS-C" and "Mild MIS-C." The "Severe MIS-C" group consisted of

intensive care unit (ICU) patients, who required positive inotropic support, fluid replacement greater than 20 cc/kg or invasive mechanical ventilation[7]. The remaining cases were classified as "Mild MIS-C." Variables studied in both groups were comparatively evaluated.

Echocardiography

Echocardiography reports were reviewed retrospectively. Patients presenting to the Pediatric Emergency Department were evaluated by a pediatric cardiologist using a Vivid E9 ECHO device (General Electric Medical Systems Vivid, USA). Echocardiographic examinations were performed using S5 and S6 probes with a frequency range between 3-7 MHz. Echocardiographic reports included images obtained in subcostal, parasternal long-axis, short-axis, apical four-chamber, five-chamber, and suprasternal positions, incorporating M-mode, 2-dimensional, and Doppler examinations which assessed hemodynamic functions, valve functions, and proximal coronary artery measurements.

Statistical Analysis

Power analysis, conducted using G*Power v 3.1.9.7 software program indicated requirement of a minimum sample size of 50 patients to achieve 80% power at a significance level of α=0.05. Statistical analyses were performed using SPSS 21.0 software. The Kolmogorov-Smirnov test was used to assess the normality of data distribution. For comparisons involving more than two groups, one-way analysis of variance (ANOVA) was employed, provided that the data exhibited homogeneity of variance. In the comparison of two independent groups, Student's t-test was applied to normally distributed data, while the Mann-Whitney U test was used for data that did not meet the assumption of normality. The chi-square test was used to compare categorical variables, and ANOVA was used for comparisons involving two or more groups. The threshold for statistical significance was set at p<0.05. These methods were rigorously applied to ensure the reliability and validity of the findings.

RESULTS

A total of 52 patients were recruited into the study within a period of two years. The median age of the patients included in the study was 8 years (minimum: 2; maximum: 17), and 59% of them were male. The median age of severe, and mild MIS-C cases were 12 (minimum: 5; maximum: 17), and 4.5 (minimum: 2; maximum: 16) years respectively with a statistically significant difference between both groups (p<0.001). Mild clinical findings were more frequently observed in patients younger than six years, while severe cases were observed more often in patients over 12 years of age (p=0.001). Although comorbidities more frequently observed in cases with severe MIS-C, intergroup difference was not statistically significant (p=1) (Table 1).

Table 1. Demographic and clinical characteristics of MIS-C cases

		Mild MIS-C n=29	Severe MIS-C (a) n=23	p-value
Demographic data	**Age (years), median (minimum-maximum)**	4.5 (2-16)	12 (5-17)	<0.001
	Age groups (years) <6 6-12 >12	 16 8 5	 2 9 12	**0.001**
	Gender Male Female	 18 11	 13 10	0.779
	Presence of comorbidity (ies) (b) No Yes	 26 3	 20 3	1
Symptoms	**Duration of febrile episodes (days), mean ± SD**	4.07±2.13	5.78±1.80	**0.003**
	Sore throat No Yes	 25 4	 21 2	0.682
	Cough No Yes	 25 4	 23 0	0.120
	Dyspnea No Yes	 27 2	 21 2	1
	Abdominal pain No Yes	 22 7	 16 7	0.755
	Vomiting No Yes	 17 12	 13 10	1
	Diarrhea No Yes	 17 12	 14 9	1

Table 1. Continued

		Mild MIS-C n=29	Severe MIS-C (a) n=23	p-value
Symptoms	**Rash**			
	No	14	16	0.162
	Yes	15	7	
	Headache			
	No	26	21	1
	Yes	3	2	
	Loss of smell and taste			
	No	28	23	1
	Yes	1	0	
	Impaired consciousness			
	No	27	19	0.387
	Yes	2	4	
Findings	**Tachypnea**			
	No	28	19	0.157
	Yes	1	4	
	Tachycardia			
	No	27	6	**<0.001**
	Yes	2	17	
	Hypotension			
	No	29	4	**<0.001**
	Yes	0	19	
	Shock (c)			
	No	29	2	**<0.001**
	Yes	0	21	
	Lymphopathy			
	No	26	21	1
	Yes	3	2	
	Conjunctivitis			
	No	19	12	0.400
	Yes	10	11	
	Peelings of lips			
	No	29	21	0.191
	Yes	0	2	
	Strawberry tongue			
	No	29	22	0.442
	Yes	0	1	
	Eyelid edema			
	No	27	19	0.387
	Yes	2	4	
	Mucocutaneous lesions (d)			
	No	13	9	0.781
	Yes	16	14	

Table 1. Continued

		Mild MIS-C n=29	Severe MIS-C (a) n=23	p-value
Findings	**Neck stiffness**			
	No	28	21	0.577
	Yes	1	2	
	Seizures			
	No	28	23	1
	Yes	1	0	

(a): MIS-C cases admitted to the ICU or those requiring shock therapy with inotropic support (≥20 cc/kg) normal saline deficit or invasive mechanical ventilation support were grouped as "Severe MIS-C".

(b): Comorbidities included hydronephrosis, L-TGA, allergic asthma, UPD, IgA deficiency, and Type 2 DM.

(c): Cases with ≥2 clinical signs of shock (prolongation in capillary refilling time, pale-cold or mottled skin, weak peripheral pulses, altered consciousness) or cases given inotropic support/NS deficit were evaluated within the scope of shock.

(d): Mucocutaneous findings include presence of one of the following: rash, conjunctivitis, lip peeling/fissuring, strawberry tongue, eyelid edema.

MIS-C: Multisystem inflammatory Syndrome in Children, NT-proBNP: N-terminal pro-B-type natriuretic peptide, RCA Z score: Z score for the right coronary artery, LCA Z score: Z score for the left coronary artery, IVIG: Intravenous immunoglobulin, L-TGA:Levo-transposition of the great arteries UPD: Uniparental disomy, ICU: Intensive care unit, IgA: Immunoglobulin A, Type 2 DM: Type 2 diabetes mellitus

In the severe MIS-C group, the mean duration of fever was statistically significantly prolonged (5.78±1.80 days (p=0.003). Other clinical findings were observed with similar frequencies between the mild and severe MIS-C groups. However, clinical findings such as tachycardia, hypotension, and shock were significantly more frequent in severe MIS-C cases (p<0.001) (Table 1).

Any statistically significant differences were not observed between both groups in terms of hemoglobin levels (p=0.847), leukocyte (p=0.143), and platelet (p=0.105) counts. However, neutrophil (p=0.043) and lymphocyte (p=0.047) counts differed significantly between groups.

When examining inflammation markers, procalcitonin (p=0.694), C-reactive protein (CRP) (p=0.138), erythrocyte sedimentation rate (p=0.321), lactate dehydrogenase (p=0.883), ferritin (p=0.042), fibrinogen (p=0.098), and D-dimer (p=0.139) values were not found to be statistically significant. The average serum albumin value was significantly lower in the severe MIS-C group (3.17±0.56) compared to the mild MIS-C group (p=0.003). Urea and creatinine values were significantly higher in the severe MIS-C group (p=0.010; p=0.012). International normalized ratio and prothrombin time

values did not show a statistically significant difference between both groups. When cardiac markers were examined, significant differences in N-terminal pro-B-type natriuretic peptide (NT-proBNP) and troponin T levels were observed between severe and mild cases of MIS-C. (p≤0.05, p<0.011, Table 2)

Statistically significant cardiological findings were detected including increased troponin levels, echocardiographic evidence of valvular insufficiency, and a decrease in ejection fraction (EF) (p=0.011, p=0.013, p<0.001, Table 3). Myocarditis was observed in 25% of patients (13 cases) without any significant relevant difference between groups of cases with severe and mild MIS-C (p=0.54). Additionally, any significant intergroup difference was not found when when compared in terms of NT-proBNP elevation, presence of pericardial effusion, coronary involvement, and Z scores according to the location of coronary involvement (Table 3).

Table 2. Laboratory values in MIS-C cases

		Mild MIS-C median (min-max)	Severe MIS-C median (min-max)	p-value
Hemogram	Hemoglobin	11.1 (9-13.1)	10.8 (7.5-16.1)	0.847
	Leukocyte	10150 (2530-29000)	12150 (3870-39800)	0.143
	Neutrophil	6850 (1610-21490)	9940 (3090-30700)	**0.043**
	Lymphocyte	1340 (460-6380)	1020 (240-6600)	**0.047**
	Platelet	223000 (76000-691000)	164000 (43000-509000)	0.105
Inflammation markers	Procalcitonin	1.95 (0.21-60)	1 (0.12-27.8)	0.694
	CRP	158±75	187±84.6	0.138
	ESR	43.5 (9-114)	34 (8-126)	0.321
	Albumin	3.67±0.50	3.17±0.56	**0.003**
	LDH	271 (158-401)	276 (86-621)	0.883
	Ferritin	288 (29.8-996)	541 (34-1779)	**0.042**
	Fibrinogen	584 (270-880)	512 (191-1016)	0.098
Biochemistry	Glucose	105 (56-224)	108 (63-149)	0.852
	Urea	19 (10-32)	26 (13-188)	**0.010**
	Creatine	0.39 (0.2-0.9)	0.56 (0.31-4.49)	**0.012**
	Na	133±3.09	133±5.8	0.810
	AST	25 (11-74)	28 (10-98)	0.472
	ALT	19 (7-73)	29 (8-124)	0.253
	Triglyceride	183 (119-253)	225 (98-523)	0.423
Coagulation markers	INR	1.1 (0.9-1.58)	1.1 (0.8-11)	0.440
	PTZ	25.7±3.12	25.5±3.11	0.992
Cardiac markers	NT-proBNP	942 (50-17310)	3354 (113-33841)	**0.05**
	Troponin T, ng/L			**0.011**
	Low	22	9	
	High	7	14	
COVID	**COVID PCR**			0.330
	Negative	25	20	
	Positive	0	1	
	COVID serology			0.330
	Negative	1	3	
	Positive	25	20	

CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, LDH: Lactate dehydrogenase, AST: Aspartate amnotransferase, ALT: Alanne amptransferase, INR: International normalized ratio, PTZ: Partial thromboplastin time, PCR: Polymerase chain reaction, MIS-C: Multisystem inflammatory Syndrome in Children, Min-max: Minimum-maximum, Na: Carbon, NT-proBNP: N-terminal pro-B-type natriuretic peptide, COVID: Coronavirus disease

When comparing treatment methods, IV inotropes and steroids were significantly more frequenty used in severe cases of MIS-C (p<0.001; p=0.033). Administration frequency of intravenous immunoglobulin and antibiotics did not differ between both groups (Table 3).

All cases (n=52; 100%) admitted to the ICU were hospitalized for treatment either in the ICU (38.4%) or monitored in the general pediatric unit (61.6%). The severe MIS-C group was observed more frequently in the ICU (p<0.001). The median hospital stay was 10.5 days (minimum: 4; maximum: 27). Hospital stay of the severe MIS-C group that was admitted to the ICU was statistically significant longer than the group that was not (p<0.001; Table 3).

DISCUSSION

In clinical settings, MIS-C commonly presents with fever, myocarditis, and shock. Recent recommendations increasingly emphasize these clinical manifestations[8,9]. In our study, the severe MIS-C group exhibited longer duration of fever, along with the presence of shock, tachycardia, and hypotension. The prolonged febrile episodes suggest an extended inflammatory process, potentially contributing to the increased severity of the illness. In patients with severe MIS-C, protracted fever and shock may indicate a more severe disease course.

The literature indicates that lymphopenia, hypoalbuminemia, and elevated ferritin levels are significant diagnostic parameters of MIS-C as also emphasized in newly developed recommendations[6,8,10-13]. In our study, as inflammatory markers lymphopenia (1020 cells/μL), hypoalbuminemia (3.45±0.58 g/dL), and increased ferritin (541 μg/L) levels were significantly, and more frequently detected in the severe MIS-C group compared to the mild MIS-C group which suggests the importance of monitoring lymphopenia and albumin levels in tracking disease progression and determining prognosis. As expected, ferritin levels were higher in

Table 3. Cardiac investigations, treatment modalities and outcomes in MIS-C cases

		Patients, n	Mild MIS-C patients, n	Severe MIS-C patients, n	p-value
Cardiac markers and echocardiographic findings	Increased troponin levels, n (%)	21	7	14	**0.011**
	Increased NT-proBNP levels	49	28	21	1
	Myocardite	13	4	9	0.54
	Coronary involvement	6	2	4	0.387
	LCA Z scores Perivascular hyperechogenicity Dilatation only Small aneurysm	 2 1 2	 1 1 1	 1 0 1	0.840
	RCA Z scores Perivascular inflammation Hyperechogenicity Small aneurysm Medium-sized aneurysm	 2 1 1	 1 0 1	 1 1 0	0.548
	Pericardial effusion	11	6	5	1
	Valve insufficiency	15	4	11	**0.013**
	Decreased ejection fraction	23	4	19	**<0.001**
Medications used for treatment	Inotropes	15	0	15	**<0.001**
	IVIG	49	27	22	1
	Streoids	37	17	20	**0.033**
	Antibiotics	48	25	23	0.120
Outcome	**Hospitalization** In service In intensive care unit	 32 20	 29 0	 3 20	**<0.001**
	Hospitalization, days, median (min-max)	10.5 (4-27)	9 (4-15)	15 (9-27)	**<0.001**

LCA: Left coronary artery, RCA: Right coronary artery, IVIG: Intravenous Immunoglobulin

the severe MIS-C group than in the mild MIS-C group, serving as a significant indicator of disease severity. Elevated CRP has been emphasized as a significant diagnostic parameter of MIS-C[14]. However, in our study, while elevation of CRP was an important diagnostic parameter at the onset of the disease it was not useful for determining disease severity. Further research should be conducted to determine a cut-off value for differential diagnosis between severe and mild disease. Although neutrophil, creatinine, and urea are apparently clinically significant biomarkers in severe MIS-C, their values remained within the reference range, precluding their use in disease assessment.

In cases with MIS-C, the prognostic significance of cardiac markers has been substantially emphasized in the literature[10,15-19]. In the study by Bichali et al.[20], elevated NT-proBNP values demonstrated higher diagnostic specificity and sensitivity in identifying cardiogenic shock. Our study revealed significantly elevated NT-proBNP and troponin levels in severe cases with MIS-C. These cardiac enzymes are significant prognostic markers in cases with MIS-C, and the presence of serious myocarditis in cases with severe MIS-C is a crucial finding, highlighting the need for clinicians to exercise greater vigilance in practice.

Any statistically significant difference was not observed between both groups in terms of COVID-PCR and serological test results. Our study, expectedly indicates that most cases had a prior COVID-19 infection 4-6 weeks before their presentation[21]. Although serology tests performed 4-6 weeks after recovery from COVID-19 infection revealed the presence of MIS-C in most patients, this finding was not sufficient to differentiate between severe and mild disease presentations. The underlying mechanism linking MIS-C with a COVID-19 infection suffered 4-6 weeks priorly is complex and not fully understood. Further observation and research are warranted to elucidate this relationship.

In MIS-C, cardiac involvement and echocardiographic findings include reduced ventricular EF, mitral regurgitation, pericardial effusion, and coronary artery involvement[22-26]. Echocardiographic findings are highly significant prognostic markers. Our study found that reduced EF and valve insufficiency were significant indicators in patients with clinically worsening conditions, differentiating between mild and severe MIS-C. A key finding of our study is the concordance of these echocardiographic findings with elevated troponin levels (Figure 1). Although coronary involvement may affect long-term prognosis, it isn't significant in determining disease severity at initial presentation. Pericardial effusion has been observed with similar frequency in both mild and severe cases, which is frequently encountered in mild cases of viral infections.

Treatment approaches for patients diagnosed with MIS-C vary based on the clinical severity of the disease. Herber et al.[27] demonstrated that patients with elevated NT-proBNP and troponin levels often require intensive care. In the literature, myocardial dysfunction has been associated with shock in these patients[26]. Our data corroborate these findings, indicating that patients with elevated NT-proBNP and troponin levels exhibit

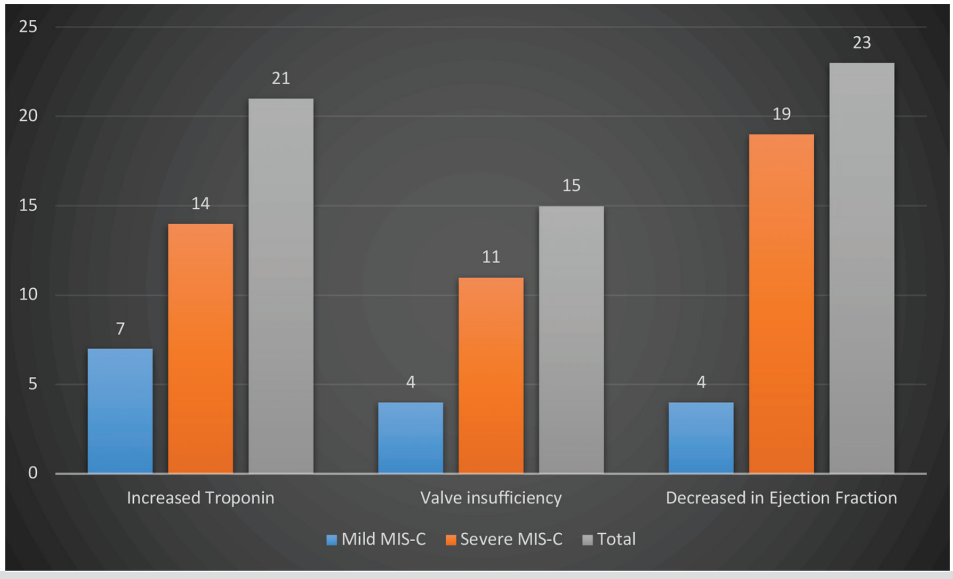

Figure 1. Significant cardiac markers and echocardiographic findings

shock and clinical manifestations of severe MIS-C. Compared to mild MIS-C cases, severe MIS-C cases are characterized by a significant need for inotropic support and prolonged ICU stay. All patients who received initial treatment with inotropic medications required ICU admission. The duration of stay in the ICU was prolonged in the severe MIS-C group (median 15 days). Patients were discharged from the ICU after inotropic medications were discontinued and hypotension and hemodynamic parameters improved. In our clinic, the prominent use of steroids in severe MIS-C cases was a notable finding. Intravenous pulse steroids were administered to severe MIS-C patients in shock during their ICU stay.

Study Limitations

Certain limitations were inherent in our study. The single-center study design, coupled with the relative rarity of cases with MIS-C, constrained the sample size, thereby potentially affecting the generalizability of the findings. The need for intensive care follow-up was determined based on echocardiography findings, which is quikly performed and inexpensive coronary imaging. Future research may include more detailed examinations of the coronary arteries using advanced imaging techniques such as computed tomography angiography and magnetic resonance imaging.

CONCLUSIONS

The clinical recognition of MIS-C, a novel illness emerging after the COVID-19 pandemic, is increasingly important. Even though we may encounter it less frequently, MIS-C remains a condition that requires recognition due to its potential for mortality and long-term sequelae. Classifying MIS-C as either severe or mild can aid clinicians in diagnosis and modify treatment strategies. This classification allows for the prioritization of rapid intervention for patients with severe MIS-C. When evaluating MIS-C, the following findings should raise suspicion for severe disease: fever lasting longer than 5 days, signs of hypotension, tachycardia, and shock; detection of inflammatory markers such as lymphopenia, unexpectedly lower serum albumin levels, increased levels of ferritin and cardiac markers like troponin and NT-proBNP; and echocardiographic findings of reduced EF and valve insufficiency.

