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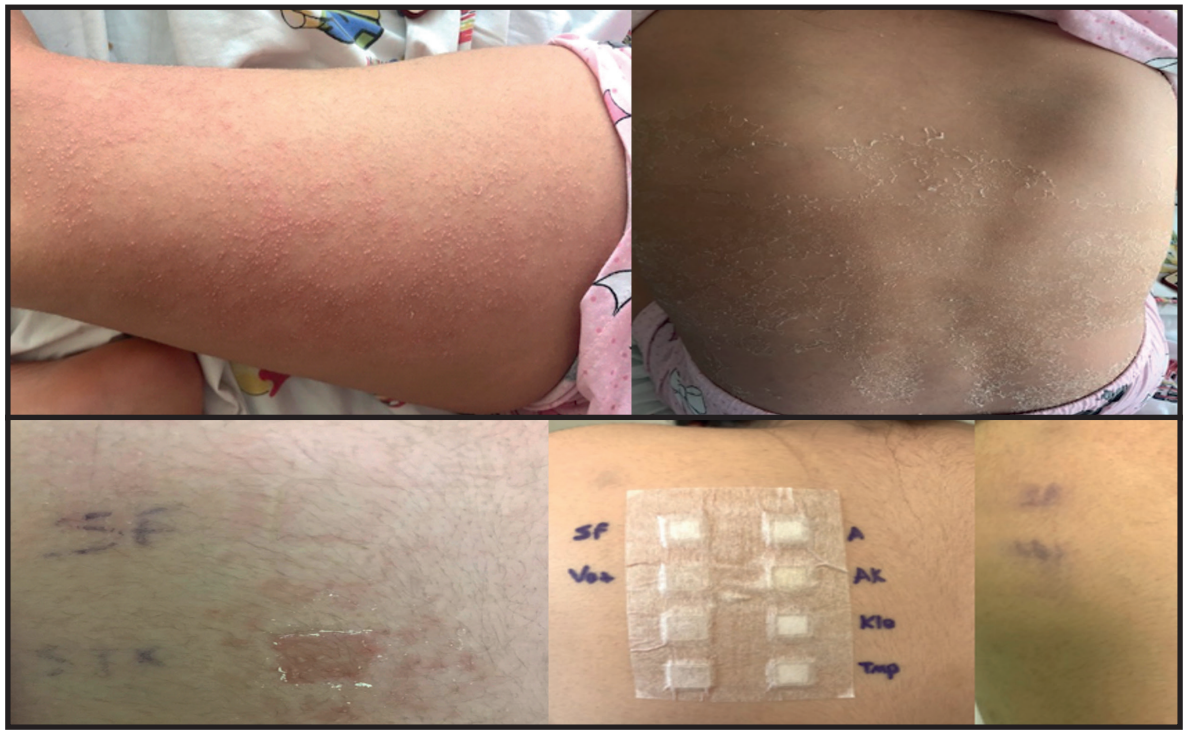

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Original Articles

Case Reports

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Original Article

The impact of illness perception on medication adherence in pediatric patients with familial Mediterranean fever

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ABSTRACT

Objective: Poor adherence to medications is an important problem, especially in patients with chronic diseases such as familial Mediterranean fever (FMF). In this study, we aimed to evaluate medication adherence in pediatric FMF patients and investigate the relationship between disease perception and treatment compliance.

Method: Pediatric patients (<18 years old) with a diagnosis of FMF and at least six months of follow-up period participated in the study. Patient perceptions of illness and medication adherence were measured via a brief illness perception questionnaire (brief IPQ) and the Medication Adherence Scale in FMF Patients (MASIF), respectively.

Results: A total of 50 patients (46% girls, n:23) with a median age of 9.9 (IQR 5.9-15.8) years were included. The median age at diagnosis was 5.4 (IQR 3.2-10.1) years. Twenty-eight patients (56%) had good medication adherence (the MASIF score>60), while 44% of the patients were non-adherent to the treatment. Patients aged under 12 years of age were more adherent to colchicine treatment than those over 12 years of age (68.2% vs. 25.0%, p= 0.002). The comparison of the illness perception and medication adherence revealed higher brief IPQ total scores in patients who adhered to the treatment (median 48.5 vs 52.5, p=0.037). We found significant differences in timeline scores between patients who were adherent and those who were non-adherent to the treatment (p=0.01).

Conclusion: Non-adherence to medication is an important and widespread problem, particularly among adolescent patients. Perceptions of the illness and beliefs about the duration of the disease may affect adherence to treatment. Medication adherence should be routinely assessed at follow-up visits and educational interventions might improve adherence to the treatment.

Keywords: Familial Mediterranean fever, medication adherence, illness perception

INTRODUCTION

Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurrent febrile attacks and serositis (e.g., peritonitis, pericarditis, synovitis). The Mediterranean fever (*MEFV*) gene responsible for FMF encodes a protein called pyrin.[1] Mutated pyrin causes uncontrolled production of interleukin-1β and increased inflammatory response.[2,3] Attacks usually last for 12-72 hours.[4] The goal of the treatment is to prevent complications that occur as a result of chronic inflammation, such as amyloidosis, and to control attacks. Colchicine is the mainstay of FMF treatment. Some patients have an attack despite colchicine treatment. Although colchicine resistance may be observed in some of the FMF patients, non-adherence to

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colchicine treatment should be investigated first in these cases.[5] Melikoglu et al.[6] evaluated 108 FMF patients and found that 11% of patients identified as unresponsive to colchicine treatment actually had inadequate medication adherence. A Medication Adherence Scale for Familial Mediterranean Fever (MASIF) was developed in a cohort of Turkish children in 2015.[7] Sönmez et al.[8] evaluated drug compliance using the MASIF scale in 82 pediatric FMF patients and found that 33 patients were non-adherent with their medication. Meanwhile, they found that the number of attacks, hospitalization in the last six months, and admissions to the hospital and the emergency department were significantly higher in non-adherent patients.

There are many factors that influence adherence to treatment, such as socio-economic factors, health system-related factors, or patient-related factors. Illness perception is one of the most important factors in medication adherence. A brief illness perception questionnaire was developed to provide a quantitative assessment of illness perception.[9] It evaluates cognitive illness representations, emotional representations (concerns and emotions), and comprehension of illness. The relationship between illness perception and medication adherence has been investigated in many diseases. However, there is a lack of data in the literature on the illness perception of FMF patients.

In this study, we aimed to evaluate medication adherence in pediatric FMF patients and investigate the relationship between disease perception and treatment compliance.