Ethics

Ethics Committee Approval: After approval obtained from the Ege University Medical Research Ethics Committee, patient data were accessed retrospectively (approval number: 22-8.1T73, dated: 25.08.2022).

Informed Consent: Retrospective study.

Footnotes

Author Contributions

Surgical and Medical Practices: O.A., E.U.S., Concept: Z.Ş.B., Design: T.K.G., G.A., R.E.L., Data Collection or Processing: O.A., T.K.G., Analysis or Interpretation: C.T., A.Y., G.A., E.U.S., Literature Search: O.A., E.U.S., Writing: O.A.

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

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Original Article

Allergen Sensitization Profiles and the Diagnostic Value of Total IgE, Eosinophil and Basophil Levels in Predicting Atopy in Allergic Diseases in Children

Çocuklarda Alerjik Hastalıklarda Atopiyi Öngörmede Total IgE, Eozinofil ve Bazofil Düzeylerinin Tanısal Değeri ile Alerjen Duyarlanma Profilleri

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ABSTRACT

Objective: Allergy is a hypersensitivity reaction triggered by various factors through immunological mechanisms. Elevated serum total immunoglobulin E (IgE) and peripheral blood eosinophil levels are commonly observed in allergic diseases; however, these biomarkers are not specific to allergy. This study aimed to evaluate the diagnostic value of serum total IgE, eosinophil, and basophil levels in predicting atopy.

Method: Atopic and non-atopic patients under 18 years of age diagnosed with atopic dermatitis, food allergy, allergic rhinitis, or asthma were compared in terms of serum total IgE levels, eosinophil, and basophil counts.

Results: A total of 673 patients including 406 (60.3%) atopic and 267 (39.7%) non-atopic cases constituted the study population. Most frequently sensitization developed to egg in atopic dermatitis, and food allergy, to tree pollens in allergic rhinitis, and to house dust mite in asthma. Elevated total IgE levels were significantly associated with atopy in patients with allergic rhinitis and asthma, with odds ratios of 3.33 and 16.37, respectively ($p<0.001$). The optimal predictive cut-off value of serum total IgE for atopic asthma was calculated as 108.5 kU/L, with a sensitivity of 85.6% and specificity of 76.6%. Similarly, a significant association was observed between eosinophilia and atopy in allergic rhinitis and asthma, but not in atopic dermatitis.

Conclusions: Our findings suggest that serum total IgE is a sensitive and specific biomarker for predicting atopy in patients with asthma.

Keywords: Allergic diseases, atopy, children, eosinophil, total IgE

ÖZ

Amaç: Alerji, çeşitli faktörlerle tetiklenen immünolojik mekanizmalar yoluyla ortaya çıkan bir aşırı duyarlılık reaksiyonudur. Serum total immünoglobulin E (IgE) ile kan eozinofil düzeylerinin alerjik hastalıklarda artmış olması yaygın bir durumdur ancak bu artış yalnızca alerjiye özgü değildir. Bu çalışmada, serum total IgE, eozinofil ve bazofil düzeylerinin atopiyi belirlemedeki tanısal değeri araştırılmıştır.

Yöntem: Atopik dermatit, besin alerjisi, alerjik rinit veya astım tanısı almış 18 yaş altı hastalardan veri toplanmıştır. Atopik ve atopik olmayan hastalar; serum total IgE düzeyleri, kan eozinofil sayıları ve bazofil sayıları açısından karşılaştırılmıştır.

Bulgular: Çalışmaya toplam 673 hasta dahil edilmiş olup bunların 406'sı (%60,3) atopiktir, 267'si (%39,7) ise atopik değildir. Atopik dermatit ve besin alerjisinde en sık duyarlanma yumurtaya; alerjik rinitte, ağaç polenine; astımda ise ev tozu akarına karşı saptanmıştır. Alerjik rinit ve astım hastalarında total IgE yüksekliği, atopiyi öngörmede sırasıyla 3,33 ve 16,37 kat artmış risk ile anlamlı şekilde ilişkili bulunmuştur ($p<0,001$). Atopik astım hastalığını öngören serum total IgE için kestirim değeri 108,5 kU/L olarak hesaplanmış olup, duyarlılığı %85,6 ve özgüllüğü %76,6'dır. Benzer şekilde, alerjik rinit ve astımda eozinofili varlığı ile atopi arasında anlamlı bir ilişki saptanırken, atopik dermatitte bu ilişki gösterilememiştir.

Sonuç: Verilerimiz, serum total IgE düzeylerinin; duyarlılık ve özgüllük oranları dikkate alındığında, astımda atopinin varlığını öngörmede faydalı bir parametre olduğunu göstermektedir.

Anahtar kelimeler: Alerjik hastalıklar, atopi, çocuklar, eozinofil, total IgE

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INTRODUCTION

Allergy is a hypersensitivity reaction that develops through immunological mechanisms induced by various triggers. Atopic dermatitis, food allergy, allergic rhinitis, and asthma constitute the allergic march[1]. Recently, an increase in the prevalence of allergic diseases has been observed worldwide[2,3].

Although elevated total serum immunoglobulin E (IgE) levels and increased eosinophil counts in blood are frequently seen in allergic diseases, this increase is not specific to allergic conditions alone. High serum IgE levels can also be encountered in a variety of clinical entities such as parasitic infestations, infections, malignancies, and immunodeficiencies[4]. On the other hand, some allergic diseases may present without elevated eosinophil or IgE levels. Unlike the Basophil Activation Test, which is highly sensitive in detecting atopic allergy, the clinical significance of absolute peripheral basophil count remains unclear[5]. Therefore, studies continue to search for more definitive clues and specific diagnostic methods helpful in the diagnosis and monitoring of allergic diseases.

The objectives of this study are to determine whether serum total IgE, eosinophil, and basophil levels are elevated in patients with allergic diseases followed in a tertiary care hospital in Turkey, and also to investigate whether these laboratory parameters have diagnostic value in identifying atopy. In addition, as a secondary objective, the distribution of common allergen sensitization patterns among different allergic disease groups will also be analyzed to provide contextual information for interpreting these laboratory findings.

MATERIALS and METHODS

This retrospective, single-center, cross-sectional study was conducted at a tertiary care hospital that serves as a referral center for pediatric patients. Patients under the age of 18 with allergic symptoms who had been clinically diagnosed with atopic dermatitis, food allergy, allergic rhinitis, or asthma between January 2018 and January 2021 were included in the study if they had undergone both skin prick and allergen-specific IgE tests. The diagnoses were established according to the following guidelines: Hanifin and Rajka[6] criteria for atopic dermatitis, European Academy of Allergy and Clinical Immunology guidelines for food allergy, Allergic Rhinitis and its Impact on Asthma guidelines for alleric rhinitis and the Global Initiative For Asthma guidelines for asthma[7-9].

The medical records of the patients were reviewed retrospectively after obtaining approval from the University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, Local Research Ethics Committee (approval number: 2021/17-02, dated: 04.11.2021). Patients with known chronic diseases (such as immunodeficiency), parasitic infections, or chronic drug users, as well as those with missing either complete blood count or serum total IgE test results, were excluded from the study to minimize factors that could affect total IgE, eosinophil, or basophil levels. Data including age, sex, allergic disease diagnosis, serum total IgE levels, eosinophil and basophil counts/percentages, skin prick test, and allergen-specific IgE test results were recorded in case report forms.

In the study, ALK-Abello prick test solutions were used for the skin prick tests. Inhalant allergens included house dust mites, mold, grass pollens, tree pollens, cat dander, dog dander, and cockroach. Food allergens included egg white, egg yolk, cow's milk, wheat flour, peanut, and soy flour. An induration of ≥3 mm compared to the negative control was considered a positive result.

The specific IgE test was performed using the IMMULITE® 1000 immunoassay analyzer and the enzyme-linked immunosorbent assay (ELISA) method, with values of 0.35 kU/L or higher considered positive. Specific IgE testing for egg, milk, grass pollens, and house dust mite was performed individually. In addition, standardized allergen panels were used. The inhalant panel consisted of *Dermatophagoides pteronyssinus*, cat dander, dog dander, horse dander, cockroach, and *Cladosporium herbarum,* while egg, milk, codfish, wheat, peanut, and soybean included in the food panel. The serum total IgE test was also conducted using the IMMULITE® immunoassay analyzer and the ELISA method, and values of 100 kU/L or higher were defined as elevated IgE levels. Eosinophil and basophil counts were determined using the Sysmex XN-1000™ Automated Hematology Analyzer and the flow cytometry method. Eosinophilia was defined as an eosinophil count greater than 450/mm³ or its percentage above 4%, while basophilia was defined as a basophil count greater than 100/mm³ or a percentage above 1%.

The patients with allergic symptoms and a clinical diagnosis of allergic diseases (atopic dermatitis, food allergy, allergic rhinitis, or asthma) were classified into two groups: the atopic group (case group), with at least one positive skin prick test or allergen-specific IgE test result, and the non-atopic group (control group), with

negative results in both tests despite the presence of allergic symptoms.

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). All numerical and categorical data were evaluated using descriptive statistical methods. Non-parametric continuous numerical variables were described using the median and interquartile range (IQR), while categorical variables were presented as numbers and percentages.

A multivariate logistic regression analysis was conducted to evaluate the relationship between atopy and peripheral blood parameters (elevated serum total IgE levels, eosinophilia, and basophilia) in different allergic diseases. Results were reported as odds ratios (OR), 95% confidence intervals (CIs), and p-values. Receiver operating characteristic (ROC) analysis and the Youden index were used to determine the cut-off values of serum total IgE levels, eosinophil counts, and percentages that best predicted atopic disease. Results with a p-value <0.05 were considered statistically significant.

RESULTS

A total of 673 participants including 423 (62.9%) male and 250 (37.1%) female patients were included in the study. The patients received the diagnosis of asthma (n=299; 44.4%), allergic rhinitis. (n=206; 30.6%), atopic dermatitis (n=89; 13.2%), and food allergy (n=79; 11.7%). The median age of the patients was 60 months (IQR: 36-96). A majority of patients with atopic dermatitis (80.9%, n=72) and food allergy (78.5%, n=62) were aged 12 months or younger. Atopy was detected in 60.3% (n=406) of the patients. Table 1 presents the demographic and clinical characteristics of the patients.

According to serum-specific IgE test results, the rates of sensitization to any allergen were 80.9% (n=72) in atopic dermatitis, 94.9% (n=75) in food allergy, 53.4% (n=110) in allergic rhinitis, and 30.1% (n=90) in asthma. Based on skin prick test results, the rates of sensitization to any allergen were 62.9% (n=56) in atopic dermatitis, 86.1% (n=68) in food allergy, 63.6% (n=131) in allergic rhinitis, and 33.1% (n=99) in asthma. When both tests were evaluated together, the overall rates of atopy were 85.4% (n=76) in atopic dermatitis, 100% (n=79) in food allergy, 68.0% (n=140) in allergic rhinitis, and 37.1% (n=111) in asthma.

According to serum-specific IgE test results, the most common sensitizing allergen in patients with atopic dermatitis and food allergy was egg, with sensitization rates of 75.3% and 74.7%, respectively. In patients with allergic rhinitis and asthma, the most common sensitization was to grass pollens, with sensitization rates of 30.1% and 9.4%, respectively. Table 2 shows the specific IgE test results of the patients.

According to the skin prick test results, food allergens were the most frequently identified sensitizers in patients with atopic dermatitis (62.9%) and food allergy (84.8%). The most common food allergen was egg with indicated sensitization rates in atopic dermatitis (58.4%) and in food allergy, (64.6%) followed by milk (20.2% vs 39.2%) and cereals (16.9% vs 8.9%).

Sensitizations to tree nuts, legumes, and seeds were less frequent. Sensitization to multiple food allergens was observed in 31.6% of the patients with food allergy. In patients with allergic rhinitis the most common sensitization was to tree pollens (32.0%), while in

Table 1. Demographic and clinical characteristics of the patients

Characteristics	
Gender, n (%)	
Male	423 (62.9)
Female	250 (37.1)
Allergic diseases, n (%)	
Atopic dermatitis	89 (13.2)
Food allergy	79 (11.7)
Allergic rhinitis	206 (30.6)
Asthma	299 (44.4)
Age (months), median (IQR)	
Atopic dermatitis	11 (6-12)
Food allergy	12 (7-12)
Allergic rhinitis	84 (60-132)
Asthma	72 (48-96)
Total patients	60 (36-96)
Atopy, n (%)	
Present	406 (60.3)
Absent	267 (39.7)
Laboratory findings, median (IQR)	
Serum total IgE (kU/L)	99.6 (34.0-313.0)
Eosinophil count (/mm^3)	350 (190-630)
Basophil count (/mm^3)	40 (30-50)
IQR: Interquartile range	

patients with asthma, it was to house dust mites (18.1%). Table 3 presents the skin prick test results.

Elevated serum total IgE levels was detected in 47.8% (n=143), eosinophilia in 47.2% (n=141), and basophilia in 5.4% (n=16) of the patients of the patients diagnosed with asthma. In patients with asthma, a significant association was found between elevated serum total IgE levels and atopy (OR: 16.37; 95% CI: 8.531-31.412; p<0.001). The presence of eosinophilia was also significantly associated with atopy (OR: 1.99; 95% CI: 1.086-3.631; p=0.026). However, no significant relationship was observed between the presence of basophilia and atopy in patients with asthma (OR: 3.15; 95% CI: 0.754-13.121; p=0.116).

Relatively higher serum total IgE levels were observed in 60.7% (n=125), eosinophilia in 50.5% (n=104), and basophilia in 6.8% (n=14) of the patients diagnosed with allergic rhinitis. Among patients with allergic rhinitis, atopy was significantly associated with elevated serum total IgE levels (OR: 3.33; 95% CI: 1.737-6.379; p<0.001) and eosinophilia (OR: 2.81; 95% CI: 1.441-5.493; p=0.002). There was no statistically significant association between basophilia and atopy (OR: 5.02; 95% CI: 0.626-40.218; p=0.129).

Age-stratified analysis revealed differences in serum total IgE levels of the patients with atopic dermatitis. Relatively higher serum total IgE levels were observed in 23.6% of those aged ≤12 months and 41.2% of those older than 12 months. Overall, 27.0% (n=24) of patients

Table 2. Serum-specific IgE sensitization rates according to type of allergic disease

	Atopic dermatitis, (n=89), n (%)	Food allergy, (n=79), n (%)	Allergic rhinitis, (n=206), n (%)	Asthma, (N=299), n (%)
Serum-specific IgE sensitization to:	72 (80.9)	75 (94.9)	110 (53.4)	90 (30.1)
Egg	67 (75.3)	59 (74.7)	3 (1.5)	0 (0.0)
Milk	23 (25.8)	48 (60.8)	1 (0.5)	0 (0.0)
Food panel	33 (37.1)	34 (43.0)	3 (1.5)	0 (0.0)
Inhalant panel	0 (0.0)	1 (1.3)	73 (35.4)	63 (21.1)
Grass pollens	0 (0.0)	0 (0.0)	62 (30.1)	28 (9.4)
House dust mites	0 (0.0)	0 (0.0)	16 (7.8)	21 (7.0)

IgE: Immunoglobulin E

Table 3. Sensitization rates based on skin prick test results classified according to types of allergic disease

Sensitization	Atopic dermatitis (n=89), n (%)	Food allergy (n=79), n (%)	Allergic rhinitis (n=206), n (%)	Asthma (n=299), n (%)
Sensitization to:	56 (62.9)	68 (86.1)	131 (63.6)	99 (33.1)
House dust mites	1 (1.1)	0 (0.0)	45 (21.8)	54 (18.1)
Tree pollens	1 (1.1)	1 (1.3)	66 (32.0)	41 (13.7)
Grass pollens	1 (1.1)	0 (0.0)	49 (23.8)	29 (9.7)
Mold	0 (0.0)	0 (0.0)	38 (18.4)	40 (13.4)
Cat danders	0 (0.0)	0 (0.0)	33 (16.0)	31 (10.4)
Dog danders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cockroach	0 (0.0)	0 (0.0)	6 (2.9)	5 (1.7)
Egg	52 (58.4)	51 (64.6)	2 (1.0)	0 (0.0)
Milk	18 (20.2)	31 (39.2)	2 (1.0)	0 (0.0)
Cereals	15 (16.9)	7 (8.9)	3 (1.5)	1 (0.3)
Tree nuts	3 (3.4)	1 (1.3)	1 (0.5)	0 (0.0)
Legumes	1 (1.1)	2 (2.5)	0 (0.0)	0 (0.0)
Seeds	2 (2.2)	1 (1.3)	0 (0.0)	0 (0.0)

Table 4. Association between peripheral blood markers and atopy in patients with different allergic diseases				
Allergic disease	**Predictor variable**	**Odds ratio**	**95% CI**	**p-value**
Asthma	Elevated total IgE (≥100 kU/L)	16.37	8.531-31.412	<0.001
	Eosinophilia	1.99	1.086-3.631	0.026
	Basophilia	3.15	0.754-13.121	0.116
Allergic rhinitis	Elevated total IgE (≥100 kU/L)	3.33	1.737-6.379	<0.001
	Eosinophilia	2.81	1.441-5.493	0.002
	Basophilia	5.02	0.626-40.218	0.129
Atopic dermatitis	Elevated total IgE (≥100 kU/L)	5.06	0.608-42.017	0.134
	Eosinophilia	2.99	0.857-10.414	0.086
	Basophilia	-	-	0.999
CI: confidence interval				

presented with elevated serum total IgE values, while indicated number (%) of patients had eosinophilia (n=66; 74.2%) or basophilia (n=3; 3.4%). In patients with atopic dermatitis, any significant correlations were not found between atopy and elevated serum total IgE values, eosinophilia, or basophilia (p>0.05). Among those diagnosed with food allergy, elevated serum total IgE values were detected in 50.0% of those aged ≤12 months and 76.5% of those older than 12 months. Overall, indicated number (%) of patients had elevated serum total IgE values (n=44; 55.7%), eosinophilia (n=48; 60.8%) and basophilia (n=3; 8%). Since all patients diagnosed with food allergy were in the atopic group, predictive analyses for atopy could not be performed for this group. Table 4 displays the relationships between peripheral blood parameters and atopy across different types of allergic diseases.

According to the Youden Index, the optimal cut-off value of serum total IgE for predicting atopic asthma was calculated as 108.5 kU/L [area under the curve: 0.854 [95% CI: 0.811-0.897], p<0.001], with a sensitivity of 85.6% and specificity of 76.6%. Furthermore, in patients with asthma, a significant correlation was found between the number of sensitizations identified by the skin prick test and serum total IgE levels (r=0.532, p<0.001).

DISCUSSION

This study focused on evaluating whether elevated serum total IgE, eosinophil, and basophil levels at the time of diagnosis can serve as predictive markers for atopy in various allergic diseases observed in a pediatric hospital setting. Additionally, skin prick and serum-specific IgE test results of the patients were assessed to determine atopy profiles of these patients. Egg was found to be the most common sensitizing allergen in patients with atopic dermatitis and food allergy, while tree pollens were the most common allergens in allergic rhinitis, and house dust mites in asthma. In asthmatic patients, elevated total IgE levels increased the likelihood of atopy by 16.4 times, and the cut-off value of total IgE for predicting atopy in asthma was calculated as 108.5 kU/L.

There is a strong association between atopic dermatitis and food sensitization, and early detection of these entities is essential to prevent disruption of the skin barrier[1]. Previous studies have shown that egg and milk are the most frequently observed allergens in food allergies in patients with atopic dermatitis, while rates of sensitivities to peanuts, soy, wheat, and fish vary across populations[10–14]. Consistent with the literature, our study found that egg was the most common sensitizing allergen based on serum-specific IgE results in patients diagnosed with atopic dermatitis. Wahn et al.[15] observed that sensitization to food allergens generally develops within the first year of life, while severity of sensitization to aeroallergens increases with age. In our study, 80.9% of patients with atopic dermatitis were infants, which explains their low sensitization rates to aeroallergens.

Avoiding trigger allergens plays a crucial role in the management of allergic rhinitis. Therefore, understanding the distribution of aeroallergens in the region where patients reside is necessary. According to our skin prick test results, the most common allergens inducing epicutaneous sensitization among children with allergic rhinitis were tree pollens (32.0%), followed by grass pollens (23.8%) and house dust mites (21.8%). In studies conducted in South Korea, USA, and China, house dust mites were reported as the most common allergens in children with allergic rhinitis[16-18]. According to relevant studies performed in various regions of

Turkey the most common allergens were house dust mites in İstanbul, and grass pollens in Sakarya[19,20]. The regional distribution of aeroallergen sensitization in our study is likely to be influenced by regional climatic features, vegetation, and allergen diversity. Additionally, the finding that sensitization was detected in only 68% of patients diagnosed with allergic rhinitis can be explained by the preexisting local allergic rhinitis in some patients.

In our study, the most common allergen sensitization detected by skin prick test in asthmatic children was to house dust mites (18.1%). Similarly, the literature supports that house dust mites are major aeroallergens involved in the development of asthma and also the most commonly detected sensitizers in skin prick testing[21]. A 16-year longitudinal study conducted in İstanbul on allergen sensitization in children with asthma reported a decline in sensitization rates to house dust mite since 2001, possibly attributed to periodic education on preventive measures against this allergen[22].

Marsh et al.[23] identified 100 kU/L as the optimal serum total IgE level to distinguish allergic conditions in adults, and this cut-off value is widely used. However, due to the dynamic nature of serum total IgE levels in children, its association with the risk of allergen sensitization and atopic disease remains unclear. Wong et al.[24] reported that in infants younger than 6 months, total IgE levels rarely exceeded 100 kU/L due to immature IgE production, making it unsuitable for predicting disease in this age group. In our study, serum total IgE levels did not predict atopy in patients with atopic dermatitis which may be explained by the fact that most of these patients were under 12 months old, resulting in an uneven age distribution and age-dependent increase in total IgE levels. Although a higher rate of elevated serum total IgE values was observed in patients older than 12 months with atopic dermatitis, the relatively small number of patients in this age group limits the interpretation of this finding.

In contrast to atopic dermatitis, our study found a significant association between atopy and elevated serum total IgE levels in patients with allergic rhinitis and asthma. This finding supports the presence of a strong relationship between serum total IgE levels and atopy, especially in respiratory allergies. Gergen et al.[25] also reported significantly elevated total IgE levels in individuals aged 6 and above with asthma who were sensitized to at least one specific allergen. Similarly, Sherrill et al.[26] demonstrated a significant relationship between skin prick test positivity and high serum total IgE levels in asthmatic children.

In our study, elevated serum total IgE emerged as a strong predictor of atopy in patients with asthma, with an OR of 16.37. Based on this significant value, a ROC analysis was conducted to assess the predictive power of total IgE for atopic asthma. With a threshold of 108.5 kU/L, this biomarker had 85.6% sensitivity and 76.6% specificity in predicting atopy in patients with asthma. These findings suggest that serum total IgE could be a meaningful biomarker for predicting atopy in asthmatic children. However, we believe that this cut-off value should be validated in multicenter studies with larger sample sizes.

Eosinophilia has been identified as a risk factor for severe atopic dermatitis. Infants with eosinophilia and a family history of atopy have an increased risk of developing allergic diseases within the first 6 years of life[27-30]. Although eosinophilia was detected in 74.2% of patients with atopic dermatitis in our study, no significant association was found between eosinophilia and atopy. In a study examining the clinical significance of eosinophilia in food allergy, Noh et al.[31] reported a correlation between eosinophilia and food allergy in patients with atopic dermatitis. They observed a decrease in eosinophil counts following elimination diets and an increase after intake of oral food challenges. They also found eosinophilia in 63.0% (85/135) of patients with atopic dermatitis and food allergy. Similarly, 60.8% of patients with food allergy in our study had eosinophilia.

In our study, a significant association was found between eosinophilia and atopy in patients with allergic rhinitis and asthma. Similar findings have been reported in the literature. For example, Winther et al.[32] showed that eosinophil counts in patients with allergic rhinitis increased during the pollen season and returned to baseline after the season. Özçeker et al.[19] also reported a significant association between eosinophilia and allergen sensitization in allergic rhinitis. These results are consistent with our findings. On the other hand, the relationship between eosinophil counts and clinical severity of allergic rhinitis remains controversial in the literature, and there is no consensus on this issue[33,34].

Hu et al.[28] reported a significantly higher prevalence of basophilia in patients with atopic dermatitis compared to healthy controls, and that patients with severe atopic dermatitis had significantly higher basophil counts compared to those with mild disease. However, our

study did not find basophilia to be a significant predictor of atopy.

Study Limitations

This study has several limitations. Firstly, the inclusion of different allergic diseases resulted in a heterogeneous study population. This issue was solved by conducting separate analyses based on initial diagnoses. The lack of a homogeneous age distribution due to differing age ranges at the time of diagnosis represents another limitation. Furthermore, as the classification of atopic and non-atopic groups relied solely on skin prick test and allergen-specific IgE results, potential false-negative results might have led to misclassification of some patients. Additionally, our study was single-center and retrospective in design. The findings need to be supported by larger scale multicenter studies.

CONCLUSION

In conclusion, our findings suggest that serum total IgE may serve as a valuable biomarker for predicting atopy, particularly in children with asthma, and could support the diagnostic process in clinical practice. It is important to ensure the absence of comorbid conditions when interpreting these laboratory values. Furthermore, given the age-dependent increase in total IgE levels, its use may be limited in children under the age of one year.

Ethics

Ethics Committee Approval: The medical records of the patients were reviewed retrospectively after obtaining approval from the University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, Local Research Ethics Committee (approval number: 2021/17-02 dated: 04.11.2021).

Informed Consent: Retrospective study.

Footnotes

Author Contributions

Concept: Ç.Ö., İ.A.H., N.G., Design: Ç.Ö., İ.A.H., Data Collection or Processing: Ç.Ö., İ.A.H., M.Ş.K., C.Ş.K., Analysis or Interpretation: Ç.Ö., C.Ş.K., Ö.S., Literature Search: Ç.Ö., D.C., N.G., Writing: Ç.Ö., İ.A.H., M.Ş.K., C.Ş.K., Ö.S., D.C., N.G.

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Original Article

Retrospective Review of COVID-19 Polymerase Chain Reaction Test Results of a Children's Hospital According to Person and Time Characteristics

Bir Çocuk Hastanesinde COVID-19 Polimeraz Zincir Reaksiyonu (PCR) Test Sonuçlarının Kişi ve Zaman Özelliklerine Göre Retrospektif İncelemesi

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ABSTRACT

Objective: This study aims to describe the patient and temporal characteristics of the polymerase chain reaction (PCR) test results for children who underwent Coronavirus Disease 2019 (COVID-19) testing at a pediatric hospital between January 1, 2021, and August 31, 2022.

Method: This descriptive archival study was conducted by examining the records of COVID-19 PCR test results (n=36, 102) performed at a pediatric hospital located in the Aegean Region. Demographic data, the time the test performed, and characteristics of the PCR test results obtained from the records. Ethical approval for the study obtained from the relevant ethics committee of the hospital where the research conducted. Statistical analysis of the data performed using the SPSS 27.0 trial version. Statistical significance was considered at $p<0.05$.

Results: The average age of the children included in the study was X=8.25±5.56, with 56.6% being male. The highest proportion of children tested with PCR found to be 1-year-olds, at 11.7%. Of the 36,102 children who were tested, 12.7% had a positive PCR result, with the average age of these children being χ=8.48±5.66 and 52.3% were male. PCR positivity rates vary across different months. A statistically significant difference was found in PCR test results based on the gender of the children ($p<0.05$). The PCR positivity rates varied significantly by season (χ^2=420.323, $p<0.001$). Regression analysis conducted in our study demonstrated that gender and seasonal variables were significant determinants of PCR outcomes.

Conclusion: The PCR test results of children suspected of having COVID-19 found to vary according to gender and season.

Keywords: COVID-19, Severe Acute Respiratory Syndrome Coronavirus 2, child, epidemiological study

ÖZ

Amaç: Bu çalışmanın amacı, 1 Ocak 2021 ile 31 Ağustos 2022 tarihleri arasında bir çocuk hastanesinde Koronavirüs Hastalığı 2019 (COVID-19) testi yapılan çocuklara ait polimeraz zincir reaksiyonu (PCR) test sonuçlarının hasta ve zamana ilişkin özelliklerinin tanımlanması amaçlanmıştır.

Yöntem: Tanımlayıcı nitelikteki bu arşiv çalışması, Ege Bölgesi'nde yer alan bir çocuk hastanesinde gerçekleştirilen COVID-19 PCR test sonuçlarına (n=36.102) ait kayıtların incelenmesiyle yürütülmüştür. Kayıtlardan, demografik bilgiler, testin yapıldığı zaman ve PCR test sonuçlarının özelliklerine ilişkin veriler elde edilmiştir. Bu çalışmanın yürütülebilmesi için ilgili araştırmanın yürütüldüğü hastaneden etik kurul onayı alınmıştır. Verilerin istatistiksel analizleri SPSS paket programı 27.0 deneme sürümünde yapılmıştır. İstatistiksel anlamlılık düzeyi $p<0,05$ olarak kabul edilmiştir.

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Bulgular: Çalışmaya dâhil edilen çocukların yaş ortalaması χ=8,25±5,56 olup, %56,6'sı erkektir. PCR testi yapılan çocuklar arasında en yüksek oran %11,7 ile 1 yaş grubundadır. Test yapılan 36.102 çocuğun %12,7'sinde PCR sonucu pozitif olup, bu çocukların yaş ortalaması χ=8,48±5,66 olup, %52,3'ü erkektir. PCR pozitiflik oranlarının aylara göre değişiklik göstermektedir. Çocukların cinsiyetine göre PCR test sonuçlarında istatistiksel olarak anlamlı bir fark bulunmuştur (p<0.05). PCR pozitiflik oranlarının mevsimlere göre anlamlı farklılık gösterdiği belirlenmiştir (χ^2=420,323, p<0,001). Çalışmamızda regresyon analizinde cinsiyet ve mevsimlerin PCR sonucunda etkili olduğu bulunmuştur.

Sonuç: COVID-19 şüphesiyle test yapılan çocuklara ait PCR test sonuçlarının cinsiyet ve mevsime göre değişkenlik gösterdiği saptanmıştır.

Anahtar kelimeler: COVID-19, Şiddetli Akut Solunum Yolu Sendromu Koronavirüs 2, çocuk, epidemiyolojik çalışma

INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) firstly identified in Wuhan city of China in December 2019, is a new viral respiratory disease characterized by respiratory symptoms of fever, cough, and shortness of breath. It is transmitted through droplets and contact[1]. The COVID-19 pandemic has had the most significant impact on older adults, individuals with chronic health conditions, ethnic minorities, low-income groups, and those experiencing housing insecurity[2]. Although the COVID-19 pandemic tended to have a milder course in children compared to other risk groups, still its clinically significant outcomes in children should not be underestimated[3].

Early diagnosis of COVID-19 disease is crucial for controlling its progression and limiting its spread within the population[4]. Therefore, there is a need for establishing diagnostic methods that provide fast and accurate results at an early stage so as to prevent further spread of COVID-19 disease in the future[4]. Among these tests, the reverse transcription-polymerase chain reaction (rRT-PCR) test, which detects the RNA of the virus, has been recognized as the gold standard in a large-scale study involving 12,270 cases[5]. Consequently, the rRT-PCR test contributes to the early diagnosis of patients, isolation of the patients, treatment, and the reduction of secondary infections among close contacts and health care workers, thereby limiting the transmission of the disease among individuals in the community and aiding in disease prevention[6]. The American Academy of Pediatrics reported that, as of May 11, 2023, more than 15 million children had tested positive for COVID-19 disease, representing 17.9% of all cases, with an incidence rate of 20,718 cases per 100,000 population[7]. In Turkey, due to the lack of published national data illustrating the impact of the COVID-19 pandemic on children, the diagnosis of COVID-19 disease in this population and related clinical and epidemiological characteristics have been limited to findings retrieved from various sample groups[8]. According to a retrospective study involving 10,157 children tested for COVID-19 disease in Turkey, 12.5% of children aged 10 to 18 had received COVID-19 diagnosis[9]. Another study determined that 6.4% of children under the age of 15 in Turkey tested positive for COVID-19[10]. In a study, the researchers retrospectively examined data from 1,156 children who tested positive for COVID-19 in Turkey, and reported that 50.3% of these children were male, with an average age of 10.7 years, and 23.2% of them were over the age of 15. While symptoms of COVID-19 disease , such as fever (50.4%), cough (46.9%), and sore throat (12.4%), were identified in indicated incidence rates[11]. Although there are retrospective studies examining COVID-19 PCR test results in the adult population in Turkey[12-14], studies examining COVID-19 PCR test results in children are limited in number[11,15,16]. Moreover, the retrospective studies cited in the literature regarding children's health conditions during the COVID-19 pandemic have limitations in terms of sample size and the time periods covered by them[17]. In light of these facts, this study aims to describe the COVID-19 PCR test results of children applied to a children's hospital between January 1, 2021, and August 31, 2022, focusing on individual and temporal characteristics.

MATERIALS and METHODS

This study is a descriptive design-based registry investigation. The population of the study includes all children aged 0-18 years (n=36,102) who were suspected of having symptomatic or asymptomatic COVID-19 disease, and underwent PCR testing at Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital of the Health Sciences University between January 1, 2021, and August 31, 2022, without distinction between hospital wards. The entire study population has been accessed. The research data were obtained from the hospital management system records, and examined in a secure environment provided by the institution. The data was retrieved regarding total number of PCR test samples with negative/positive results, and the number of hospitalized children diagnosed with COVID-19 disease. Demographic characteristics of the children, such as age and gender, as well as the timing of the test and the features of the PCR test results, were extracted from the records.

Real-time PCR tests were performed using the DS Coronex COVID-19 multiplex RT-quantitative-PCR detection kit (DS Bio and Nano Technology, Turkey) on the Montania 4896 (Anatolia Geneworks, Turkey) device.

Statistical Analysis

Statistical analyses were performed using the SPSS software, version 27.0. The data were expressed in terms of frequencies, percentages and means. The chi-square test was used to assess the significance of the correlations between the variables and regression analysis was performed using the significantly relevant parameters. Statistical significance was considered at a level of $p<0.05$. Ethical approval for the conduct of this study was obtained from the Ethics Committee of University of Health Sciences Turkey, Dr. Behçet Uz Children's Diseases and Surgery Training and Research Hospital Clinical Research on November 24, 2022, with protocol number 776 and decision number 2022/20-11.

RESULTS

The average age of children (male: 56.6%, and female: 44.4%) who underwent PCR testing due to suspected COVID-19 disease was 8.25±5.56 years. Small percentage (12.7%) of 36,102 children had positive PCR test results. Male children comprised 52.3% of the study population who had positive PCR test results.

Figure 1 shows the age distribution of children who underwent PCR testing for suspected COVID-19 disease. Upon examination of the distribution diagram, it can be observed that the highest testing rate, (11.7%) is found among children aged one year.

The highest and the lowest PCR test positivity rates for COVID-19 disease among children in the year 2021 were detected in September (15.0%) and June (3.8%) 2021, respectively (Figure 2).

The highest and the lowest PCR test positivity rates for COVID-19 disease among children in the year 2022 were detected in February (25.9%), and May (4.1%), respectively (Figure 3).

Figure 4 presents the age distribution of children who tested positive for PCR. According to this distribution, 14.3% of the children who tested positive for PCR were one year old.

The results of the comparison of PCR test results stratified by sex in 2021 are presented in Table 1. Among the individuals who tested positive for COVID-19, 50.6% of them were male and 49.4% of them were female. Statistical analysis indicated a highly significant difference in PCR test results based on the gender of the children, as evidenced by a chi-square statistic of $X^2=38.775$ ($p<0.001$).

The comparison of PCR test results categorized by sex in 2022 is illustrated in Table 2. Among the individuals who tested positive for COVID-19 disease, 53.9% were male and 36.1% were female. The statistical analysis demonstrated a significant difference in PCR test results based on the children's gender, with a chi-square value of $X^2=6.694$ ($p<0.010$).

The distribution of children who had positive PCR test results stratified by seasons is presented in Table 3.

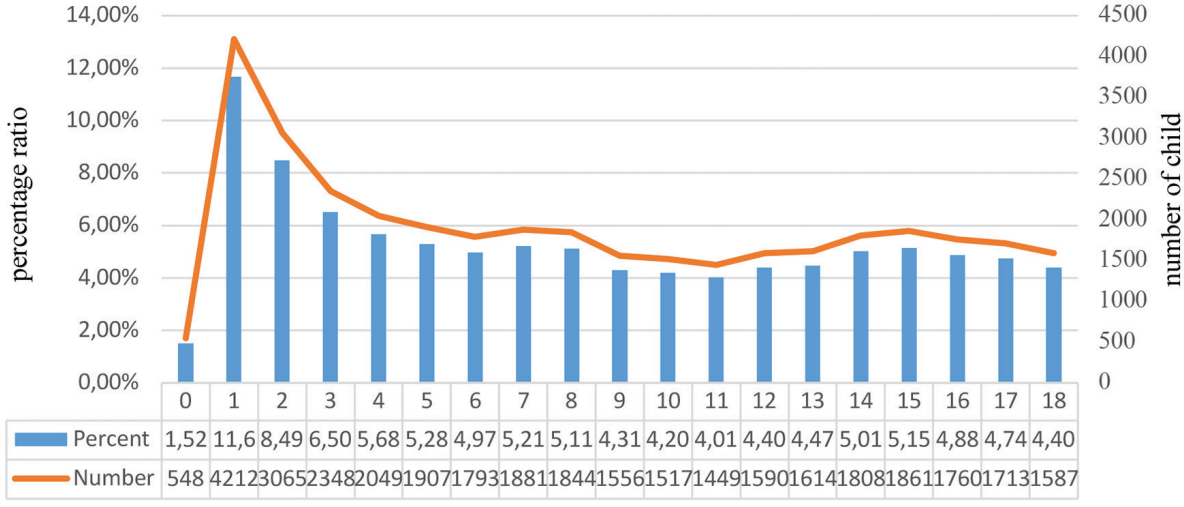

Figure 1. Age distribution of children who underwent PCR testing

PCR: Polymerase chain reaction

A statistically significant difference in PCR positivity rates across the seasons was observed, as indicated by a chi-square statistic of X^2=420.323 (p<0.001).