MATERIAL AND METHODS

Study population

This is a cross-sectional study. Pediatric patients (<18 years old) who were followed up with the diagnosis of FMF between December 2021 and October 2022 in Aydın Obstetrics and Pediatrics Hospital, Department of Pediatric Rheumatology participated in the study. The clinical diagnosis of FMF was made according to the Yalçınkaya-Özen criteria.[10] Patients with at least six months of follow-up period were included in the study. There were 78 FMF patients who applied to the pediatric rheumatology outpatient clinic during the study period. Patients with a shorter follow-up period (<6 months) (n=19) and those who refused to participate in the study (n=9) were excluded from the study. The demographics (age, sex, age at diagnosis), *MEFV* gene analysis results, and clinical presentations of the patients were recorded. Afterward, the patient's medication adherence and disease perceptions were evaluated.

Assessment of the medication adherence

The MASIF scale was used to evaluate medication adherence (Supplementary Table S1).[7] The scale consists of 18 questions and the questions are classified into 4 groups: knowledge about the medication (1st, 10th, 13th, and 16th questions), adherence to the treatment (2nd, 5th, 6th, 8th, 15th, and 17th questions), barriers to drug use (4th, 7th, 12th, 14th, and 18th questions), and the factors that may increase adherence (3rd, 9th, and 11th questions). Each item was scored ranging from 1 to 5 (1=strongly agree, 2=agree, 3=no idea, 4=disagree, 5=strongly disagree). A total score above 60 points was considered "good medication adherence" while a score below 60 points was considered "poor drug compliance". For patients under the age of 7, only the parents answered the questions, whereas the patients over the age of 7 answered the questions together with their parents. In addition, we investigated whether there was a difference in drug compliance rates in patients over 12 years of age, which corresponds to the adolescence period, compared to those under 12 years of age.

Assessment of the illness perception

The brief illness perception questionnaire (brief IPQ) which was developed by Broadbent et al.[9] in 2006 was used for the evaluation. It consists of eight items plus the causal questions: assessment of consequences (item 1), timeline (item 2), personal control (item 3), treatment control (item 4), identity (item 5), concern (item 6), illness comprehensibility (item 7), and emotional response (item 8) (Supplementary Table S2). Causal representation was evaluated with an open-ended question asking patients to write down the three most important causal factors in their illness. (Item 9). All questions except one open-ended question (item 9) were scored on a numerical rating scale from 0 to 10. The eight-item brief IPQ was also used in the study.

Ethics Committee Approval: This study was approved by the Aydın Adnan Menderes University Non-Invasive Clinical Research Ethics Committee (Approval number: 2022/186) and was conducted according to the guidelines of the Declaration of Helsinki.

Statistical analyses

The SPSS version 20.0 (Armonk, NY: IBM Corp) package program was used in the statistical analyses. Descriptive statistics were presented as frequencies (n (%)) for categorical data and median (interquartile range [IQR]) for numerical data. Visual (histograms and probability plots) and analytical methods (the Kolmogorov-Smirnov and Shapiro-Wilk tests) were used to decide whether

a variable had a normal distribution. The Chi-square test or Fisher's exact test (when the values observed in cells did not meet the assumptions of the Chi-square test) was used for the comparison of categorical variables. With regard to distribution characteristics, the Student's t-test was used for normally distributed parameters and the Mann-Whitney U test for non-normally distributed parameters in the intergroup comparison. The associations between the MASIF score and brief IPQ, which were non-normally distributed, were calculated using the Spearman test. A p-value of less than 0.05 was used to define statistical significance.

RESULTS

A total of 50 patients, 23 of whom were girls (46%) were included in the study. The median age of the patients was 9.9 (IQR 5.9-15.8) years and the median age at diagnosis was 5.4 (IQR 3.2-10.1) years. 28 patients (56.0%) were under the age of 12. The median follow-up time was 2.2 (IQR 1.1-6.7) years. The clinical presentations of the patients were as follows in decreasing order: fever (n=45, 90%), abdominal pain (n=40, 80%), arthralgia (n=27, 54%), chest pain (n=14, 28%), arthritis (n=10, 20%), and erysipelas-like erythema (n=4, 8%). Six patients had an additional disease: five had asthma and one had a diagnosis of epilepsy. However, none of them were taking oral medication regularly for these diagnoses. Fifteen (30%) of the patients were homozygous, 25 (50%) were heterozygous, and 10 (20%) were compound heterozygous. The allele frequencies of the *MEFV* mutations were M694V (53.3%), E148Q (16.0%), M680I (13.3%), V726A (12.0%), R761H (4.0%), and P369S (1.3%). Colchicine was used on a twice-daily dosage schema in 47 patients, and a once-daily dosage schema in three patients. Patients were using colchicine at a median dose of 1 mg (range 0.5 mg to 2 mg).

Evaluation of the medication adherence

The median scores of the items of the MASIF were shown in Table 1. Twenty-eight patients (56%) had good medication adherence (the MASIF score>60), while 44% of the patients were non-adherent to the treatment. The median age of patients with good medication adherence was lower compared to those of non-adherent patients (15.3 (IQR 9.3-17.0) vs 7.5

Table 1. Evaluation of the medication adherence of the patients

The item of the medication adherence scale in FMF patients (MASIF) (min-max score)	The median scores of patients (IQR)
I know about my illness and I am aware that my treatment will continue for a long time (0-5)	1 (1-2)
I sometimes forget to take my medication (0-5)	2 (2-4)
I rely on the treatment prescribed for my disease (0-5)	1 (1-2)
I refrain from others when taking drugs (0-5)	4 (4-5)
Continuous drug usage affects my daily life (0-5)	4 (3-4)
When I am out of home, I forget to take my drugs	2 (2-4)
I wish this disease had a treatment without drugs (0-5)	2 (1-3)
I sometimes do not take my drugs on time because of my daily routine (0-5)	2 (1-4)
I think my illness will get better, if I use my drug regularly (0-5)	2 (1-3)
I know the adverse effects of the drug (0-5)	3 (2-3)
I need to be convinced to use my medication regularly, for a long time (0-5)	4 (2-4)
I'm afraid that continuous drug use may lead to other diseases (0-5)	3 (2-4)
If I leave my drug, my disease may worsen (0-5)	2 (1-3)
I could not get used to using my drug regularly (0-5)	4 (2-4)
When I realise that I forgot to take my medication, I take my drug even it is de-layed, I do not skip doses (0-5)	2 (1-2)
When I disrupt my drug my complaints may increase (0-5)	2 (1-2)
I am tired of continuous drug use (0-5)	3 (2-4)
I think it is quite difficult to use medicine in multiple doses during a day (0-5)	3 (2-4)

FMF: familial Mediterranean fever; IQR: interquartile range.