A multiple regression analysis was conducted to assess the influence of three independent variables i.e. age, gender and season on PCR test results, as illustrated in Table 4. The analysis revealed that the predictive model was statistically significant, with an F statistic of 91.396 (p<0.001). Together, these three variables accounted for 1.3% of the variance in PCR test outcomes. Notably, both gender and season had a statistically significant effect on PCR test results, with t-values of 8.922 (p<0.001) and 10.263 (p<0.001), respectively. The 95% confidence intervals were (1.17-1.25) for gender and (4.48-4.49) for seasons.

DISCUSSION

This study aimed to analyze the descriptive data pertaining to PCR test results of children who underwent

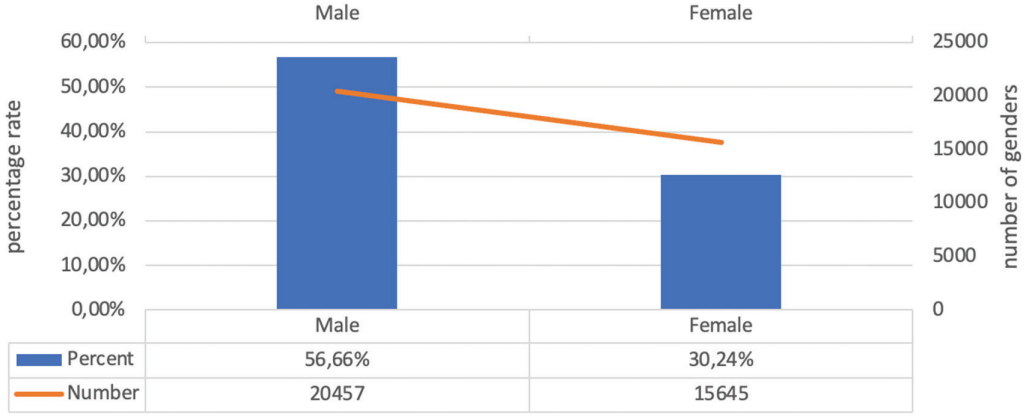

Figure 2. Gender distribution of children underwent PCR testing

In the study, 56.6% of the 36.102 children who underwent PCR testing were male.

PCR: Polymerase chain reaction

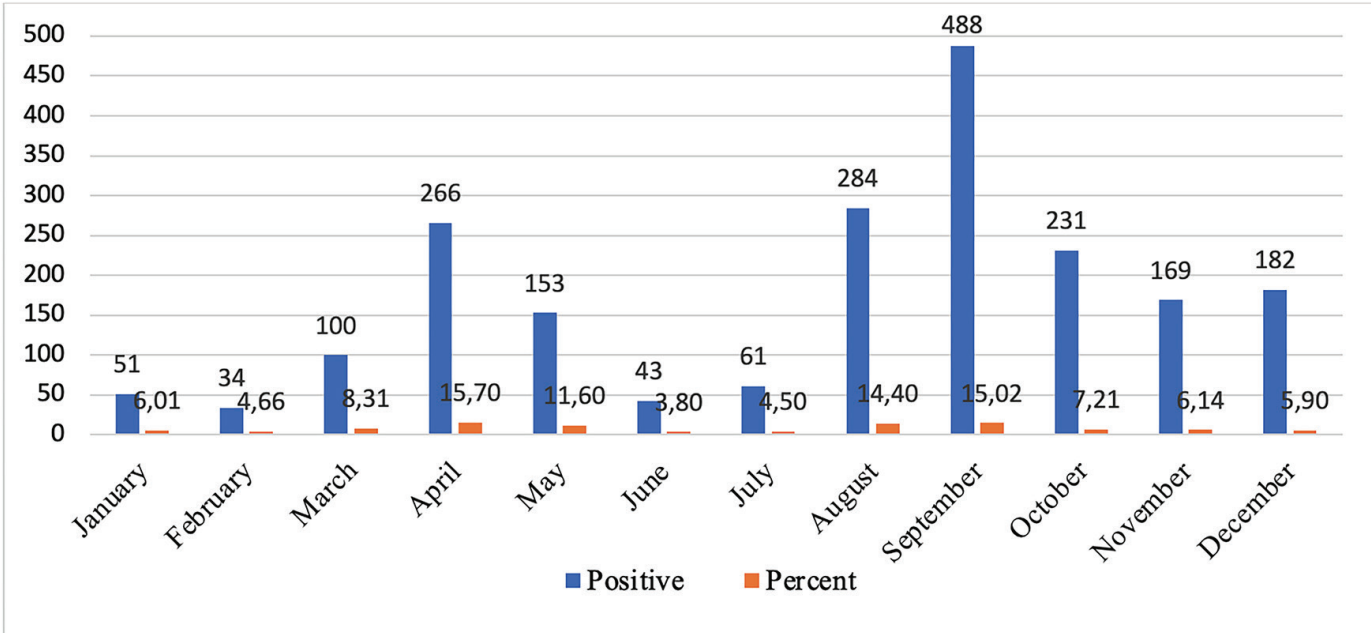

Figure 3. Distribution of children with positive COVID-19 test results by months (2021)

COVID-19: Coronavirus Disease 2019

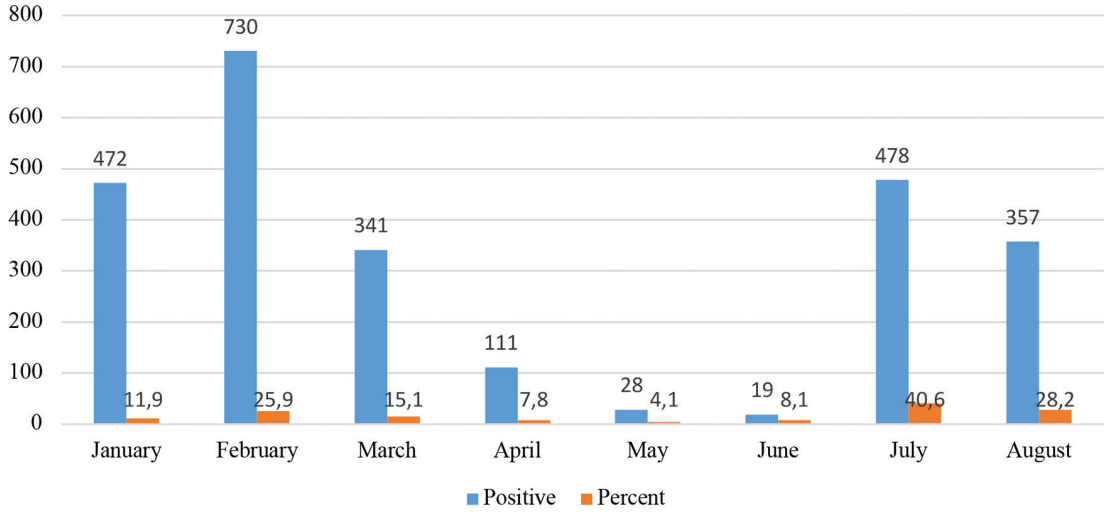

Figure 4. Distribution of children with positive COVID-19 test results by months (2022)
COVID-19: Coronavirus Disease 2019

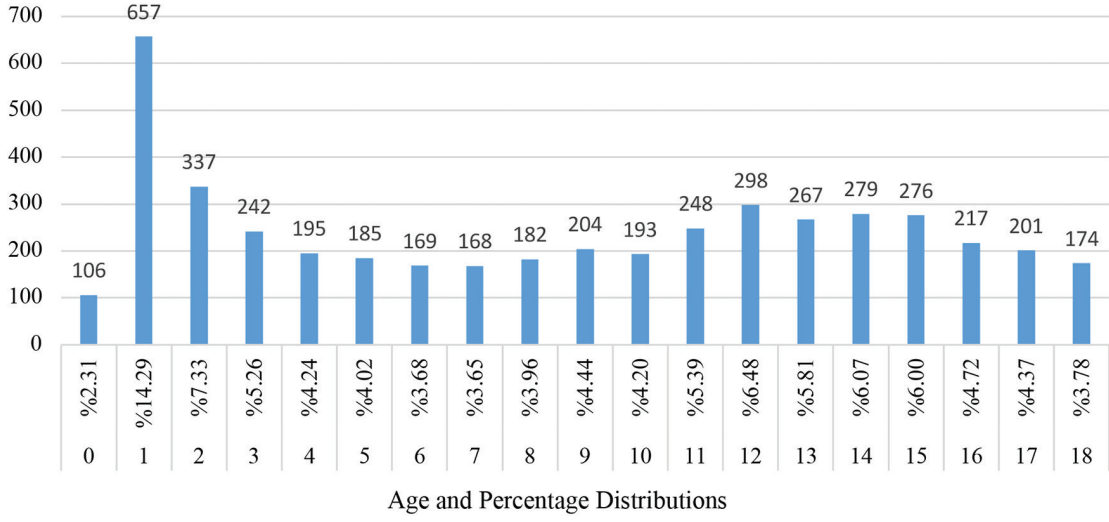

Figure 5. Age distribution of children with positive PCR test results
PCR: Polymerase chain reaction

Table 1. Comparison of PCR test results by gender of children (2021)

	PCR test results				Test value*
	Negative		Positive		
Gender	**n**	**%**	**n**	**%**	
Female	8748	41.9	1022	49.4	X^2=38.775
Male	11864	58.1	1040	50.6	**p<0.001
Total	20612	100.0	2062	100.0	

*: Pearson's chi-squared test **p<0.001, PCR: Polymerase chain reaction

Table 2. Comparison of PCR test results based on the gender of the study participants (2022)					
	PCR test results				Test value*
	Negative		Positive		
Gender	n	%	n	%	
Female	4704	33.2	1167	36.1	X^2 =6,694
Male	6188	56.8	1369	53.9	**p<0.010
Total	10892	100	2536	100	
*: Pearson's chi-squared test **p <0.05, PCR: Polymerase chain reaction					

Table 3. Distribution of children with PCR test positivity by seasons (2021)		
Seasons	PCR (+) number of cases	Test value*
Spring	519	X^2 =420,323 **p<0.010
Summer	388	
Autumn	888	
Winter	267	
Total	2062	
*Pearson's chi-squared test **p <0.05, PCR: Polymerase chain reaction		

Table 4. Multiple regression analysis of PCR test results										
	B	SE	β	t	p	95% Confidence interval		F	Model (p)	Adjusted R square
						Lower limit	Upper limit			
Age	-0.002	0.000	-0.027	-3.954	0.000	-0.003	-0.001	91.396	0.000	0.013
Gender	0.053	0.006	0.063	8.922	0.000	0.042	0.065			
Seasons	0.023	0.002	0.072	10.263	0.000	0.019	0.028			
p=0.001*, SE:Standard error, PCR: Polymerase chain reaction										

testing for COVID-19 at a pediatric hospital between January 1, 2021, and August 31, 2022, with an emphasis on individual and temporal characteristics. Although the COVID-19 pandemic has generally exerted a lesser severity on children in comparison to other high-risk groups, the impacts on this demographic parameter are far from negligible[18]. According to the most recent report issued by the American Academy of Pediatrics since the onset of the pandemic, over 15 million children had undergone PCR testing, with a positivity rate of 17.9%[7]. In the current study, 12.6% of the children assessed for COVID-19 suspicion were PCR positive. While this rate diverges from the figures reported by the European Academy of Pediatrics regarding children diagnosed with COVID-19 disease, a similar investigation conducted earlier during the pandemic indicated an incidence rate of 12.3% among children[19]. These disparities may be attributed to variations in the severity of the pandemic across different countries, as well as the characteristics of the regions where the respective studies were conducted.

In a research analyzing the results of PCR tests conducted on children, the distribution of cases by age group has been extensively examined[20-22]. In the present study, an analysis of the age distribution of children who underwent PCR testing for COVID-19 disease revealed a higher positivity rate among 1- and 2-year-old age groups. Conversely, children under 1 year of age exhibited the lowest positivity rates (Figures 1 and 5). These findings contrast with a study conducted in our country, which reported a higher percentage of positive PCR results in 0-1 year age group relative to other age categories[20]. Similarly, another investigation indicated that children under 1 year of age displayed the highest PCR positivity rate among all age groups[21].

The study conducted by Wali et al.[22] attributed the elevated PCR positivity rate in children under 1 year to an increased likelihood of viral transmission from mothers during pregnancy or postpartum period. In the present study, it is posited that the transmission of COVID-19 disease within the 1-2 year age group may be influenced by exposure to infected family members and

close contacts. The relatively low incidence of positive PCR results in children under 1 year may be indicative of enhanced protective measures provided by their families.

Furthermore, another study found that children aged 15 and older had a higher positivity rate compared to younger cohorts, while the PCR positivity rate within the 1-year-old group was notably low[11]. When interpreting the divergent results reported across these studies, it is imperative to consider variables such as the timing of data collection, sample size, and the geographic context of the research.

When examining the temporal distribution of PCR test results for the children participating in the study, particularly noticeable and higher positivity rates were observed starting from August 2021 (Figure 3 and 4). This finding aligns with the information stated in a report by the American Academy of Pediatrics, which mentioned that "the positivity rate for PCR tests among children steadily increased from August 2021 to May 2022"[7]. These results suggest that the reopening of schools and the commencement of face-to-face education in Turkey as of August 2021 may have contributed to increased interactions among children, particularly in school settings and public transportation, thereby influencing the outcomes.

Several studies have investigated the seasonal variations in the positivity rates of COVID-19 disease among children over time[23-25]. In line with this research, our study also identified distinct seasonal differences in the number of children who tested positive for PCR, revealing a higher incidence of positive cases during the spring and autumn months (Table 3). Consistent with our findings, studies by Abbas et al.[24] and Lota-Salvado et al.[26] also reported an increase in the number of children testing positive for COVID-19 disease during the spring and autumn months. Given that the transmission dynamics of the COVID-19 virus resemble those of the influenza virus, which tends to peak during seasonal transitions, the higher positivity rates observed in spring and autumn can be regarded as a predictable outcome.

In examining the impact of children's gender on PCR test results, this study revealed that both in 2021 and 2022, male children exhibited a higher PCR positivity rate compared to female children ($p<0.05$). This observation aligns with existing literature, which suggests that such differences may be attributable to biological characteristics. Research indicates that girls tend to demonstrate greater adherence to hygiene practices aimed at protecting themselves against COVID-19 disease. Conversely, boys have been observed to comply with preventive behaviors at a lower rate, including frequent handwashing, mask-wearing, and adherence to stay-at-home recommendations[26]. Contrary to our findings, some studies have found no gender-based differences in PCR test results for COVID-19 diagnoses in children[27-29]. These differences in the literature highlight the need for more comprehensive studies with larger sample sizes to conduct gender-based comparisons of COVID-19 test results.

The Centers for Disease Control and Prevention indicated that the reasons for the observed differences in the frequency or severity of COVID-19 disease between genders are not well understood[30].This situation may be attributed to the small sample size of the studies conducted, the course of COVID-19 disease, and non-compliance with individual and societal preventive measures. There is a need for studies that explore the relationship between gender and PCR test results in children in Turkey.

It was determined that gender of the children positively affected PCR test results which may be due to various factors, such as the family environment in which the children are raised, their surroundings, and their attitudes towards hygiene (Table 4). Similarly, Bialek et al.[31] identified gender as a risk factor for testing positive in PCR tests which is consistent with the findings of our study. However, contrarily, Sena et al.[32] reported that gender of the adolescents was not associated with a diagnosis of COVID-19 disease.

It was also found that age did not significantly affect PCR test results of children (Table 4). This may be due to the uniformity of immune system development among children. Consistent with our findings, Güven and Buluş[33] concluded in their study that age was not a determining factor in PCR test results in children. However, other studies have reported conflicting results, indicating that age can be a risk factor in diagnosing COVID-19 disease[32-34]. Furthermore, it was observed that seasonal factors positively influenced PCR test results of children (Table 4). This finding may be explained by the progression of the pandemic, the public health measures implemented at different times and the administration of vaccines to children as a preventive measure. Further studies are needed to explain the seasonal variations in PCR test results among children in Turkey. In line with our findings, Arciniegas et al.[35] reported seasonal

differences in the distributions of PCR test results. They suggested that this variation may be due to fewer tests being conducted and thus lower rates of diagnosis being made during certain seasons.

Study Limitations

The data in this study comprise results of PCR tests of children suspected of having COVID-19 disease, performed at a single hospital over a period of 12 months in 2021 and 8 months in 2022. Consequently, the findings cannot be generalized to all children with COVID-19 disease in Turkey. Additionally, as this study is based on a record review, more detailed inquiries regarding the children's vital signs, chronic illness status, family history of PCR positivity, medication usage, and disease characteristics were not conducted. These limitations should be taken into account when interpreting the results and their implications for broader pediatric populations.

CONCLUSION

We examined the results of PCR tests conducted on children and found that the number of tests and positive results in the 1-year age group were higher than in other age groups. Additionally, the number of children with positive PCR test results increased from August 2021 onwards. A significant relationship was found between gender of the patients and PCR test results, and a seasonal variation in the rates of PCR positivity was identified. In the context of the ongoing uncertainty surrounding the course of future outbreaks of the COVID-19 disease , this study can contribute to implementation of public health measures and health policies. Based on these findings, we recommend conducting further systematic reviews or meta-analyses focusing on children diagnosed with or suspected of having COVID-19 disease .

Ethics

Ethics Committee Approval: Ethical approval for the conduct of this study was obtained from the Ethics Committee of University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Clinical Research on November 24, 2022, with protocol number 776 and decision number 2022/20-11.

Informed Consent: Retrospective study.

Footnotes

Author Contributions

Concept: Ö.K., F.Y.A., A.U.T., F.Z., N.E.,Ş.Ş.,M.Y.Ç., E.C., Design: Ö.K., F.Y.A., A.U.T., Data Collection or Processing: Ö.K., F.Y.A., A.U.T.,N.B., B.C., F.Z., N.E.,Ş.Ş.,M.Y.Ç., E.C., Analysis or Interpretation: Ö.K., F.Y.A., A.U.T., Literature Search: Ö.K., F.Y.A., A.U.T.,N.B., B.C., F.Z., N.E.,Ş.Ş.,M.Y.Ç., E.C., Writing: Ö.K., F.Y.A., A.U.T.,N.B., B.C.

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Original Article

Comparison of Mortality Classifications and Prediction of Morbidity Risk Factors in Esophageal Atresia/Tracheoesophageal Fistula Patients

Özofagus Atrezisi/Trakeoözofageal Fistül Olgularında Mortalite Sınıflandırmalarının Karşılaştırılması ve Morbidite Risk Faktörlerinin Belirlenmesi

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ABSTRACT

Objective: The aim of the study is to compare the mortality rates in cases with esophageal atresia/tracheoesophageal fistula (EA/TEF) using Spitz and Okamoto prognostic classifications as the predictive power of the presence of major cardiac anomalies alone, and to reveal specific risk factor indicators predicting early-stage postoperative morbidities.

Method: Archive files of the patients with the diagnosis of EA/TEF admitted between between January 2000 and May 2020 were retrospectively reviewed. Archive files of the patients were reviewed in terms of their demographic information, disease characteristics, the surgeries they had undergone, postoperative outcomes, early complications, and morbidities developed during follow-up and secondary surgical interventions. Morbidities were divided into three groups as gastrointestinal, respiratory, and developmental complications.

Results: The Okamoto and Spitz classifications were valid in predicting mortality, but the Okamoto classification provided statistically more significant prognostic data. The presence of major cardiac anomalies alone was not significant in predicting mortality. All morbidities were found to be at a higher rate in cases with prematurity and in the presence of accompanying congenital syndrome. The time to removal of postoperatively inserted thoracic and nasogastric tubes, length of hospital stay, and duration of postoperative mechanical ventilation were positively correlated with the development of all morbidities. Anastomotic leakage and development of recurrent fistula were found to worsen especially respiratory morbidities. However, among all morbidities, long-gap EA was not a significant risk factor.

Conclusion: The presence of a major cardiac anomaly, regardless of birth weight, is insufficient to predict mortality. Although Okamoto and Spitz classifications remain valid for predicting mortality, Okamoto classification was a more powerful predictor of mortality. Knowing morbidity-specific risk factors for each of them will guide the follow-up of EA/TEF patients in order to reduce the incidence rates of gastrointestinal, respiratory, and developmental morbidities.

Keywords: Esophageal atresia, tracheoesophageal fistula, mortality, morbidity

ÖZ

Amaç: Bu çalışmanın amacı, özofagus atrezisi-trakeoözofageal fistül (ÖA/TÖF) tanılı olgularda, Spitz ve Okamoto mortalite sınıflamaları ile yalnızca majör kardiyak anomali varlığının mortaliteyi öngörmedeki yeterliliğinin karşılaştırılması ve erken postoperatif morbiditeyi öngören özgül risk faktörlerinin belirlenmesidir.

Yöntem: 2000-2020 yılları arasında ÖA/TÖF tanısı ile izlenen hastalar retrospektif olarak değerlendirildi. Demografik veriler, hastalık özellikleri, cerrahi süreç, postoperatif erken komplikasyonlar, morbiditeler ve sekonder cerrahi girişimler incelendi. Morbiditeler gastrointestinal, solunum ve gelişimsel olmak üzere üç grupta sınıflandırıldı.

Bulgular: Okamoto ve Spitz sınıflamalarının her ikisi de mortalite öngörüsünde geçerliliğini korumakla birlikte, Okamoto sınıflamasının prediktif gücünün istatistiksel olarak daha yüksek olduğu gösterildi. Sadece majör kardiyak anomali varlığı, mortaliteyi öngörmede belirleyici olmadığı görüldü. Prematürite ve eşlik eden konjenital sendrom varlığı, tüm morbiditeler ile anlamlı ilişkili bulundu. Postoperatif toraks tüpü ve nazogastrik sonda çekilme süresi, uzun hastanede yatış ve mekanik ventilasyon süresi tüm morbiditelerin gelişimiyle pozitif korelasyon gösterdi. Özellikle anastomoz kaçağı ve rekürren fistül gelişimi respiratuar morbiditeleri anlamlı düzeyde arttırdığı ortaya kondu. Bununla birlikte, tüm morbiditeler arasında uzun segmentli ÖA anlamlı bir risk faktörü olarak saptanmadı.

Sonuç: Majör kardiyak anomalilerin varlığı tek başına mortaliteyi öngörmek için yetersizdir. Okamoto sınıflaması, Spitz'e kıyasla daha güçlü olmakla birlikte her ikisi de mortalite öngörüsünde geçerlidir. Her bir morbiditeye özgü risk faktörlerinin bilinmesi, gastrointestinal, solunum ve gelişimsel morbiditelerin azaltılması amacıyla EA/TEF hastalarının takibine yön verecektir.

Anahtar kelimeler: Özofagus atrezisi, trakeoözofageal fistül, mortalite, morbidite

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INTRODUCTION

Esophageal atresia (EA) represents the most frequently observed congenital malformation of the esophagus, which occurs in 1/2500 to 1/4000 live births[1]. The most typical form of anomaly is characterized by proximal EA and distal tracheoesophageal fistula (TEF) in 85-88% of the cases[2]. Besides, 30-60% of the cases with EA/TEF were most commonly accompanied by cardiac (35%), vertebral, anorectal, renal, and extremity anomalies[1,2]. In these cases, the presence and severity of additional congenital anomalies are among the key determinants influencing both mortality and morbidity.

The principle of surgery in EA is to provide esophageal continuity by anastomosing the cut ends of the esophagus. The most accepted anatomical classification today is the Gross anatomical classification[2]. In terms of reducing and preventing mortality and morbidity in EA cases, it is important to correct the accompanying anomalies besides primary surgical repair.

In 1994, Spitz et al.[3] developed a mortality risk classification by categorizing patients into three risk groups according to their birth weights and the presence of major congenital heart disease (MCHD). Later in 2009, Okamoto et al.[4] re-evaluated and revised this classification dividing patients into four groups[3,4]. MCHD is defined as cyanotic or atrioventricular ductal and as well as left-to-right shunt pathologies that require surgery before the age of 1 year[3]. Finally, in 2020, Lazow et al.[5] reported that low birth weight was not a determining factor in mortality classification. The Spitz mortality classification allocated patients into low, medium, and high risk groups based on a birth weight limit of 1.5 kg and the presence of major cardiac anomalies[3]. In the Okamoto classification, the birth weight threshold was increased to 2 kg and patients were allocated into:low, medium, relatively high, and high risk groups depending on the presence of a major cardiac anomaly[4].

There isn't any accepted classification that predicts morbidity. However, Lazow et al.[5] presented male gender, prematurity, prenatal diagnosis, and the need for preoperative mechanical ventilation as markers for index admission morbidity.

Recent developments in neonatalogy and surgical technique have led to changes in causative factors that decrease mortality. However, the survival rates have increased, in parallel with a decrease in the incidence rates of late complications and morbidities.

Postoperative morbidities include respiratory problems, dysphagia; need for nutritional support; esophageal stricture; gastroesophageal reflux (GER); additional postoperative surgical interventions; enteral nutrition (tube feeding); need for gastrostomy as causative factors for gastrointestinal morbidity and developmental delay[6].

On esophagography, adequate anastomotic width, the absence of significant dilation in the proximal esophagus, and minimal peristaltic waves in the distal esophagus suggest the presence of a motility disorder. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition guidelines define benign refractory esophageal anastomotic strictures in children as strictures that cause dysphagia despite at least five dilations performed at intervals of no more than four weeks, in the absence of endoscopically observed inflammation[6,7]. Hospital readmissions due to pneumonia within the first two years following surgical repair are common, and patients experiencing two or more episodes are classified as having recurrent pneumonia[8]. During surgical procedures, a "long gap" is defined when, after mobilizing both esophageal segments, the distance between the two cut ends measures 2 cm or more, or exceeds the length of two thoracic vertebrae[9,10]. Secondary surgeries include anti-reflux procedures (most frequently Nissen fundoplication), gastrostomies, and gastric pull-up.

This study aims to evaluate the predictive power of the Spitz and Okamoto classifications, as well as the presence of major cardiac anomalies per se in foreseeing hospital mortality in patients with EA/TEF. Additionally, the study aims to identify individually independent risk factors for early postoperative morbidities by analyzing ample and detailed data regarding EA/TEF.

MATERIALS and METHODS

After obtaining Institutional Ethical Board of University of Health Sciences Turkey İzmir Dr. Behçet Uz Child Diseases and Surgery Training and Research Hospital Clinical Research Ethics Committee approval (approval number: 444, dated: 07.02.2020), data of 211 patients diagnosed with EA/TEF and treated primarily at our institution between January 2000 and May 2020 were retrospectively collected. Patients operated at external centers, misdiagnosed cases, those without accessible medical records, patients died before being operated, or had been followed up for less than two years were excluded from the analysis. The demographic

and basic clinical data related to the presence of prematurity polyhydramnios, a major or minor cardiac anomaly, the type of delivery, the gender of the patient and the concomitancy with either V- Vertebral anomalies (omurga anomalileri) A, Anal atresia, C, Cardiac defects, T, Tracheo-esophageal fistula, E,Esophageal atresia, R, Renal anomalies, L, Limb anomalies (VACTERL) or non-VACTERL syndromes (presence of two or more components associated with VACTERL) were collected. Data regarding disease characteristics and surgery performed, included type of EA (according to Gross classification A, B, C, D, E, and F), length of gap between esophageal cut ends, presence of esophageal elongation procedure, and postnatal age at operation (days). Data on the postoperative period encompassed duration of postoperative invasive mechanical ventilation; feeding with a nasogastric catheter (N/G); follow-up with a chest tube; time to the first oral feeding; first symptomatic stricture and dilation performed; need for prokinetic and inhaled medical treatment; presence of early complications (re-canalization of fistula or anastomotic leakage); total number of dilations perfomed; presence of GER; need for secondary operations (anti-reflux, colonic pull-through, gastric pull-up procedures); and long-term morbidity outcomes (follow up results are limited to two years because of high burden of immigrant patients).

Morbidities that occurred during follow-up period were divided into three groups as gastrointestinal (dysphagia, GER, anastomotic leak, anastomotic stenosis), respiratory (asthma-like symptoms, recurrent pneumonia, cyanotic spells), and developmental (nutritional supplement need, percentile growth charts) morbidities.

In the mortality group, patients who were diagnosed and operated upon during their first hospitalizations were included in the study. Deceased patients after discharge were not included. Patients were evaluated according to their birth weights, and the presence of MCHD (if any).

Statistical Analysis

Descriptive statistics were presented as mean ± standard deviation, median, and range (minimum-maximum) based on the distribution characteristics of continuous variables. Categorical variables were expressed as frequencies and percentages. The normality of numerical variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For comparisons between two independent groups, the Independent Samples t-test was applied to normally distributed variables, whereas the Mann-Whitney U test was used for non-normally distributed variables. The Pearson's chi-square test and Fisher's exact test were used to compare categorical variables between groups. Factors associated with mortality were examined through univariate logistic regression analysis. All statistical analyses and graphical outputs were performed using Jamovi (Version 1.6.3) and JASP (Version 0.13.1) softwares. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 152 patients who did not meet the exclusion criteria were included in the study. Data of 79 (52%) male, and 73 (48%) female patients were included in the statistical analysis. The mean birth weight, and birth age of the patients were 2509.7±653.2 g, and 37±2.7 weeks, respectively. An accompanying syndrome was detected in 87 (57.2%) patients, and morbidities of 74 (85.1%) syndromic patients were associated with VACTERL (Table 1). Ninety percent (n=136) of the cases had type C EA/TEF according to the Gross classification. The median hospital stay was 22 days.

Mortality

In our study, the index admission mortality rate for EA/TEF patients was found to be 25% (n=38).

The Spitz classification placed 65.8% (n=100) of the patients in the low mortality risk group. While 32.2% (n=49) of the cases were in the medium, and only 2% (n=3) of them in the high risk groups. Based on the Okamoto classification system, 53.3% (n=81), 16.4% (n=25), 23.0% (n=35), and 7.2% (n=11) of the cases were in the low, medium, relatively high, and high mortality risk groups, respectively (Table 2).

While statistical analysis confirmed the validity of both the Spitz and Okamoto mortality classifications, logistic regression analysis showed that the Okamoto classification exhibited greater predictive accuracy for mortality ($p<0.001$). The isolated presence of a major cardiac anomaly showed no statistically significant association with mortality prediction. ($p=0.156$) (Table 2).

Morbidity

The morbidity analysis was performed on 95 patients, excluding those with isolated TEF, esophageal web, and patients who died during the initial hospitalization. Early complications were observed in 27.1% of the patients, including recanalization of arteriovenous fistula (n=7) and anastomotic leakage (n=25). The esophagus-

Table 1. Patient demographics and basic clinical data	
	Numerical, and categorical variables
Gender, n (%)	
Male	79 (52)
Female	73 (48)
Mean (±SD) birth weight (g)	2509.7±653.2
Gestational age (weeks) (mean ±SD)	37±2.,7
Antenatal diagnosis, n (%)	9 (5.9)
Prenatal consultancy, n (%)	133 (87.5)
Polyhydramnios, n (%)	39 (25.7)
Family history of EA/TEF, n (%)	2 (1.3)
Prematurity, n (%)	36 (23.7)
Presence of a syndrome, n (%)	87 (57.2)
Syndromic entities, n (%)	
VACTERL	74 (85.1)
Others	13 (14.9)
Mortality, n (%)	38 (25)
EA type (Gross classification), n (%)	
A	9 (6)
C	136 (90.1)
E	6 (4)
Esophageal gap, n (%)	
Short	98 (75.4)
Long (>2 vertebrae, >2cm)	32 (24.6)
Gap Length (cm) (min-max)	1.5 (0.0-7.0)
Need of preoperative mechanical ventilation , n (%)	33 (21.7)
Age at the time of definitive surgery (days) median (min-max))	3.0 (0.0-90.0)
Anastomosis, n (%)	
Tension-free	121 (80.1)
Tensioned	30 (19.9)
Placement of thoracic tube, n (%)	148 (97.4)
Perioperative placement of nasogastric tube, n (%)	151 (99.3)
Lengthening procedure (myotomy/flap from upper pouch), n (%)	11 (7.2)
Bronchoscopy and esophagoscopy, n (%)	152 (100)
Time to thoracic tube removal (days), median (min-max)	8.0 (0.0-55.0)
Time to nasogastric tube removal (days) median (min-max)	12.0 (0.0-270.0)
Length of hospital stay (days) median (min-max)	22.0 (3.0-270.0)
Postoperative duration of mechanical ventilation (days) median (min-max)	6.0 (0.0-86.0)
Duration of noninvasive ventilation (days) median (min-max)	3.0 (0.0-10.0)
Time to the first postoperative oral feeding (days) median (min-max)	10.0 (3.0-100.0)
Gastrostomy, n (%)	15 (10.0)
Colonic transposition, n (%)	1 (0.7)
Gastric pull-up procedure, n (%)	6 (3.9)
Total oral feeding at discharge, n (%)	100 (87.7)

stomach-duodenum passage radiographs of only 4 cases revealed the existence of anastomotic stenosis, However, 52.7% (n=59) of patients manifested symptoms of anastomotic stenosis. Respiratory morbidities were detected in 57.7% of these patients.

Gastrointestinal Morbidities

Development of symptomatic anastomotic stenosis (56.8%), application of esophageal dilatation (60%), enteral tube feeding during follow-up (4.2%), presence of dysphagia (36.8%), and development of GER (54.7%) detected in respective percentages of patients were defined as gastrointestinal morbidities. Prolonged mechanical ventilation, delayed removal of the N/G and chest tubes, presence of associated syndromes, and long-gap EA were identified as statistically significant risk factors indicating gastrointestinal morbidities (p<0.001). Polyhydramniosis, prematurity, and long-gap atresia were found to be the risk factors for the development of GER (p<0,001) (Table 3).

Respiratory Morbidities

Respiratory morbidities were seen in 52.6% of patients. Prolonged mechanical ventilation, and hospital stay, delayed removal of the N/G and thorax tubes, early need for esophageal dilatation, and requirement for additional oxygen were statistically significant risk factors (p<0.001) (Table 4).

Developmental Morbidities

Developmental delay was detected in 4.2% of the cases during follow-up. Accompanying syndromic

Table 1. Continued

	Numerical, and categorical variables
Inhaler usage at discharge, n (%)	61 (55.0)
Early complications (anastomotic leak/fistula recanalization), n (%)	32 (27.1)
Esophageal dilatation, n (%)	57 (60)
Anastomotic stenosis, n (%)	54 (56.8)
Need for additional dietary supplements	87 (77.7)
Respiratory problems, n (%)	50 (52.6)
Dysphagia, n (%)	35 (36.8)
Gastroesophageal reflux, n (%)	52 (54.7)
Postoperative follow-up period (years) median (min-max)	5.0 (0.0-17.0)

EA/TEF: Esophageal atresia and tracheoesophageal fistula, VACTERL: Vertebral defects, A, Anal atresia, C, Cardiac defects, T, Tracheo-esophageal fistula, E,Esophageal atresia, R, Renal anomalies, L, Limb anomalies

Table 2. Mortality Data

	Survival status		**p-value**	**Odds ratio (95 % CI)**	**p-value*** **
	Survived (n=114)	**Deceased (n=38)**			
Major cardiac anomaly, n(%)					
None	83 (72.8)	23 (60.5)	0154*	1.75 (0.81-3.77)	0.156
Present (Ref.)	31 (27.2)	15 (39.5)			
Okamoto risk classification, n(%)					
Low risk (Ref.)	69 (60.5)	12 (31.6)			
Medium risk	14 (12.3)	11 (28.9)	<0001*	4.52 (1.66-12.28)	**0.003**
Relatively high risk	29 (25.4)	6 (15.8)		1.19 (0.41-3.47)	0.751
High risk	2 (1.8)	9 (23.7)		25.87 (4.97-134.77)	**<0.001**
Spitz risk classification, n(%)					
Low (Ref.)	80 (70.2)	20 (52.6)	0007**		
Medium	34 (29.8)	15 (39.5)		1.76 (0.81-3.85)	**0.154**
High	0 (0)	3 (7.9)		N/A	

Ref.: Reference, *: Pearson's chi-square test, **: Fisher-Freeman-Halton test, ***: Logistic regression test, CI: Confidence Interval, N/A: Not applicable

anomalies, prolonged postoperative mechanical ventilation, delayed removal of the N/G and chest tubes, and extended hospital stay were determined to be significant risk factors (p<0.001). Prematurity, gastroesophagel reflux and cardiac anomalies did not demonstrate a statistically significant association with developmental morbidities (p>0.001) (Table 5).

Secondary Surgical Interventions

Forty percent of the patients in the study group required secondary surgery. While anti-reflux (Nissen fundoplication) was the most common surgical intervention performed, 14 patients underwent gastrostomy, and 4 cases underwent both procedures. A gastric pull-up procedure was performed in six patients (Table 6).

Table 3. Gastrointestinal morbidities

	None	Present	p-value
	Anastomotic stricture		
Duration of postoperative mechanical ventilation (days) median (min-max)	4 (0-68)	6 (0-60)	**0.050****
Anti-reflux procedure, n (%)	6 (15)	19 (35.2)	**0.026***
	Esophageal dilation		
Duration of postoperative mechanical ventilation (days) median (min-max)	4 (0-68)	6 (0-60)	**0.026****
Anti-reflux procedure median (min-max)	5 (13.2)	20 (35.1)	**0.017***
Presence of a gap between esophageal cut ends, n (%)	28 (73.7)	52 (91.2)	**0.044***
Gap length, n (%)			
Short Long	23 (82.1) 5 (17.9)	41 (78.8) 11 (21.2)	0.953*
	Dysphagia		
Total number of dilations median (min-max)	0 (0-6)	3 (0-16)	<0.001**
Presence of accompanying syndrome, n (%)	20 (33.3)	22 (64.7)	0.003*
Gap length, n (%)			
Short Long	37 (78.8) 10 (21.3)	26 (81.3) 6 (18.8)	0.784*
Gender, n (%)			
Male Female	36 (60) 24 (40)	11(32.4) 23 (67.6)	**0.010***
Prematurity, n (%)	8 (133)	4 (11.8)	0.999*
	Gastroesophageal reflux		
Polyhydramnios, n (%)	16 (37.2)	8 (15.4)	**0015***
Prematurity, n (%)	10 (23.3)	2 (3.8)	**0005***
Cardiac anomalies, n (%)	38 (88.4)	49 (94.2)	**0461***
Accompanying syndromes, n (%)	18 (41.9)	25 (48.1)	**0545***
	Need for enteral tube feeding		
Time to thoracic tube removal (days) median (min-max)	7 (2-55)	21.5 (13-23)	**0.003****
Time to nasogastric tube removal (days) median (min-max)	10 (0-270)	112.5 (40-251)	**0.002****
Length of hospital stay (days) median (min-max)	24 (8-270)	121.5 (60-251)	**0.004****
Duration of postoperative mechanical ventilation (days) median (min-max)	5 (0-68)	39 (26-60)	**0.001****
Time to the first postoperative oral feeding (days) median (min-max)	10 (0-65)	35 (0-72)	**0.161****
Time to the first esophageal dilation (months) median (min-max)	5 (1-96)	1.5 (0.5-3)	**0.027****
Presence of accompanying syndromes, n (%)	39 (42.9)	4 (100)	**0.039***

*: Pearson chi-square or Fisher's exact test, **: Independent samples t-test, ***: Mann-Whitney U test

DISCUSSION

Improvements in neonatal intensive care, advancements in surgical methods, and preoperatively applied technical innovations, combined with multidisciplinary postoperative follow-up, have been shown to enhance survival rates and quality of life in these patients.