(IQR 5.1-12.2), p=0.002). The patients aged under 12 years of age were also more adherent to colchicine treatment than those over 12 years of age (68.2% vs 25.0%, p= 0.002). There was no significant difference between the genders in terms of adherence to treatment. The routine daily dose of colchicine was higher in non-adherent patients compared to adherent patients (p=0.003).

Evaluation of the illness perception

The median brief IPQ score was 50.0 (IQR 45.0-55.2). The score of the brief IPQ scale showed no significant difference between genders (p=0.296). There was no significant correlation between the MASIF score and the brief IPQ score (p=0.109, r=0.230). However, the comparison of the illness perception and medication adherence revealed higher brief IPQ total scores in patients who adhered to treatment (median 48.5 vs 52.5, p=0.037). The median scores of the items of the brief IPQ and the median scores of the items of the brief IPQ according to drug compliance are summarized in Table 2 and Table 3, respectively. We found significant differences in timeline scores between patients with poor medication adherence and good medication adherence (p=0.01). In addition, the brief IPQ scores did not differ significantly between the homozygous, heterozygous, and compound heterozygous groups (p=0.111).

Table 2. Assessment of the illness perception of the patients

The item of the brief IPQ (min-max score)	The median scores of patients (IQR)
Consequences (0-10)	4 (2.7-6.0)
Timeline (0-10)	9 (5.0-10.0)
Personal control (0-10)	6.5 (4.0-9.0)
Treatment control (0-10)	8.5 (7.0-10.0)
Identity (0-10)	6.0 (3.0-8.0)
Concern (0-10)	5.0 (4.0-8.0)
Illness comprehensibility (0-10)	9.0 (6.0-10.0)
Emotional response (0-10)	5.0 (1.7-7.2)

IPQ: illness perception questionnaire; IQR: interquartile range.

DISCUSSION

Our study indicates that poor adherence to treatment, which was observed in 44% of patients, is a significant problem in FMF patients. We found that those with a greater perception of illness had better medication adherence.

The brief IPQ was used in many different diseases to examine patients' perception of illness and its relationship with medication adherence was investigated.[11-13] Tolu et al.[14] reported that a greater perception of illness was significantly associated with better medication adherence in patients with ankylosing spondylitis. Similarly, Hughes et al.[15] found that some IPQ domains were associated with medication adherence in patients with rheumatoid arthritis. In our study, medication adherence was better in patients with higher brief IPQ total scores. Also, the association between the timeline domain of brief IPQ and medication adherence was positive, indicating that those who did not believe that FMF is a long-lasting disease were experiencing poor adherence to medications. Since FMF is a life-long illness, they might have felt compelled to take the drug,

Table 3. Evaluation of the items of the brief IPQ according to treatment adherence

The item of the brief IPQ	Patients' treatment adherence according to the MASIF		p value
	Adherent patients median (IQR) (n=28)	Non-adherent patients median (IQR) (n=22)	
Consequences	4 (1-6)	5 (3-6.2)	0.490
Timeline	10 (8-10)	7 (5-10)	**0.01**
Personal control	7 (5-9.7)	6 (3.7-8)	0.08
Treatment control	9 (8-10)	8 (4-10)	0.166
Identity	5.5 (3-8)	6 (4.7-7.2)	0.615
Concern	5 (4-8)	5 (3-7)	0.269
Illness comprehensibility	9 (8-10)	9 (6-10)	0.443
Emotional response	5 (2-7.7)	5 (2-6.2)	0.664

IPQ: illness perception questionnaire; IQR: interquartile range; MASIF: medication adherence scale in FMF patients.

which can have numerous consequences if they do not adhere to the treatment. It seems plausible that receiving information about the disease, especially the duration of the disease, might improve drug compliance.

Colchicine prevents the development of amyloidosis by reducing the frequency and severity of febrile attacks and improves the patient's quality of life.[16] Adherence to colchicine treatment has a direct impact on patient outcomes. The frequency of non-adherent patients to colchicine treatment according to MASIF was similarly reported as 40.2% in pediatric FMF patients.[8] In another study evaluating 171 pediatric FMF patients, 17.5% of the patients were reported to be non-adherent. However, a questionnaire was not used to assess drug compliance in this study.[17] Tekgöz et al.[18] also reported that when patients were asked whether they were regular colchicine users, 66.5% of adult FMF patients said that they were regular colchicine users. However, when adherence was evaluated using the Compliance Questionnaire on Rheumatology (CQR) scale, the rate of non-adherent patients was 83.8%. Poor medication adherence is a significant issue for physicians to be aware of. The use of scales may also be more appropriate for an accurate assessment of medication adherence.

In our study, non-adherence to medication was more frequent in patients over 12 years of age. Similarly, a study of 378 pediatric FMF patients investigated medication adherence according to age. Medication adherence was reported to be 90.5% in patients ≤ 5 years, 64.4% in patients 6–11 years, and 58.3% in patients≥12 years.[19] Poor adherence to medication in adolescents has been reported not only in FMF patients but also in other chronic diseases.[20,21] In children under 12 years of age, drugs are usually administered by parents, whereas children over 12 years of age generally take their own medication and take responsibility. Physicians should be attentive to poor adherence to treatment during the adolescent years.

Study limitations

There are some limitations of our study. First, other factors that may influence medication adherence, such as patient-related factors, financial barriers, and sociocultural factors, were not evaluated. The second limitation is the retrospective nature of the study and the single-center design. Multicenter studies with large numbers of patients are needed to accurately determine the impact of illness perceptions on medication adherence. Despite these limitations, to our knowledge, this is the first study evaluating the brief IPQ in pediatric FMF patients and examining the association between medication adherence and patients' perception of illness.

CONCLUSION

The patient's perception of the illness is important and affects medication adherence. Non-adherence to medication was found more often in patients over 12 years of age. Physicians should routinely assess medication adherence, especially in the adolescent period, and informing patients about their disease (especially the duration of the disease) might improve drug compliance.

Ethical approval

This study has been approved by the Aydın Adnan Menderes University Non-Invasive Clinical Research Ethics Committee (approval date 10/11/2022, number 2022/186). Written informed consent was obtained from the participants.

Author contribution

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

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Conflict of interest

The authors declare that there is no conflict of interest.