The male-to-female patient ratio in our study was determined to be 1.08, which is consistent with the literature[11]. We observed polyhydramnios in 39 cases (25.7%) during antenatal follow-ups, whereas Lazow's[5] study reported a higher rate (31.2%) of polyhydramnios. Leibovitch's[11], 21-year retrospective study revealed a prematurity rate of 36.2% in their cases, while Sulkowski's[12] national cohort discosed a prematurity rate of 37% in EA/TEF cases. However, our study found a lower prematurity rate of 23.7% in comparison with previously published data. This discrepancy may be attributed to differences in referral patterns, regional variations in perinatal care, and the characteristics of the study population.

Thanks to modern advancements in mechanical ventilation and monitoring protocols in neonatal

Table 4. Respiratory morbidities

	None	Present	p-value
Birth weight (g) (mean ± SD)	2569.1±540.9	2730.7±628.3	0.191***
Age at surgery (days), median (min-max)	2 (1-20)	3 (0-85)	0.160**
Time to thoracic tube removal (days) median (min-max)	7 (2-17)	8 (3-55)	0.037**
Time to nasogastric tube removal (days) median (min-max)	10 (0-31)	12 (3-270)	**0.037****
Length of hospital stay (days) median (min-max)	20 (8-115)	33.5 (8-270)	**0.004****
Duration of postoperative mechanical ventilation (days) median (min-max)	3 (0-26)	6 (0-68)	**0.014****
Time to the first postoperative oral feeding (days) median (min-max)	10.5 (1-60)	3.5 (0.5-96)	**0.050****
Total duration of postoperative O_2 requirement (days) median (min-max)	6.5 (3-28)	9.5 (2-98)	**0.036****
Cardiac anomalies, n (%)			
Minor **Major**	30 (71.4) 12 (28.6)	30 (71.4) 12 (28.6)	0.999*
Gender n (%)			
Male Female	26 (59.1) 18 (40.9)	22 (45.8) 26 (54.2)	0.204*
Prematurity n (%)	5 (11.4)	7 (14.6)	0.647*
Accompanying syndromes n (%)			
VACTERL Others	19 (86.4) 3 (13.6)	17 (85) 3 (15)	0.999*
EA type (Gross classification) n (%)			
A C	1 (2.3) 43 (97.7)	5 (10.4) 43 (89.6)	0.206*
Gap length n (%)			
Short Long	33 (82.5) 7 (17.5)	28 (75.7) 9 (24.3)	0.461*
Early complications (anastomotic leak/fistula recanalization) n (%)	8 (18.2)	16 (33.3)	0.098*
Anti-reflux procedure, n (%)	10 (22.7)	15 (31.3)	0.359*
Preoperative need for mechanical ventilation, n (%)	7 (15.9)	6 (12.5)	0.639*
Inhaler need at discharge, n (%)	4 (9.1)	40 (83.3)	**<0.001***
Antisecretory need at discharge, n (%)	4 (9.1)	40 (83.3)	**<0.001***
Gastroesophageal reflux, n (%)	19 (43.2)	30 (62.5)	0.064*

*: Pearson chi-square or Fisher's exact test, **: Independent samples test, VACTERL: Vertebral defects, A, Anal atresia, C, Cardiac defects, T, Tracheo-esophageal fistula, E,Esophageal atresia, R, Renal anomalies, L, Limb anomalies, EA: Esophageal atresia

intensive care units, low and/or very-low-birth-weight patients can survive at a higher rate. In 1994, Spitz modified the risk classifications based on the presence of cardiac anomalies and birth weight, and since then, it has been recognized as the most frequently preferred prognostic classification system[2]. In 2009, Okamoto introduced a new prognostic classification, emphasizing that major cardiac anomalies serve as a more reliable predictor of survival compared to low birth weight. In the literature various index admission mortality rates have been reported for patients with EA/TEF by Okamoto et al.[4] (19.8%), Leibovitch et al.[11] (13.8%), Lazow et al.[5] (5.1%). In our study, the overall index admission mortality rate for EA/TEF patients was found to be higher, at 25%. The higher prevalence of accompanying major cardiac anomalies and late presentation of high burden of immigrant patients escaping from the war prevailing in the Middle East countries could explain the relatively high mortality rates observed in our clinic. An analysis of recent data reveals a decline in mortality rates, decreasing to 20% over the past decade and further reducing to 14.8% in the last five years. The diversity in mortality rates observed in this study and the literature raises questions about the validity of the defined classifications and the importance of the presence of cardiac anomaly regardless of birth weights. We conducted a regression analysis to confirm our hypothesis that being low birth weight is a less important factor for the prediction of survival. In our study we have considered the presence of major cardiac

Table 5. Developmental morbidities

	None	Present	p-value
Birth weight (g) (mean ±SD)	2690.5±536.6	2639.9±595.8	0.732***
Age at surgery (postnatal days) median (min-max)	3 (1-20)	21.5 (13-23)	0.930**
Time to thoracic tube removal (days) median (min-max)	7 (2-55)	112.5 (40-251)	**0.003****
Time to nasogastric tube removal (days) median (min-max)	10 (0-270)	121.5 (60-251)	**0.002****
Length of hospital stay (days) median (min-max)	24 (8-270)	21.5 (13-23)	**0.004****
Duration of postoperative mechanical ventilation (days)	5 (0-68)	39 (26-60)	**0.001****
Time to first postoperative oral feeding (days) median (min-max)	10 (0-31)	10 (0-72)	0.552**
Cardiac anomalies, n (%)			
Minor Major	14 (73.7) 5 (26.3)	48 (70.6) 20 (29.4)	0.792*
Gender, n (%)			
Male Female	12 (60) 8 (40)	36 (48) 39 (52)	0.34*
Prematurity, n (%)	3 (15)	9 (12)	0.712*
Presence of accompanying syndrome, n (%)	5 (25)	38 (50.7)	**0.04***
Associated anomalies, n (%)			
VACTERL Others	3 (60) 2 (40)	33(86.8) 5 (13.2)	0.180*
EA type (Gross classification), n (%)			
A C	3 (15) 17(85)	3 (4) 72 (96)	0.105*
Gap length, n (%)			
Short Long	12 (75) 4 (25)	52 (81.3) 12 (18.7)	0.727*
Early complications (anastomotic leak/ fistula recanalization), n (%)	21(23.1)	3 (75)	**0.048***
Anti-reflux procedure, n (%)	4 (20)	21(28)	0.470*
Preoperative need for mechanical ventilation, n (%)	6 (30)	8 (10.7)	0.068*
Gastroesophageal reflux, n (%)	11(55)	41(54.7)	0.979*

*: Pearson chi-square or Fisher's exact test, **: Independent samples test,***: Mann-Whitney U test, VACTERL: Vertebral defects, A, Anal atresia, C, Cardiac defects, T, Tracheoesophageal fistula, E,Esophageal atresia, R, Renal anomalies, L, Limb anomalies, EA: Esophageal atresia

Table 6. Secondary surgical interventions	
	n (%)
Gastrostomy	14 (9.2)
Anti-reflux procedure	25 (16.4)
Colonic transposition	1 (0.7)
Gastric pull-up	6 (3.9)

disease alone to assess the predictive power of the Spitz and Okamoto mortality risk classifications. The results showed that both the Spitz and Okamoto mortality risk classifications remain valid for EA/TEF patients treated at our hospital, but the Okamoto classification was more effective in predicting mortality. Furthermore, it was found that the presence of a major cardiac anomaly alone, independent of birth weight, was not an adequate predictor of mortality in these patients, differing from the findings reported by Lazow et al[5]. After analyzing the results, we have confirmed that birth weight remains a significant factor in predicting risk of mortality among EA/TEF patients. Our study population of 152 cases consisted of 2 extremely low birth weight, 14 very low birth weight, and 80 low birth weight patients. Although the prematurity rate in our study (23.7%) was lower than those reported in other series, the presence of low birth weight should be emphasized as a significant predictor of mortality.

In our study, major cardiac disease was present in our 46 (30.2%) patients. In their study Lazow et al.[5] reported major cardiac anomalies in 20.9% of their cases. The literature demonstrates that associated anomalies occur in 30-70% of cases with EA/TEF. In Sulkowski's[12] national cohort, 83.5% of the cases had been reported to have at least one accompanying anomaly. In our study, 87 (57.2%) patients had accompanying syndromes. Among these anomalies, 85% of them were VACTERL associations.

Although significant progress has been made in preoperative and postoperative management, along with advancements in surgical techniques used for the treatment of EA/TEF, both early and long-term gastrointestinal, respiratory, and developmental morbidities continue to be reported. To better predict the course of clinical outcomes in this patient group, potential neonatal, preoperative, intraoperative, and postoperative risk factors for the development of complications were evaluated. Since the disease is an anatomical defect affecting the functional and anatomical integrity of the gastrointestinal system, all cases had morbidities related to the gastrointestinal system.

In our study, we observed long-gap EA in 24.6% (n=32) of cases. considerably higher than those reported in the literature (i.e., Spitz et al.[13], 9.4%, and Lazow et al.[5] 12.6%). However, long-gap EA wasn't a statistically significant predictive factor for postoperative morbidity, as expected.

Anastomotic stricture and esophageal dysmotility are common complications that develop following surgical repair. Stricture and dysmotility often indicate significant morbidity, requiring repeated interventions and multiple dilatations before achieving a satisfactory outcome. Approximately 50% of cases with EA/TEF require esophageal dilations[14]. In our study, 55.3% of patients underwent esophageal dilations.

Various studies have reported the incidence of postoperative anastomotic stricture—despite the lack of a universally accepted definition—to range between 17% and 60%[15]. In the present study, its incidence was identified as 52.7%.

Between 53% and 92% of the patients with EA/TEF experience dysphagia during the postoperative period[16]. Dysphagia occurred in 35.8% of patients in our cohort, representing a lower incidence compared to prior reports in the literature. Factors identified as significant contributors to gastrointestinal morbidities included polyhydramnios, prematurity, associated syndromic anomalies, prolonged hospitalization, the esophageal gap length (regardless of its size), extended duration of postoperative mechanical ventilation, prolonged retention of the N/G and chest tubes, and the need for early esophageal dilatation.

Respiratory problems in cases of EA/TEF encompass many underlying mechanisms that begin to take effect in the early years of life. Therefore, early detection and treatment of pulmonary morbidity are important to prevent development of pulmonary dysfunction and serious long-term complications. Generally, respiratory problems in the early period, seen in about 10-20% of the cases, develop due to anastomotic leakage, recurrent fistula, and anastomotic stricture[9]. In our study, early stage complications (recurrent fistula and anastomotic leakage) were present in 27.1% of our cases.

We found that having other concomitant health problems, significant delay in removing both N/G catheter and chest tubes following surgery, prolonged hospital stay and postoperative mechanical ventilation, requirement for esophageal dilation at an early stage, and inhaler drug requirement after discharge were risk

factors for developing respiratory morbidities. Lazow et al.[5] reported that preoperative mechanical ventilation was required in 14.6% of their patients, whereas our study revealed a higher rate of 21.7%. Chetcuti and Phelan.[17] found that respiratory problems affected 46% of EA/TEF cases, both in the short and long-term (1-37 years of age). In the short term, we observed respiratory morbidity in 57.7% of our patients. In our study, developmental retardation was observed at a rate of 78.9%, exceeding the rates previously reported in the literature. In Leibovitch's[11] study, developmental retardation was observed in 41.3-43.5% of cases within the first two years of life, and it was shown that with advancing age, this developmental delay disappeared, and these patients caught up with their peers in the age range of 16-21 years. Consistent with risk factors for respiratory morbidities, the presence of syndromic anomalies, prolonged postoperative mechanical ventilation, delayed withdrawal of N/G catheters and chest tubes, recurrence of fistula or anastomotic leakage in the short term, and prolonged hospitalization were identified as contributing factors of growth retardation during the first two years of follow-up.

Published studies have shown that the incidence rates of GER in individuals with EA/TEF range from 34% to 58%[16,18-20]. Our study detected GER in 52.3% of cases, in line with the literature. In our clinic, although 52.3% of operated cases of EA/TEF had GER, half of these patients responded to medical treatment. A secondary surgical intervention was performed in 40% (n=38) of patients postoperatively. Anti-reflux surgery was the most common procedure which was performed on 48% of patients with GER disease. In 23% of cases, gastrostomy was performed, while anti-reflux surgery combined with gastrostomy surgery was performed in 10% of cases. Besides, 7.8% (n=3) of cases underwent a gastric pull-up surgery.

Study Limitations

A key limitation of our study is its retrospective design covering 20 years, during which evolving medical and surgical practices resulted in formation of a heterogeneous study population. Secondly, the study relies on data obtained from medical record files. It was observed that all operated cases were not consistently followed up at our clinic. Therefore, considering the average durations of follow-ups, the results of the patients' two-year follow-ups have been taken into account for evaluation.

In this study, it was proven that having a major cardiac anomaly alone, regardless of birth weight, was not sufficient to predict mortality in patients with EA/TEF. Regression analysis demonstrated that the currently used mortality classifications separately proposed by Spitz and Okamoto were still valid; however, the Okamoto classification was more powerful in terms of mortality prediction.

By elaborating postoperative gastrointestinal, respiratory, and developmental morbidites in cases with EA, specific risk factors for predicting each of these morbidities have been revealed in detail.

CONCLUSION

In conclusion, the risk factors predicting all three morbidities have been identified as the presence of polyhydramnios, prematurity, associated syndromes, prolonged duration of postoperative mechanical ventilation and hospital stay, delayed removal of the N/G and chest tubes, and the need for early esophageal dilation. Anastomotic leakage, recurrent fistula development, and the requirement for inhaler therapy at discharge were found to increase, especially respiratory morbidities. Nevertheless, the long gap between esophageal cut ends wasn't a significant risk factor among all morbidities.

Identifying these risk factors in patients with EA/TEF will assist in counseling families during the neonatal period. Early identification of potential morbidities and prompt initiation of treatment may improve the quality of life of these patients.

Ethics

Ethics Committee Approval: Institutional Ethical Board of University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Clinical Research Ethics Committee approval with approval number: 444, dated: 07.02.2020.

Informed Consent: Retrospective study.

Footnotes

Author Contributions

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

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Original Article

Evaluation of Nutritional Anemia Status and Iron Parameters in Cases with Bladder-Bowel Dysfunction

Mesane Barsak Disfonksiyonu Olan Olgularda Beslenmeye Bağlı Anemi Durumu ve Demir Parametrelerinin Değerlendirilmesi

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ABSTRACT

Objective: Bladder-bowel dysfunction (BBD) is a clinical condition in which both bladder and bowel functions are impaired. Constipation is often associated with BBD. This study aimed to estimate nutritional parameters and anemia in patients with BBD.

Method: The study included 189 patients aged between 60 months and 18 years who were admitted to Bakırçay University Çiğli Training and Research Hospital. Their bladder symptom scores, iron parameters, and hemoglobin levels were evaluated.

Results: It was determined that levels of blood hemoglobin and iron parameters were deficient in patients with constipation complaints who were particularly consuming unhealthy diets.

Conclusion: It is important to evaluate nutritional status, fluid intake, constipation management, anemia, and iron parameters in patients with BBD. With appropriate treatment, we can improve their quality of life and prevent complications.

Keywords: Anemia, bladder-bowel dysfunction, iron parameters

ÖZ

Amaç: Mesane-barsak disfonksiyonu (MBD), mesane ve bağırsak fonksiyonlarının birlikte bozulduğu klinik bir durumdur. Kabızlık genelikle mesane-barsak disfonksiyonu ile ilişkilidir. Bu çalışma, MBD'li hastalarda beslenme parametrelerini ve anemiyi değerlendirmeyi amaçlamıştır.

Yöntem: Çalışmaya Bakırçay Üniversitesi Çiğli Eğitim ve Araştırma Hastanesi'ne başvuran, 60 ay ile 18 yaş arasında 189 hasta dahil edilmiştir. Bu hastaların mesane semptom skorları, demir parametreleri ve hemoglobin düzeyleri değerlendirilmiştir.

Bulgular: Kabızlık şikayeti olan olgularda kan hemoglobin ve demir parametrelerinin düşük olduğu ve özellikle bu olguların sağlıksız beslenmeye eğilimli olduğu görülmüştür.

Sonuç: MBD'li hastalarda beslenme durumu, sıvı alımı, kabızlık yönetimi, anemi ve demir parametrelerinin değerlendirilmesi önemlidir. Uygun tedavi ile yaşam kalitesi arttırılabilir ve kompliksyonlar önlenebilir.

Anahtar kelimeler: Anemi, mesane-barsak disfonksiyonu, demir parametreleri

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INTRODUCTION

Bladder-bowel dysfunction (BBD) is a clinical condition in which both bladder and bowel functions are impaired[1]. A close interaction exists between the bladder and bowel due to common innervation (sacral nerves) and related pelvic floor muscles. When we look at the pathophysiology of BBD, chronic contraction of the anal sphincter also causes contraction of the pelvic floor muscles, resulting in secondary detrusor sphincter dyssynergia. In addition, rectal distension due to constipation puts pressure on the posterior wall of the bladder, leading to inadequate bladder emptying and detrusor instability[2]. Constipation which has been shown to occur in 30% to 88% of children with bladder dysfunction has been frequently evaluated in the literature as being associated with bladder dysfunction[3]. Underlying etiologies include neurological and functional disorders, incorrect and inadequate toilet habits, psychological factors such as stress and trauma, and recurrent urinary tract infections (UTIs). Patients may present to pediatrics, pediatric nephrology, and pediatric urology clinics with frequent urination,

nocturnal and/or daytime urinary incontinence, an urge to urinate, constipation and/or fecal incontinence, and a sense of incomplete bladder emptying[4]. Its incidence in children peaks at 5-7 years of age and is more common in girls than in boys[5]. In the evaluation of cases with BBD, detailed patient history and physical examination, voiding diary, calculation of bladder-bowel symptom scores, dietary habits that may cause constipation, complete urinalysis and urine culture, lumbosacral radiography, urinary system ultrasonography, estimation of residual urine and uroflowmetry are being used. Treatment methods include behavioral therapy, drug therapy, bowel management, physical therapy for pelvic muscles, and, rarely, surgical intervention[6,7]. Increased awareness in the BBD has led to establishment of better diagnostic criteria and treatment methods.[8] Evaluating nutritional status, anemia, and iron parameters in patients with BBD is essential. In these patients, detection and appropriate treatment of iron and other mineral deficiencies in particular can improve quality of life and prevent complications in these patients. In this study, we aimed to determine the relationship of these parameters with BBD by evaluating the nutritional and iron parameters, symptoms of constipation, and anemia of these cases.