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Supplementary Table S1. Medication Adherence Scale in FMF Patients (MASIF) (Likert scale is used as 1=strongly agree, 2 = agree, 3 = no idea, 4 = disagree, and 5 = strongly disagree. A total score above 60 points was considered "good medication adherence" while a score below 60 points was accepted as "poor drug compliance")

No	Items	Strongly agree	Agree	No idea	Disagree	Strongly disagree
1.	I know about my illness and I am aware that my treatment will continue for a long time.					
2.	I sometimes forget to take my medication.					
3.	I rely on the treatment prescribed for my disease.					
4.	I refrain from others when taking drugs					
5.	Continuous drug usage affects my daily life.					
6.	When I am out of home (on vacations, travels, etc.) I forget to take my drugs.					
7.	I wish this disease had a treatment without drugs.					
8.	I sometimes do not take my drugs on time because of my daily routine.					
9.	I think my illness will get better, if I use my drug regularly.					
10.	I know the adverse effects of the drug.					
11.	I need to be convinced to use my medication regularly, for a long time.					
12.	I'm afraid that continuous drug use may lead to other diseases.					
13.	If I leave my drug, my disease may worsen.					
14.	I could not get used to using my drug regularly.					
15.	When I realise that I forgot to take my medication, I take my drug even it is delayed, I do not skip doses.					
16.	When I disrupt my drug my complaints may increase.					
17.	I am tired of continuous drug use.					
18.	I think it is quite difficult to use medicine in multiple doses during a day.					

Supplementary Table S2. The brief illness perception questionnaire (brief IPQ)										
How much does your illness affect your life?										
0	1	2	3	4	5	6	7	8	9	10
no affect at all										severely affects my life
How long do you think your illness will continue?										
0	1	2	3	4	5	6	7	8	9	10
a very short time										forever
How much control do you feel you have over your illness?										
0	1	2	3	4	5	6	7	8	9	10
absolutely no control										extreme amount of control
How much do you think your treatment can help your illness?										
0	1	2	3	4	5	6	7	8	9	10
not at all										extremely helpful
How much do you experience symptoms from your illness?										
0	1	2	3	4	5	6	7	8	9	10
no symptoms at all										many severe symptoms
How concerned are you about your illness?										
0	1	2	3	4	5	6	7	8	9	10
not at all concerned										extremely concerned
How well do you feel you understand your illness?										
0	1	2	3	4	5	6	7	8	9	10
don't understand at all										understand very clearly
How much does your illness affect you emotionally? (e.g. does it make you angry, scared, upset or depressed?)										
0	1	2	3	4	5	6	7	8	9	10
not at all affected emotionally										extremely affected emotionally

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Original Article

Is there a role for caudal anesthesia on postoperative urethrocutaneous fistula in children undergoing hypospadias surgery?

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ABSTRACT

Objective: Hypospadias is defined as incomplete closure of the penile structures during embryogenesis. Surgical correction induces various complications, including urethrocutaneous fistula (UCF). The aim of this study was to determine the risk factors for the occurrence of UCF in children undergoing hypospadias repair under caudal anesthesia.

Method: The medical records of children undergoing hypospadias repair between January 2013 and July 2018 were included. Data on patients' age, body weight, height, type of repair procedure, type of hypospadias, duration of surgery, and hospitalization, and postoperative complications were analyzed.

Results: The mean age of the 122 patients was 4.8±3.7 years. The type of surgery performed was tubularized incised plate urethroplasty (Snodgrass) in 90 (73.8%) and meatal advancement and glanuloplasty (MAGPI) in 32 (26.2%) children. Sixteen (13.1%) children had postoperative complications, all of which were UCF. No statistical association was found between postoperative UCF and patient variables.

The most common complication of hypospadias repair is UCF, which occurs mostly in the immediate postoperative period.

Conclusion: Hypospadias repair can result in complications. UCF remains a significant problem in the postoperative period. All patients underwent caudal block and despite the previous literature, we experienced lower rates of penile engorgement and postoperative UCF. These results showed that there was no cause-and-effect relationship between the caudal block and UCF. We think that the development of a urethrocutaneous fistula is mostly related to surgical causes and well-designed, prospective, and controlled studies are required to elucidate this issue.

Keywords: Caudal block, hypospadias, penile engorgement, tissue edema, urethrocutaneous fistula

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INTRODUCTION

Hypospadias is defined as a urethral opening along the ventral side of the penis, resulting from incomplete closure of the penile structures during embryogenesis. It is one of the most common pediatric urological conditions, with a multifactorial etiology and a prevalence of approximately 18.6 per 10,000 births.[1] Hypospadias varies considerably in terms of presentation and severity. The aim of repair is to normalize functions and cosmetic appearance. The postoperative complication rate for distal hypospadias has been reported to be approximately 10%; however, this rate may be higher when repairing proximal defects.[2] The incidence of postoperative urethrocutaneous fistula (UCF) has been reported to range from 4% to 28%.[3] Previous studies have mostly focused on the severity of the congenital defect (the location of the urethral meatus) or the type of surgical technique used in the analysis of operative success.[4]

Caudal block (CB) is one of the most popular types of regional anesthesia used as an adjunct to general anesthesia in children undergoing inguinal or genital surgery. It provides reliable postoperative analgesia in children, with a reasonable safety profile and few complications. It has been suggested that caudal anesthesia increases the risk of surgical complications.[5] It is therefore an ongoing debate in pediatric anesthesia whether CB should be abandoned for hypospadias correction. The repair of hypospadias helps to correct both cosmetic and functional abnormalities. Spraying of the urinary stream, inability to urinate in a standing position, potential difficulties in sexual intercourse and fertility issues, and decreased satisfaction with genital appearance can be corrected surgically.[6] However, this highly technical surgery can result in significant complications, such as meatal stenosis, urethrocutaneous fistula, and urethral stricture. Although UCF is common after hypospadias repair, pre- and intraoperative risk factors for its development are not yet well-known. Whether CB increases the risk of UCF development has been a recent topic of discussion. The aim of this study was to determine the risk factors for UCF in children undergoing hypospadias repair under caudal anesthesia.

MATERIAL AND METHODS

After obtaining the approval of the Local Ethics Committee (Protocol# 2018/1456), we conducted a retrospective review of the medical records of children who had undergone a hypospadias repair between January 2013 and July 2018 in Aydın Adnan Menderes University, Medical Faculty, Training and Research Hospital. Only the cases that had undergone surgery more than six months previously were included in the study, since fistula formation may be delayed for up to six months. Patients with incomplete medical records, patients who had undergone a multi-step hypospadias repair or a revision surgery, patients with disorders of sexual development, connective tissue and bleeding disorders, and patients with a follow-up period of less than six months were excluded from the study.