MATERIALS and METHODS

Ethical Considerations

The study was carried out with the permission of the İzmir Bakırçay University Clinical Researches Ethics Committee (decision no: 1240, dated: 18.10.2023). All procedures were carried out in accordance with the World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects.

Patient Selection and Evaluation

The scope of the study included patients who applied to İzmir Bakırçay University Çiğli Training and Research Hospital Pediatric Nephrology Outpatient Clinic due to BBD and incontinence between November 2023 and May 2024. A detailed history of the patients was taken, and bladder-bowel dysfunction symptom scores (BBDSS) were calculated. The BBD scale used is shown in Figure 1 and Table 1. A total of 189 patients older than 60 months with a BBDSS of 13 and above were evaluated. Patients were informed about the study, and consent forms were obtained. Weight, height, body mass index (BMI) percentiles, and standard deviation scores (SDS) were calculated according to age of the patients. Dietary habits, water consumption, and fiber intake of the patients were questioned. Those with and without constipation and/or fecal incontinence were grouped. Serum creatinine levels, presence of anemia, and iron parameters of the patients were scanned retrospectively from the system. Estimated glomerular filtration rates (eGFRs) of all patients were calculated using the Schwartz formula [glomerular filtration rate (GFR)= 0.41x height in cm/serum creatinine (mg/dL)]. The relationship between symptom scores, laboratory findings, and clinical status of the patients was evaluated.

Statistical Analysis

The SPSS package program (IBM SPSS Statistics for Windows, version 25.0. Armonk, NY: IBM Corp, 2017) was used for statistical analyses. Variables with normal distribution were shown as mean values ± standard SDS, variables with abnormal distribution as median (range), values and the rest were expressed as frequencies. The chi-square test was used to compare categorical variables between groups. The Kolmogorov-Smirnov test was used to evaluate the normal distribution of continuous variables between groups. All parameters were distributed abnormally, so they were evaluated using the Mann-Whitney U test. For this study, $p<0.05$ was considered as level of statistical significance.

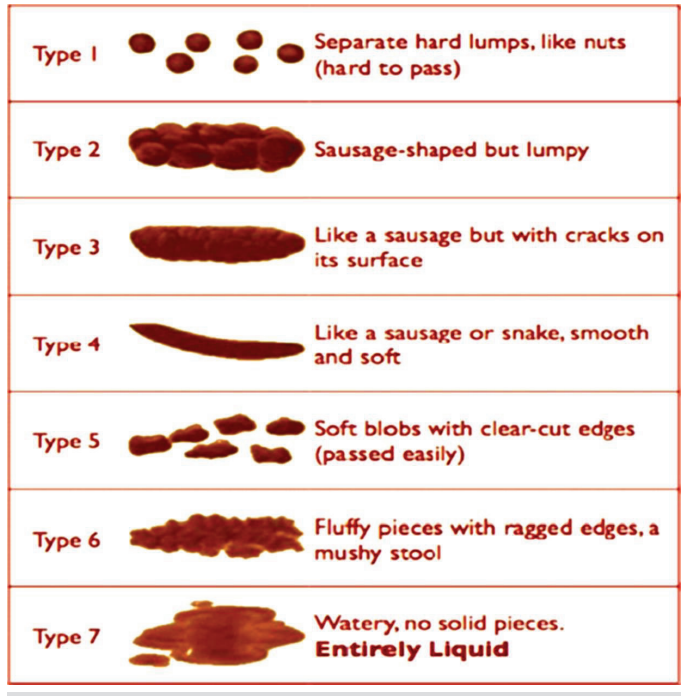

Figure 1. Bladder-bowel symptom scores

Table 1. Bristol stool scale					
Do you wet your underwear during the day?	Never - 0	1 day a week - 1	2-3 times a week - 2	4-5 times a week - 3	Everyday - 4
How much do you wet your underwear?	I don't wet my underwear - 0	Slightly moist - 1	Moist - 2	Wet - 3	Soaking wet - 4
The number of times you go to the toilet during the day.	1-2 times - 4	3-4 times - 2	5-6 times - 0	7-8 times - 2	More than 8 - 4
How many times a day do you feel an urgent need to go to the toilet to pee ?	Never - 0	Less than half the time - 1	Half the time - 2	More than half the time - 3	Everyday - 4
How many times a day you hold your pee by crossing your legs or sitting?	Never - 0	Less than half the time - 1	Half the time - 2	More than half the time - 3	Everyday - 4
Do you feel pain while peeing?	Never - 0	Less than half the time - 1	Half the time - 2	More than half the time - 3	Everyday - 4
Do you wet your bed at night?	Never - 0	3-4 times a month - 1	1-2 times a week - 2	4-5 times a week - 3	Everynight - 4
Do you wake up at night to pee?	Never - 0	3-4 times a month - 1	1-2 times a week - 2	4-5 times a week - 3	Everynight - 4
Is your urine flow stops and then starts again during peeing?	Never - 0	Less than half the time - 1	Half the time - 2	More than half the time - 3	Everyday - 4
Do you either force yourself to go to pee, or wait?	Never - 0	Less than half the time - 1	Half the time - 2	More than half the time - 3	Everyday - 4
Frequency of your bowel movements (frequency of defecation).	More than once a day - 0	Everyday - 1	Every 2 days - 2	Every 2 days - 3	Less than 1 in 3 days - 4
My poop is hard-the answer should be given according to the Bristol stool scale criteria.	Never - 0	Less than half the time - 1	Half the time - 2	More than half the time - 3	Everyday - 4
Do you poop in your Underwear?	Never - 0	1-2 times a week - 1	3 times a week - 2	4-5 times a week - 3	Everyday - 4

RESULTS

Patients who were 60 months and older and applied to pediatric nephrology clinic of our hospital were evaluated. A total of 189 patients with a BBDSS of 13 and above were included in our study. Our study population consisted of 137 (72.5%) female and 52 (27.5%) male patients. The mean (range) ages of our female [11.2 (5-17.6) years], and male [9.8 (5-17.3) years] patients were as indicated. BMI SDS of male and female patients did not differ significantly (p=0.92). As the BMI SDS increased in both girls and boys, the BBDSS score also increased in correlation (r=0.781). The mean BBDS scores were 15.2 (13-33) in boys and 19.8 (13-34) in girls. When the constipation and fecal incontinence (encopresis) conditions of our patients were evaluated, 114 girls and 46 boys had constipation. In addition, 29 girls and five boys had encopresis. The mean blood creatinine value of the patients was 0.57±0.21 mg/dL, and all patients had normal creatinine values according to age and height. The eGFR of all patients was calculated using the Schwartz formula, and all patients had normal eGFR. There was no evidence of chronic kidney disease in any patient. Cases with neurogenic bladder or spinal dysraphism were not evaluated in the study. According to the World Health Organization criteria, since cases over 60 months of age were also included in our study, the hemoglobin (Hb) levels below 12 mg/dL was accepted as indicative of anemia[9]. The mean Hb level of all cases was 10.4±2.1 mg/dL. All of 160 cases with constipation had relatively lower Hb levels. While, 8 of 29 patients without constipation

had anemia, significantly lower levels of Hb (below 10 mg/dL) were detected in 21 cases with encopresis. Mean hematocrit value of all patients was 37±3.7%. BBDS scores increased in a positive correlation with the increased red blood cell distribution width (r=0.812). The mean (range) serum iron [38 ug/dL (7-63)], ferritin [18 ng/mL (3-51)] values, transferrin saturation (TS) [19.3% (5.3-27.1)], and total iron binding capacity (TIBC) [469.3 ug/dL (379-517)] of the cases were also estimated BBDSS of the cases showed a negative correlation with blood iron, ferritin values, and TS (r=-0.641, -0.913, -0.856, respectively) and a positive correlation with TIBC (r=0.824). All cases with encopresis had comparatively lower serum iron, ferritin, TS, and higher TIBC values.

When the eating habits of BBD patients were examined regarding consumption of junk food, it was observed that all 189 patients consumed at least two packaged foods per week, 142 patients consumed at least one packaged food almost every day, and their daily water intake was insufficient. All patients with encopresis had moderate anemia, consumed carbonated drinks, and none of them consume vegetables.

DISCUSSION

BBD is the co-occurrence of bladder problems, especially urinary incontinence and bowel problems (and/or constipation)[10]. It is a complex condition that can seriously affect quality of life[11]. It should be considered an important public health problem as it will affect the child's life both physically and psychologically, both in the acute period and in the long term. Early diagnosis and treatment with a multidisciplinary approach are critical to prevent complications[12].

Based on literature data, bladder dysfunction is more common in girls[13]. In our study, 72.5% of the cases were girls. Overweight, obesity, behavioral eating problems, especially constipation, fecal incontinence and other symptoms are associated with bladder and bowel dysfunction[14]. Our study has shown that increases in BMI SDS correlate positively with higher BBDS scores. Although reportedly the development of voiding dysfunction may accelerate the development of UTIs, some studies in the literature have indicated that children with voiding dysfunction are prone to UTI and kidney damage[15]. In the long term, BBD can lead to the development of chronic inflammation and anemia. The risk of colonization of the bladder with pathogenic microorganisms and incidence of UTI increases, especially in patients with significant residual urine due to dysfunctional voiding[16]. Recurrent UTIs are becoming a public health problem, especially in developing or underdeveloped countries, as they cause considerable morbidity and mortality when left undiagnosed.

Patients with bowel dysfunction may experience constipation, fecal incontinence, or irregular bowel movements which may prevent nutrients from being adequately absorbed from the intestines, leading to iron deficiency and anemia[12]. In our study, all patients with constipation had anemia. In particular, a fiber-free diet and consumption of ready-made foods are seen as the most critical causative factors leading to the development of constipation[17,18].

Study Limitations

This study has limitations, including its retrospective nature and the advantages of randomized controlled trials. This was a single-center study, and a limited number of patients were analyzed. However, our findings suggest that constipation patients have lower hemoglobin and iron parameters and are particularly prone to unhealthy diets.

CONCLUSION

In conclusion, evaluation of nutritional status, fluid intake, management of constipation, symptoms of anemia (if any), and iron parameters in patients with BBD carries critical importance. With appropriate treatment, we can improve the quality of life and prevent development of complications in these patients. Therefore, a multidisciplinary approach should be adopted in the management of BBD, and the nutritional status of the patients should be closely monitored.

Ethics

Ethics Committee Approval: The study was carried out with the permission of the İzmir Bakırçay University Clinical Researches Ethics Committee (decision no: 1240, dated: 18.10.2023).

Informed Consent: Patients were informed about the study, and consent forms were obtained.

Footnotes

Author Contributions

Surgical and Medical Practices: G.G.Ö., Concept: Ö.Ö.Ş., Design: G.G.Ö., Data Collection or Processing: G.G.Ö., Ö.Ö.Ş., Analysis or Interpretation: Ö.Ö.Ş., Literature Search: G.G.Ö., Writing: G.G.Ö.

Conflict of Interest: The authors declare no conflict of interest.

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Original Article

Exploring Neuropathy and Myopathy in Mitochondrial Diseases: Insights from Nerve Conduction Studies and Electromyography

Mitokondriyal Hastalıklarda Nöropati ve Miyopatinin İncelenmesi: Sinir İleti Çalışmaları ve Elektromiyografi Bulguları

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ABSTRACT

Objective: Mitochondrial diseases (MDs) are characterized by significant genetic and clinical heterogeneity. Although they are frequently investigated for potential central nervous system involvement, they can also affect the peripheral nervous system, leading to neuropathy and myopathy. The aim of this study is to determine the role of nerve conduction study (NCS) and electromyography (EMG) in the diagnosis of MD and the monitoring of peripheral nervous system involvement in patients with MD.

Method: This retrospective study examined data from 25 patients with MD. Clinical and laboratory parameters were compared between groups with and without abnormal electrophysiological findings. Additionally, subtypes of neuropathy were classified, and correlations between genotypes and phenotypes were analyzed.

Results: Neuropathy was detected at a considerable rate of 40%. The findings were predominantly consistent with the expected axonal neuropathy in MD, particularly in cases with lower limb-onset MD, although demyelinating patterns were also frequently observed. Notably, neuropathy was more prevalent in patients with mitochondrial variants than previously reported. Furthermore, physical examination findings and motor symptoms failed to predict neuropathy. Similarly, myopathic findings identified on EMG were observed even in cases without corresponding neuropathy-specific physical examination findings, motor symptoms, or elevated muscle enzyme levels.

Conclusions: The routine use of NCS and EMG serves as a valuable guide in the diagnostic process of MD. They are considered important tools for both diagnostic evaluation and ongoing monitoring of peripheral nervous system involvement.

Keywords: Mitochondrial diseases, neuropathy, nerve conduction studies, mitochondrial DNA, nuclear DNA, pediatric population

ÖZ

Amaç: Mitokondriyal hastalıklar (MH), belirgin genetik ve klinik heterojenite ile karakterizedir. Genellikle santral sinir sistemi tutulumu açısından araştırılsalar da periferik sinir sistemini de etkileyerek nöropati ve miyopati gibi bulgulara yol açabilirler. Bu çalışmanın amacı, MH'de periferik sinir sistemi tutulumunun değerlendirilmesinde ve tanı sürecinde sinir ileti çalışması ve elektromiyografinin (EMG) rolünü belirlemektir.

Yöntem: Bu retrospektif çalışmada, MH tanılı 25 hastanın verileri incelendi. Elektrofizyolojik olarak anormal bulguları olan ve olmayan gruplar arasında klinik ve laboratuvar parametreleri karşılaştırıldı. Ayrıca, nöropati alt tipleri sınıflandırıldı ve genotip-fenotip korelasyonları analiz edildi.

Bulgular: Nöropati %40 gibi yüksek bir oranda saptandı. Bulgular, özellikle alt ekstremite başlangıçlı olgularda, MH'de beklenen aksonal tip ile büyük ölçüde uyumluydu; ancak demiyelinizan nöropati de sıklıkla gözlendi. Mitokondriyal varyant taşıyan hastalarda nöropati daha önce bildirilen oranlardan daha yüksek bulundu. Ayrıca, fizik muayene bulguları ve motor semptomlar nöropatiyi öngörmede yetersizdi. Benzer şekilde, miyopati tanısında da EMG klinik ve laboratuvar tetkiklerinden üstündü.

Sonuç: Sinir ileti çalışmaları ve EMG'nin rutin kullanımı, MH'lerin tanı sürecinde değerlidir. Bu yöntemler, hem tanısal değerlendirme hem de periferik sinir sistemi tutulumunun izleminde önemli araçlar olarak kabul edilmelidir.

Anahtar kelimeler: Mitokondriyal hastalıklar, nöropati, sinir ileti çalışmaları, mitokondriyal DNA, nükleer DNA, pediatrik popülasyon

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INTRODUCTION

Mitochondrial diseases (MDs) are the most common metabolic disorders, with an incidence of approximately one in 5000 live births[1]. They exhibit considerable heterogeneity in terms of genetic inheritance mechanisms and clinical presentations[2]. Mitochondria are crucial organelles in eukaryotic cells, responsible for generating the majority of cellular energy in the form of adenosine triphosphate (ATP) via oxidative phosphorylation (OXPHOS). Genetic testing has become the primary diagnostic approach for MDs when clinical uncertainty is present. The human mitochondrial genome is a circular DNA molecule encoding components of four OXPHOS enzyme complexes and comprises 37 genes[3]. Nuclear DNA (nDNA) is essential for the formation and assembly of all other subunits within the OXPHOS complexes. Consequently, the mitochondrial proteome comprises approximately 1500 nDNA-encoded mitochondrial genes in addition to 37 genes encoded by mitochondrial DNA (mtDNA)[4]. This dual origin leads to two patterns of inheritance, and genetic testing aims to identify mutations in both nDNA and mtDNA genes[5]. Consequently, any organ systems may be involved in MD[6]. Neurologic system involvement is common in MD, while peripheral neuropathy and myopathy have been described in addition to central nervous system involvement[7-10].

Nerve conduction studies (NCS) are being conducted to establish the diagnosis of neuropathy[11]. Although challenging to perform in pediatric populations, needle electromyography (EMG) is useful for detecting neuropathic changes that cannot be identified performing NCS[12]. Furthermore, EMG can also be used to diagnose myopathy[13]. In previous studies, subgroups of patients with an established diagnosis of MD who developed neuropathy have been presented as case series, and subtypes of neuropathy have been classified[8,14,15]. However, in this already rare and heterogeneous disease group, the prevalence of neuropathy and the diagnostic value of NCS remain unclear. Although electrophysiological studies are uncomfortable procedures[16] in clinical practice they may serve as important indicators for referrals to genetic testing in order to make the final diagnosis of MD by revealing the presence of neuropathy and myopathy.

Therefore, this study aimed to determine the role of performing NCS and EMG at initial presentation—before a confirmed definitive genetic diagnosis was made—regardless of the presence of symptoms, in the diagnostic process of MD.

MATERIALS and METHODS

The Publication Ethics Statement

This study was approved by the Ethics Committee of Dokuz Eylül University Non-Interventional Studies Ethics Committee (approval number: 2024/17-21, dated: 15.05.2024).

Study Design and Participants

A retrospective analysis was conducted on patient files covering the time interval from January 2013 to May 2024 at the Department of Pediatric Neurology, Dokuz Eylül University Faculty of Medicine. The study included patients with a confirmed genetic diagnosis of MD, meeting diagnostic criteria for pathogenic or likely pathogenic variants per American College of Medical Genetics and Genomics guidelines[13]. These variants were required to affect genes associated with human disease, corresponding with the participant's phenotype, and matching the disease's mode of inheritance. Age, sex, clinical symptoms, neurologic examinations, NCS and EMG findings, brain magnetic resonance imaging (MRI), laboratory parameters and genetic results were recorded. Patients were analyzed in two groups as those with nDNA and those with mtDNA variants.

NCS

NCSs were performed using Nihon Cohden EMG/evoked potentials Measuring System Model MEB-9400K SN 80853 2011. For the evaluation of sensory and motor nerves in the upper extremity, the median nerve was assessed. In the lower extremity, the sural nerve was evaluated as the sensory nerve, while the tibial and peroneal nerves were examined as the motor nerves. The measured values were compared with age-appropriate reference values[17].

The diagnosis of demyelinating neuropathy was made based on at least one of the following criteria: conduction velocity below 75% of the age-appropriate lower limit, distal latency above 130% of the upper limit, or proximal compound muscle action potential (CMAP) amplitude equal to or less than 50% of the distal CMAP amplitude. Axonal neuropathy was diagnosed in the absence of the criteria indicating the presence of demyelinating neuropathy and when CMAP amplitude was below 80% of the age-appropriate lower limit[18]. Cases that did not fully fit into either category were classified as mixed neuropathy. Myopathy is characterized by short-duration polyphasic motor unit potentials and a complete interference pattern of low amplitude on needle EMG, while high amplitude polyphasic waves are typically observed in neuropathic cases[19].

Statistical Analysis

IBM SPSS Statistics 27.0 (SPSS Inc., Chicago, IL, USA) program was used for statistical evaluation. Descriptive variables were reported as percentages (%), means ± standard deviation, or medians accompanied by interquartile ranges (IQRs) in parentheses. Chi-squared or Fisher's exact tests were applied for categorical variables, while Mann-Whitney U-test were used for quantitative data after testing normality of variables with the Shapiro-Wilk test. A p-value below 0.05 was deemed statistically significant.