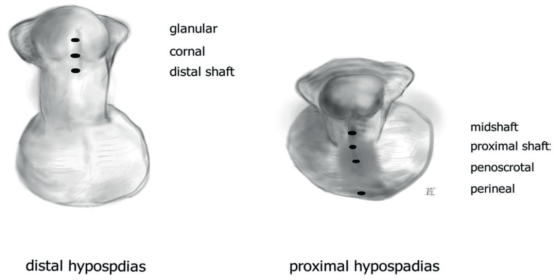

Figure 1. The position of the urethral meatus in hypospadias [1]

Figure 1. The position of the urethal meatus in hypospadias.[1]

Pediatric surgeons and pediatric anesthetists reviewed the medical records. The data recorded for the study include patients' age, body weight, height, type of hypospadias, type of repair procedure, duration of surgery and hospitalization, and postoperative complications (UCF, urethral stricture, tissue edema, hematoma in scar tissue, penile engorgement, delayed tissue repair, and inflammation).

The Snodgrass method used in the study is tubularized incised plate urethroplasty for distal hypospadias. Urethral tubularization was performed using 7.0 polydioxanone (PDS) sutures. Meatal advancement and glanuloplasty (MAGPI) started with the liberalization of the posterior part of the urethra. The urethra was attached to the tip of the glans using 7.0 PDS sutures. Afterwards, glanuloplasty was performed with 5.0 PDS sutures. Instead of cystostomy, urethral stents were used to ensure urine flow. Meatal location was defined as mid-penile, penoscrotal, glanular, coronal, perineal, or sub-coronal (Figure 1). UCF was defined as an abnormal interaction between the reconstructed urethra and the skin, causing urine leakage.

Statistical analysis

Quantitative data were expressed as mean ± standard deviation (SD), and qualitative data as number (%). The compatibility of all measurable variables with normal distribution was evaluated using the Kolmogorov-Smirnov test. Univariate analyses were performed using the Chi-square test to investigate the relationships between UCF formation and the characteristics of

the patient and operation, as well as the other postoperative complications. All analyses were conducted on SPSS® version 22 software, with a p value of <0.05 considered as statistically significant.

RESULTS

The medical records of 122 patients were complete and, therefore, included in the study. The mean age of the patients was 4.8±3.7 years. The mean body weight and height were 20.3±12.7 kg, and 92.3±26.5 cm, respectively. The type of procedure performed for hypospadias surgery was tubularized incised plate urethroplasty (Snodgrass) in 90 (73.8%) children and meatal advancement and glanuloplasty (MAGPI) in 32 (26.2%) children, all of which were performed by an expert pediatric surgeon specialized in pediatric urology. The mean duration was 2.1±0.69 hours for surgery and 6.4±1.9 days for hospitalization.

No patient received preoperative testosterone stimulation. All cases received preoperative caudal anesthesia (0.25% bupivacaine ± epinephrine) for postoperative pain management in addition to general anesthesia.

The types of hypospadias determined in our patients are shown in Table 1. The mid-penile type was the most frequently encountered complication (n=54, 44.1%). The presence of a urethrocutaneous fistula was identified in 16 (13.1%) children. The second most frequently encountered complication was the development of tissue edema, which occurred in eight (6.5%) patients. The complications determined in our patients are presented in Table 2. When the postoperative complications were analyzed, it was found that all of the other complications had occurred only in patients who had developed a urethrocutaneous fistula. Table 3 shows the coexistence of the complications determined in our study.

Table 1. The types of hypospadias in our patients (n=122)

Type of hypospadias	n (%)
Mid-penile	54 (44.3)
Penoscrotal	27 (22.1)
Glanular	21 (17.2)
Coronal	10 (8.2)
Perineal	6 (4.9)
Sub-coronal	4 (3.3)
Total	122 (100.0)

Table 2. The types of complications in our patients (n=16)

Complication	n (%)
Urethrocutaneous fistula	16 (13.1%)
Tissue edema	8 (6.5%)
Urethral stricture	5 (4%)
Penile engorgement	3 (2.4%)
Hematoma	2 (1.6%)
Inflammation	1 (0.8)
Infection	1 (0.8)
Delay in tissue repair	1 (0.8)

Univariate analysis revealed no statistically significant association between the development of postoperative UCF and the variables such as age, body weight and height, duration of surgery and hospitalization, the type of surgical technique, the development of penile engorgement, urethral stricture and hematoma, and other complications in the surgical site.

DISCUSSION

The repair of hypospadias ensures that the phallus gains strength, and a more normal-looking urethral opening is created on the glans. In this study, we investigated the rate of postoperative complications, especially urethrocutaneous fistula, in patients who had undergone hypospadias repair and found that the rate of urethrocutaneous fistula was 13.1%, which is higher than recent studies.[6,7] However, this rate can be considered within the typical range since the incidence of UCB has been reported to range between 4 and 28%.[3] The most common complication of hypospadias repair is UCF, which mostly occurs in the immediate postoperative period. It leads to secondary corrective surgery, resulting in additional cost and discomfort to the patients and their families. The reasons for the development of UCF are not fully understood. In addition to the local deficit in growth factors, the surgical technique is thought to be a key factor.[7] The results of experimental treatments, such as local or systemic, adjuvant or neoadjuvant hormonal therapies, are controversial. In addition, postoperative care, including different types of dressing and surgical material, wound status, and antibiotics, may play a role.[8]

We also investigated the associations between the development of postoperative UCF and patient variables. However, no association was found to be present. Zaidi et al.[9] found no causal relationship between the use of caudal regional anesthesia and UCF formation. Similarly, Kreysing et al.[10] observed that caudal

Table 3. The status of coexistence of complications in our patients with complications (n=16)								
Patient	**Urethro-cutaneous fistula**	**Infection**	**Delay in tissue repair**	**Tissue edema**	**Penile engorgement**	**Inflammation**	**Urethral stricture**	**Hematoma**
1	+	-	-	+	-	-	+	-
2	+	-	-	+	-	-	-	+
3	+	-	-	-	+	-	+	-
4	+	-	-	-	-	-	-	-
5	+	-	-	-	-	-	+	-
6	+	-	-	-	-	-	-	-
7	+	-	-	+	-	-	-	-
8	+	+	+	+	+	+	+	+
9	+	-	-	+	-	-	-	-
10	+	-	-	+	+	-	-	-
11	+	-	-	+	-	-	-	-
12	+	-	-	-	-	-	-	-
13	+	-	-	-	-	-	-	-
14	+	-	-	+	-	-	+	-
15	+	-	-	-	-	-	-	-
16	+	-	-	-	-	-	-	-
Total n (%)	16 (13.1)	1 (0.8)	1 (0.8)	8 (6.5)	3 (2.4)	1 (0.8)	5 (4.0)	2 (1.6)

anesthesia had no effect on complication rates. However, another report concluded that patients undergoing CB were more likely to experience complications than those who received a dorsal penile block.[11] Meanwhile, Braga et al.[12] concluded that the severity of hypospadias, and the type of regional anesthesia, was the only risk factor significantly associated with postoperative complications. All patients underwent caudal-type regional anesthesia, which prevented us from evaluating its effects in these children. Hence, other causes of UCF are discussed in our study.

Although the exact causes of fistula formation are unknown, the type of hypospadias and the surgical technique, penile size, age of the patient, experience of the surgeon, presence of postoperative edema, penile engorgement, local infection, and local ischemia have been associated with its development.[11] Kundra et al.[5] reported that the presence of tissue edema was associated with postoperative UCF. They proposed a causal relationship between CB and UCF formation. In addition, they concluded that CB resulted in penile engorgement, up to a 27% increase from the baseline, and this increased penile edema caused by delayed tissue healing, which in turn led to UCF. The incidence of urethrocutaneous fistula after hypospadias repair in their study was 19.2% and all patients had received caudal block. However, the rate of penile engorgement in our study was 2.4% and all patients had received CB, in contrast to the higher rates of fistula formation in the CB group in the study by Kundra et al.[5] The results of our study showed a lower rate compared to the results of Kundra et al.[5] In addition, since the rate of penile engorgement was 2.4%, it was thought that penile fistula was associated with surgical technique, rather than CB.

Some authors have suggested that the duration of surgery and surgeon's experience are associated with a higher incidence of UCF.[2,9] It was also reported that similar fistulae rates were observed for different repair methods.[12] In this study, neither the duration of surgery and tourniquet application nor hospitalization were associated with the development of UCF. Hypospadias is often classified as posterior, penile, or anterior, depending on the preoperative position of the meatus.[13] Similar to our study, the mid-penile type was one of the most common types in the study by Braga et al.[12] The type of hypospadias, hence

the place of the meatus, is a critical factor for the development of postoperative fistula formation. Proximal types require longer operative time and have a higher risk of subsequent tissue edema and fistulae formation. In contrast to our study, Zaidi et al.[9] reported that wound infection was associated with fistula formation and that meatal location and the use of subcutaneous epinephrine were associated with higher rates of UCF.

One of the main rules of successful hypospadias repair is to select the most appropriate technique for a given patient to achieve the best result, both functionally and cosmetically. Meatal advancement and glanuloplasty (MAGPI), which was one of the techniques used in our study, is commonly used in hypospadias surgery despite some disadvantages such as postoperative meatal regression and meatal stenosis. However, tubularized incised plate urethroplasty (Snodgrass) is less influenced by such issues. Fistulas are the most common problem in most series and can be prevented via the interposition of a barrier layer between the neourethra and the overlying glans and shaft skin closures. Duckett and Snyder reported problems in 1.2% of 1000 boys 2 months after MAGPI.[14] In our study, the type of surgery was Snodgrass in 90 (73.8%) children and MAGPI in 32 (26.2%) children, which were performed by an expert pediatric surgeon, specialized in pediatric urology. The rate of fistula was 15/90 (16.6%) in Snodgrass and 1/32 (3.1%) in MAGPI procedures. Alsharbaini et al.[15] reviewed the results of 320 cases treated by Snodgrass urethroplasty and found the UCF rate to be 2.5%. We found a higher rate (16.6%), which may be due to the lower number of cases. Stenting material may have an impact on the UCF rates. Saraç et al.[16] compared the outcomes of hypospadias repair with respect to the stenting tube/catheter types. They used the Snodgrass method in all patients and found fistula development in 31.3% of the patients who underwent stent placement using a feeding tube, and 4.39% of patients who underwent stent placement stenting using a Foley catheter. However, we used the same stenting material for all patients.

Guidelines suggest that the optimal age for hypospadias repair is between 6 and 18 months; however, the mean age of our study population was significantly higher.[6] In general, penile size is not a limiting factor for the optimal timing of hypospadias repair, since penile growth is moderate in the first few years of life. Therefore, there is no particular advantage in delaying surgery. Additionally, surgery and hospitalization are less desirable after 18 months of age, when genital awareness begins[17] Complications can occur at any age. The increased complication rate in this study cannot be attributed to the higher mean age of the study population but may instead reflect the limited interest of the families, who are primarily responsible for the care of the children.

The results of our study must be interpreted in the context of its limitations. First, due to the retrospective nature of this study, data could not be obtained for some other potential confounding factors, such as underlying disorders and anatomical properties of the penis (ventral curvature degree, glans width, etc.).[1] The degree of chordee and the length of the urethral defect or fistula formation were not evaluated in the manuscript. Additionally, our study was a single-center study reflecting the experience of a single surgeon, which limits the generalizability of the results. More extensive prospective trials are needed to identify the risk factors for UCF in hypospadias surgery.

CONCLUSION

In conclusion, hypospadias repair is a challenging procedure with potential complications. UCF remains a significant problem in the postoperative period. We found no association between the incidence of postoperative UCF and patient variables. All patients underwent caudal block and despite previous literature, we experienced lower rates of penile engorgement and postoperative UCF. These results showed that there was no cause-and-effect relationship between the caudal block and UCF. We think that the development of a urethrocutaneous fistula is mostly related to surgical causes and that well-designed, prospective, and controlled studies are required to elucidate this issue.

Ethical approval

This study has been approved by the Aydın Adnan Menderes University Non-invasive Clinical Research Ethics Committee (approval date 12/09/2018, number 2018/1456). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: DK, AOE, PDE, BM, SKÖ, MY, FG; Concept: DK, AOE, PDE, BM, SKÖ, MY, FG; Design: DK, MY, FG; Data Collection or Processing: DK, AOE, PDE, BM, SKÖ, MY, FG; Analysis or Interpretation: DK, SKÖ, İKÖ, FG; Literature Search: DK, PDE, BM, SKÖ, FG; Writing: DK, FG. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

The role of inborn errors of metabolism in the etiology of neonatal cholestasis: A single center experience

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ABSTRACT

Objective: The evaluation of patients with neonatal cholestasis is difficult due to the variety of cholestatic syndromes and non-specific clinical findings. It is important to recognize treatable diseases promptly. The aim of this study is to draw attention to suspicious markers in order to diagnose treatable metabolic diseases.