RESULTS

In this study, data of 25 cases of MD from 21 different families were analyzed. The median age of the participants was 10 years (IQR:9, range: 1-17), with males constituting 56% (n=14) of the study population. Diagnosis of MD was established in 76% (n=19) of the cases by identifying variants in nDNA, while 24% (n=6) of the diagnoses were attributed to variants in mtDNA. In the nDNA variant group, one case underwent next-generation sequencing panel for cardiomyopathy-associated gene ie. tafazzin, while another patient underwent a targeted single-gene analysis for *SURF1* gene based on clinical findings and neuropathy type, while the remaining cases were diagnosed using whole exome sequencing. In the mtDNA variant group, mutations and deletions were tested from plasma samples. The variants were most frequently identified in the *MT-ATP6* gene, observed in three cases, followed by *SURF1*, *POLG*, *NDUFA12*, and *COQ8A* genes, where each of them were reported in two cases.

Neurological symptoms were predominant in the majority of the cohort. Cognitive impairment was the most common pathology present in 18 (72%) patients, followed by motor delay in 16 (64%) cases. Seizures were reported at the time of presentation in 11 (44%) cases. Additionally, skeletal deformities were observed in 7 (28%) and muscle atrophy in 6 patients (24%) (Table 1).

MRI of the brain was conducted in 23 cases, with 15 (69.6%) cases demonstrating pathological findings. Hyperintense lesions on the T2-weighted sequences involving the basal ganglia were observed in eight (34.8%), and cortical atrophy in seven (30.4%) cases. Magnetic resonance spectroscopy revealed abnormal findings in 8 (35%) cases. An increased lactate peak was present in seven cases, while a decreased N-acetyl aspartate peak was observed in one case (Table 1).

Clinical suspicion of neuropathy was not present in all cases, as NCS were routinely performed with a preliminary diagnosis of MD at our center. Muscle weakness, defined as reduced muscle strength in at least one extremity based on the Medical Research Council scale, was observed in 15 (65%) patients, two of whom also had hypoactive deep tendon reflexes (DTRs). Based on NCS, neuropathy was observed in 10 (40%) patients (Table 1). These patients had mixed-type neuropathy with axonal predominance (n=4), demyelinating neuropathy (n=2), and axonal neuropathy (n=4). In the groups with neuropathy, most commonly the tibial and peroneal nerves were affected (n=8: 80%), while the other evaluated nerves (medial—both sensory and motor—and sural nerves) were equally affected, in 70%

Table 1. Demographic, and clinical characteristics of study subjects

		n (%)
Gender	Male	14 (56)
	Female	11 (43)
Brain MRI	Normal	8 (34.8)
	Hyperintense lesions	8 (34.8)
	Cortical atrophy	7 (30.4)
MRS	Normal	6 (43)
	Increased lactate peak	7 (50)
	decreased NAA peak	1 (7)
Variant	mtDNA	6 (24)
	nDNA	19 (76)
Cognitive impairment		18 (72)
Muscle weakness		16 (64)
Dsymorphologic features		14 (56)
Ophthalmoparesis		12 (48)
Seizures		11 (44)
Skeletal deformities		7 (28)
Hearing loss		4 (16)
DTRs	Normoactive	15 (60)
	Absent	1 (4)
	Hypoactive	2 (8)
	Hyperactive	7 (28)
NCS	Normal	11 (60)
	Neuropathy	10 (40)
EMG	Normal	1 (25)
	Myopathy	4 (75)

DTRs: Deep tendon reflexes, EMG: Electromyography, MRI: Magnetic resonance imaging, MRS: Magnetic resonance spectroscopy, mtDNA: mitochondrial DNA, NAA: N-acetyl aspartate, nDNA: Nuclear DNA, NCS: Nerve conduction study

(n=7) of the cases. On the other hand, EMG performed revealed findings consistent with myopathy in four of five cases.

The median ages of the groups with and without neuropathy were within a similar range, without any statistically significant difference. The physical examination and clinical findings of these two groups including muscle weakness, abnormal DTRs, ophthalmoparesis, dysmorphologic features, hearing loss, skeletal deformities, and muscle atrophy did not also differ significantly between groups (Table 2).

In the group with the mtDNA variant, 4 (67%) patients exhibited muscle weakness. Examination of DTRs revealed hypoactive reflexes in 2 (33%), hyperactive reflexes in 1 (17%) patient, while remaining cases had normal DTRs. None of the patients showed elevated creatine kinase (CK) levels. NCS revealed axonal polyneuropathy, predominantly affecting the lower extremities, in three cases. (50%) Needle EMG was performed in one patient, uncovering myopathic findings (Table 3).

In contrast, when looking at the group diagnosed with the nDNA variant, 12 (63.2%) patients exhibited muscle weakness. Examination of DTRs revealed hyperactive reflexes in 6 cases, while one patient had no DTRs. In the remaining patients, DTRs were normal. Elevated CK levels were detected in one patient. NCS revealed neuropathy in seven (46.6%) cases with axonal polyneuropathy predominantly affecting the lower extremities in five cases. Additionally, two cases with Surfeit 1 (*SURF1*) gene variants were identified as having demyelinating neuropathy. Needle EMG was performed in three cases, uncovering myopathic findings (Table 4).

DISCUSSION

Peripheral nervous system involvement is thought to be underdiagnosed in patients with MD, while central nervous system involvement is more predominant[10]. Previous studies indicated that peripheral neuropathy has been detected in approximately 30% of patients with MD[15,20]. In our study, this rate was significantly elevated, potentially due to the routine assessment of patients-including asymptomatic cases-through NCS. This high rate of neuropathy supports the recommendation of NCS as part of the diagnostic evaluation and an ongoing surveillance tool.

Mitochondrial neuropathy, has been found to be more frequently diagnosed in patients with nDNA variants compared to those with mtDNA variants[14]. In our study, neuropathic findings were documented at a higher rate compared to those reported in the literature. As is known axonal neuropathy is detected in cases of MD caused by mtDNA variants[14]. Similarly, our study supports this finding, as two of our cases carrying the more common *MT-ATP6* variant, which leads to the Leigh phenotype, also exhibited axonal neuropathy[21]. Among the other three variants, the *MT-CYB* variant, affecting cytochrome b, was associated with axonal neuropathy, consistent with mtDNA variants. In contrast, the *MT-ND4* variant, affecting complex I, was not associated with neuropathy but exhibited myopathic findings.

Table 2. Comparison of signs and symptoms of neuropathic patients and patients with normal electrophysiologic findings

	Neuropathy (n=10)	Normal (n=15)	p-value
Age (median, range)	8.50 (2-13)	10.0 (1-17)	0.290
Muscle weakness, n (%)	7 (70)	9 (60)	0.691
Dysmorphologic features, n (%)	6 (60)	8 (53.3)	1.000
Ophthalmoparesis, n (%)	5 (50)	7 (46.6)	1.000
Seizures, n (%)	4 (40)	7 (46.6)	1.000
Abnormal DTRs, n (%)	5 (50)	5 (33.3)	0.442
Skeletal deformities, n (%)	2 (20)	5 (33.3)	0.659
Muscle atrophy, n (%)	3 (30)	3 (20)	0.653
Visual problems,n (%)	2 (20)	4 (26)	1.000
Hearing loss, n (%)	3 (33)	1 (6.6)	0.267
Endocrine dysfunction,n (%)	1 (10)	3 (20)	0.626
Cardiomyopathy, n (%)	2 (20)	1 (6.6)	0.560

DTRs: Deep tendon reflexes

Table 3. The physical examination and electrophysiological findings, creatine kinase levels of the patients with a mitochondrial variant

Patient	Age (year)	Variants	Muscle strength/ DTRs	CK (U/L)	Median motor CMAP Amp (mV)/NCV (m/s)	Tibial motor CMAP Amp (mV)/ NCV (m/s)	Median sensory SNAP Amp (µV)/ NCV (m/s)	Sural sensory SNAP Amp (µV)/NCV (m/s)	EMG	Electrophysiological diagnosis
1	4	NC_012920.1(*MT-CO3*):m.9804G>A	Normal/ normoactive	211	5.52/34.80	4.02/38.60	16.20/40.10	18.00/34.20	-	Normal
2	12	NC_012920.1(*MT-ATP6*):m.8993T>G	Decreased/ hypoactive	107	5.00/43.60	4.17/32.30	7.00/41.40	NR	-	Axonal polyneuropathy
3	8	NC_012920.1(*MT-CYB*): m.73A>G	Normal/ hyperactive	161	7.07/56.80	2.59/36.60	52.20/39.90	NR	-	Axonal polyneuropathy
4	8	NC_012920.1(*MT-ND4*):m.11696G>A	Decreased/ normoactive	210	6.29/47.50	5.33/45.00	32.30/58.50	7.20/45.00	Reduced normal MUPs Polyphasic MUPs	Myopathy
5	1	NC_012920.1(*MT-ATP6*):m.*9077T>C*	Decreased/ hypoactive	36	5.69/38.00	4.87/39.80	5.40/35.50	7.30/35.00	-	Normal
6	3	NC_012920.1(*MT-ATP6*):m.8993T>G	Decreased/ normoactive	64	2.08/42.40	1.32/66.70	NR	20.10/32.00	-	Axonal polyneuropathy

Patients are presented according to the time of their initial presentations. Pathological findings are shown in bold letters.

Amp: Amplitude, CK: Creatine kinase, CMAP: Compound muscle action potential, DTRs: Deep tendon reflexes, NCV: Nerve conduction velocity, SNAP: Sensory nerve action potential, EMG: Electromyography, NR: No response, MUPs: Motor unit potentials

Table 4. The physical examination, electrophysiological findings and creatine kinase levels of the patients with a nuclear variant										
Patient	**Age (year)**	**Variants**	**Muscle strength/ DTRs**	**CK (U/L)**	**Median motor CMAP Amp (mV)/NCV (m/s)**	**Tibial motor CMAP Amp (mV) /NCV (m/s)**	**Median sensory SNAP Amp (μV) /NCV (m/s)**	**Sural sensory SNAP Amp (μV) /NCV (m/s)**	**EMG**	**Electrophysiological diagnosis**
7	6	NM_001195518.2 (*MICU1*):c.553C>T (p.Arg185Ter) Homozygous	Decreased/ normoactive	15076	5.43/44.50	5.33/53.20	24.40/52.00	12.10/43.00	Reduced normal MUPs Polyphasic MUPs	Myopathy
8	16	NM_018838.5 (*NDUFA12*): c.121dupG, p.Glu41GlyfsTer10 Homozygous	Decreased/ normoactive	176	5.17/60.60	5.00/49.30	48.20/55.60	13.00/50.80	Reduced normal MUPs Polyphasic MUPs	Myopathy
9	14	NM_002693.3(*POLG*): 1808T>G (p.Met603Arg) Homozygous	Decreased/ hyperactive	121	6.49/52.60	10.10/45.50	72.10/94.50	9.60/53.70	-	Normal
10	12	NM_003172.4 (*SURF1*): c.484G>A (p.Val162Met) Homozygous	Decreased / hyperactive	225	6.20/43.80	3.24/23.00	8.60/21.30	11.90/30.80	Normal	Demyelinating polyneuropathy
11	10	NM_020247.5 (*COQ8A*): c.1009G>A (p.Ala337Thr) Homozygous	Normal/ hyperactive	179	7.32/66.30	10.65/55.70	25.80/55.30	8.40/64.00	-	Normal
12	6	NM_020247.5 (*COQ8A*): c.1009G>A (p.Ala337Thr) Homozygous	Normal/ normoactive	95	3.54/45.40	4.86/43.40	22.00/55.00	5.30/48.50	-	Normal
13	1	NM_016035.5 (*CoQ4*): c.437T>G (p.Phe146Cys) Homozygous	Normal/ normoactive	63	3.37/31.00	10.93/36.10	23.20/37.60	11.30/33.50	-	Normal
14	2	NM_003172.4 *(SURF1)* c.845_846del (p.Ser282Cysfs*9) Homozygous	Decreased/ normoactive	61	2.71/29.70	1.69/20.80	15.20/31.30	NR	-	Demyelinating polyneuropathy
15	16	NM_032317.3 (*DNAJC30)*:c.352G>T (p.Glu118Ter) Homozygous	Normal/ Normoactive	120	6.24/61.00	9.52/45.70	68.40/69.60	25.80/55.60	-	Normal
16	16	NM_018838.5 (*NDUFA12*): c.121dupG, p.Glu41GlyfsTer10 Homozygous	Decreased/ normoactive	196	6.90/67.40	5.43/50.00	51.50/72.00	9.10/45.00	-	Normal

Table 4. Continued

Patient	Age (year)	Variants	Muscle strength/ DTRs	CK (U/L)	Median motor CMAP Amp (mV)/NCV (m/s)	Tibial motor CMAP Amp (mV) /NCV (m/s)	Median sensory SNAP Amp (μV) /NCV (m/s)	Sural sensory SNAP Amp (μV) /NCV (m/s)	EMG	Electrophysiological diagnosis
17	11	NM_001303 (*COX10*):c.674C>T(p. Pro225Leu) Homozygous	Decreased/ absent	29	NR	NR	0.95/25.00	6.40/46.30	-	Demyelinating polyneuropathy
18	9	NM_017909.4 (*RMND1*) c.203A>G (p.Asn238Ser) Homozygous	Decreased/ normoactive	110	12.33/51.00	2.50/44.80	27.30/54.10	3.50/36.70	Reduced normal MUPs Polyphasic MUPs	Axonal polyneuropathy, myopathy
19	8	NM_033109.4 (*PNPT1*) c.1576_1578dupGAT (p.Asp526dup) Homozygous	Decreased/ hyperactive	98	9.14/50.40	11.20/44.20	11.90/37.30	5.10/33.60	-	Axonal polyneuropathy
20	16	NM_003730.6 (*RNASET2*):c.194A>C (p.His65Arg) Homozygous	Decreased/ hyperactive	70	10.01/57.10	6.57/51.50	54.40/56.50	13.50/50.90	-	Normal
21	17	NM_000116.5 (*TAZ*) :c.718G>A (p.Gly240Arg) Homozygous	Normal/ normoactive	118	5.82/48.5	7.41/46.4	24.4/54.6	17.4/54.8	-	Normal
22	13	NM_004553.6 (*NDUFS6*):c.309+5G>A Homozygous	Decreased/ normoactive	88	7.82/38.50	NR	8.50/34.50	NR	-	Axonal polyneuropathy
23	10	NM_002693.3 (*POLG*) c.3151G>C (p.Gly1051Arg) Homozygous	Normal/ normoactive	166	5.49/49.60	4.23/43.90	20.00/60.20	10.80/44.30	-	Normal
24	5	NM_002693.3 (*POLG*) c.752C>T (p.Thr251Ile), c.1760C>T (p. Pro587Leu) Compound Heterozygous	Normal/ normoactive	52	2.80/41.3	1.8/59.5	59/56.8	15/50	-	Axonal polyneuropathy
25	15	NM_0144772.3 (*NAXE*) c.641T>G (p. Ile214Ser) Homozygous	Normal/ normoactive	155	5.41/48.9	9.53/43.2	47.6/61.20	14.9/55.6	-	Normal

Patients are presented according to the time of their initial presentations. Pathological findings are shown in bold letters.

Amp: Amplitude, CK: Creatine kinase, CMAP: Compound muscle action potential, DTRs: Deep tendon reflexes, NCV: Nerve conduction velocity, SNAP: Sensory nerve action potential, EMG: Electromyography, NR: No response, MUPs: Motor unit potentials

On the other hand, the rate of neuropathy findings in patients with nDNA variants aligns with findings reported in several other studies[8-10]. The frequency of neuropathy in patients with mtDNA variants in our study was higher than that observed in cases with nDNA variants, which may be related to the limited number of our cases. Among patients with nDNA variants, we found axonal neuropathy in five and demyelinating neuropathy in two cases. Our patients with variants in the *SURF1* gene exhibited findings of demyelinating neuropathy, consistent with previous reports[14,21]. In two cases with *POLG* variants, NCS results were normal. Since *POLG* variants have been associated with axonal neuropathy in the literature, this finding may be due to NCS being performed at an early stage[14]. In accordance with the literature data the third patient with a *POLG* variant showed electrophysiological findings consistent with axonal neuropathy despite the absence of relevant clinical signs. In this cohort axonal neuropathy was detected in cases with nDNA variants associated with the Leigh phenotype (*NDUFA12*, *NDUFS6*). This finding, which supports axonal loss, was consistent with the pathophysiology of Leigh syndrome[22].

In the case with a pathogenic *COX10* variant, severe demyelinating neuropathy was observed. Given its late onset (11- year delay), it was hypothesized that axonal loss occurred first, followed by demyelination. This assumption was further supported by previously reported biopsy findings of an adult case, which demonstrated both axonal and myelin involvement[23]. Contrary to the expected myelin loss, axonal neuropathy was observed in our case with *PNPT1* mutation[24].

Given the difficulty of performing EMG in pediatric case series, needle EMG was not performed on every patient; instead it was reserved for cases presenting with muscle weakness or where significant muscle involvement was suspected. One of these cases (Patient 7) showed elevated CK levels. In that case with a variant in the *MICU1* gene, which is associated with calcium transport, myopathy was present, consistent with the literatüre[25]. Although the absence of elevated CK levels in the other three patients suggested that EMG could be primarily reserved to diagnose myopathy, we could not ascertain its definitive diagnostic value, as it was not applied in asymptomatic cases.

We evaluated the physical examination and clinical findings of the cases with neuropathy and those with normal NCS findings, and could not find any statistically significant difference between the two groups regarding musle weakness, abnormal DTR, skeletal deformities, and muscle atrophy. This fact indicates that, although physical examination and clinical findings are important diagnostic tools, there remains a significant need for electrophysiological testing. Moreover, the absence of differences in physical findings highlights the need for repeated NCS assessments during follow-up to detect neuropathy that may develop over time.

Study Limitations

The present study is valuable as it aims to identify neuropathy and myopathy in MD, which are rare genetic disorders. However, its limitations include a small sample size, single-center design, and retrospective nature. Additionally, failure to perform needle EMG in every patient and inability to repeat NCS for patients with initially normal results represent further study limitations.

CONCLUSIONS

In this study, we observed a higher incidence of neuropathy in patients with mtDNA mutations, which contrasts with findings reported in the literature. Furthermore, an increased prevalence of neuropathy was also noted in cases with nDNA mutation. However, we were unable to demonstrate a correlation between these electrophysiological and neurological examination findings or symptoms. Additionally, a large proportion of patients with myopathy did not exhibit elevated CK levels. Therefore, NCS and needle EMG can be utilized as screening tools in cases with a clinical suspicion of MD.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Dokuz Eylül University Non-Interventional Studies Ethics Committee (approval number: 2024/17-21, dated: 15.05.2024).

Informed Consent: Retrospective study.

Footnotes

Author Contributions

Surgical and Medical Practices: P.T.K., A.İ.P., A.S.H., N.A., U.Y., Concept: H.B.Ş., P.T.K., A.İ.P., A.A., A.S.H., N.A., U.Y., Design: H.B.Ş., P.T.K., A.İ.P., A.A., A.S.H., N.A., U.Y., Data Collection or Processing: H.B.Ş., M.B., Ç.G., Analysis or Interpretation: H.B.Ş., M.B., Ç.G., A.A., Literature Search: H.B.Ş., M.B., Ç.G., A.S.H., Writing: H.B.Ş., P.T.K., A.İ.P., N.A., U.Y.

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