Method: The presented retrospective study included patients with cholestasis in the first three months of life. The study was conducted between 2018 and 2021 at Diyarbakır Children's Hospital, Türkiye.

Results: 253 patients presenting with neonatal cholestasis were retrospectively evaluated. 174 patients (68.77%) were examined for intrahepatic cholestasis. 16.6% of the patients were diagnosed with an infection, 13.43% with TPN-related cholestasis, 8.3% with IEM, 7.11% with cystic fibrosis, 4.74% with endocrinopathy, 4.34% patients with Alpha-1 antitrypsin deficiency, 2.76% with idiopathic neonatal hepatitis, 1.97% with genetic syndrome, 1.58% with PFIC, and 0.79% patients with Alagille syndrome. IEM-related patients (21) were diagnosed with tyrosinemia type 1, galactosemia, Niemann-Pick type A, glycogen storage disease type 3, peroxisomal disorders, fatty acid oxidation defects, mitochondrial DNA depletion syndrome, citrine deficiency, Niemann-Pick Type C and bile acid synthesis defect. Plasma tyrosine and methionine levels were high in patients with not only tyrosinemia type 1, but also galactosemia and citrine deficiency. Therapeutic plasma exchange was performed in two patients with fatty acid oxidation disorders.

Conclusion: Neonatal cholestasis poses a diagnostic challenge for clinicians. Delayed referral to a specialist for treatable metabolic diseases may increase mortality and morbidity. IEMs are observed more frequently in the etiologies of neonatal cholestasis in Türkiye due to high parental consanguinity and inadequate newborn screening programs. Treatable disorders should be considered early, as therapeutic interventiosn can be lifesaving. It also helps in genetic counseling, prenatal diagnosis for future pregnancies.

Keywords: Neonatal cholestasis, intrahepatic cholestasis, galactosemia, hereditary tyrosinemia

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INTRODUCTION

Neonatal cholestasis (NC) is a condition characterized by jaundice and conjugated hyperbilirubinemia that begins in the first months of life and affects approximately 1 in 2500 live births.[1] Etiologic categories include both extrahepatic and intrahepatic disorders, such as extrahepatic biliary atresia, idiopathic neonatal hepatitis, stones, plugs or sclerosis of the biliary tract, infections, total parenteral nutrition (TPN) related, endocrinopathies, chromosomal abnormalities, vascular abnormalities, toxin and drug exposures, hypoxia/ischemia, and inborn errors of metabolism.[2] Clinical and laboratory findings of many diseases with neonatal cholestasis are similar to each other. It is important to distinguish between intrahepatic and extrahepatic causes and to recognize treatable diseases promptly. It is extremely important to take a detailed history and perform a complete physical and neurological examination to formulate possible differential diagnoses. This approach is lifesaving and it should not be disregarded that inborn errors of metabolism (IEM) are underdiagnosed.[3] The most common metabolic etiologies of neonatal cholestasis are tyrosinemia type 1, galactosemia, Niemann Pick Type A, B, C, fatty acid oxidation disorders, urea cycle disorders, bile acid synthesis defects, progressive familial intrahepatic cholestasis (PFIC) I-III, peroxisomal disorders, and mitochondrial DNA depletion syndromes.[3,4] Diagnosis can be guided by a detailed history as well as pathological changes of blood ammonia, glucose, lactate, ketone bodies, and pH. Diagnostic laboratory evaluation of neonatal cholestasis should be comprehensive and initiated early. In some diseases, such as hereditary tyrosinemia type 1, galactosemia, and citrin deficiency, the outcome is excellent with early diagnosis and treatment.[5] Even in the absence of effective treatment, infants with progressive liver disease benefit from medical treatment and optimal nutritional support for complications of cholestasis and possibly cirrhosis. The aim of this study is to evaluate and understand the underlying metabolic causes and consequences of patients with neonatal cholestasis. It is also intended to draw attention to suspicious markers in order not to underdiagnose treatable metabolic diseases.

Here, we report data from patients presenting with neonatal cholestasis (n=253), in which we specifically define the metabolic etiology (n=21), providing a clinically focused overview of the differential diagnosis.

MATERIAL AND METHODS

The present retrospective, cross-sectional, single-center study included patients who presented with direct hyperbilirubinemia with onset in the first three months of life. The study was conducted between 2018 and 2021 at the Pediatric Nutrition and Metabolism and Pediatric Gastroenterology and Hepatology Departments, Diyarbakır Children's Hospital, Türkiye. All samples were analyzed by the same laboratory using the same technique. Plasma amino acid levels were determined by the LC-MS/MS kit (Shimadzu LCMS-8040 Liquid Chromatography Mass Spectrometer, ImmuChrom GmbH kit). Urinary organic acid analysis was semi-quantitative, by modifying the method described by Christou et al.[6] Patients with missing data were excluded. Informed consent was obtained from all individuals. The study was performed in accordance with the Declaration of Helsinki and was approved by the Local Ethics Committee of the Diyarbakir Gazi Yaşargil Research and Training Hospital (Date: 02.07.2021 / No: 819).

Statistical analysis

Statistical analyses of the data were performed using the SPSS software package for Windows software package (ver.18.0; SPSS Inc., Chicago, IL, USA). As descriptive statistics, numbers, and percentages for categorical variables, mean ± standard deviation or median (minimum-maximum) were used for numerical variables. The distribution of data was evaluated using the Shapiro-Wilk test. For numerical comparisons, the Student's t-test or Mann-Whitney U test was used to assess differences between two groups according to the normal distribution of the measured parameters.

RESULTS

253 patients (131/122, M/F) were retrospectively reviewed. 79 patients (31.22%) were referred to another center with the suspected diagnosis of extrahepatic cholestasis after the initial evaluation. 174 patients (68.77%) were examined for intrahepatic cholestasis. 135 (72/63, F/M) patients from 130 different families were diagnosed with non-IEM intrahepatic neonatal cholestasis (IHNC) etiologies. 18 (7.11%) patients were undiagnosed. 42 (16.6%) patients were diagnosed with an infection, 34 (13.43%) patients with TPN-related cholestasis, 21 (8.3%) patients with IEM, 18 (7.11%) patients with cystic fibrosis, 12 (4.74%) patients with endocrinopathy, 11 (4.34%) patients with alpha-1 antitrypsin deficiency, seven (2.76%) patients with idiopathic neonatal hepatitis, five (1.97%) patients with genetic syndrome, four (1.58%) patients with PFIC and two (0.79%) patients with Alagille syndrome in 156 patients. All patients are listed in Figure 1 by etiology. 21 (11/10, F/M) patients from 21 different families were diagnosed with IEM. The patients were diagnosed with tyrosinemia type 1 (n=4, 19.04%), galactosemia (n=4, 19.04%), Niemann-Pick type A (n=3, 14.28%), glycogen storage disease type 3 (n=2, 9.52%), peroxisomal disorders (n=2,

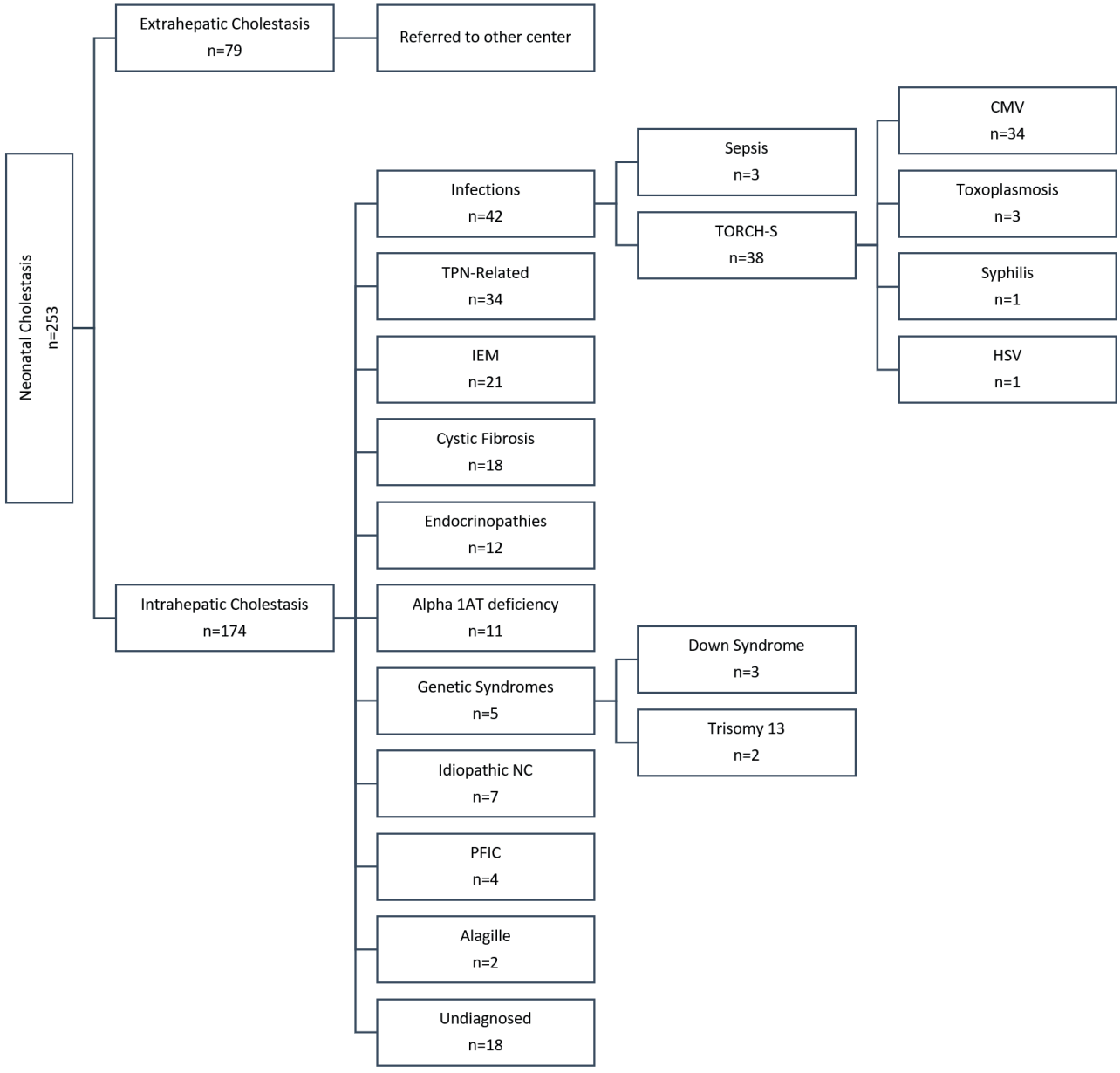

Figure 1. Etiology of the neonatal cholestasis patients in our cohort

9.52%), fatty acid oxidation defects (n=2, 9.52%), mitochondrial DNA depletion syndrome (n=1, 4.76%), citrin deficiency (n=1, 4.76%), Niemann-Pick Type C (NPC, n=1, 4.76%), and bile acid synthesis defect (n=1, 4.76%) in IEM.

We evaluated the patients in two groups, the IEM group and the non-IEM IHNC group. While the consanguinity rate was 90.47% in IEM patients and 25.18% in non-IEM patients. The family history rate was 14.28% in IEM patients, while it was 3.7% in non-IEM IHNC patients. In IEM patients, all patients were born at term with an uneventful delivery, whereas in non-IEM patients, the rate of prematurity was 22.22%, and the rate of hypoxia was 11.85%.

Clinical findings

The mean age of the initial clinical symptom was 38.61±28.38 days (min:7 max:89) and the mean age at the diagnosis was 56.66±34.16 days (min:11- max:112) in the IEM group. The mean age of the initial clinical symptom was 26.42±14.25 days (min:2

max:89) and the mean age at diagnosis was 35.21±22.6 days (min:13- max:108) in the non-IEM group. The most common clinical findings in the IEM group were jaundice (66.66%), hepatomegaly (52.38%), and hypotonia (28.57%), whereas, in the non-IEM group, it was jaundice (92.5%). Hepatomegaly was observed more in the IEM group than in the non-IEM group. Splenomegaly was detected in two patients with Niemann-Pick Type A/B and NPC during the follow-up. Multisystem involvement was observed in 17 (80.95%) IEM patients and 15 (8.62%) non-IEM patients.

Laboratory findings

When ALT values were compared, no statistically significant difference was found between the two groups, however, AST values were significantly higher in the OIHNC group ($p<0.05$). When the bilirubin values of the patients were compared, no significant difference was found between the two groups. A comparison of the findings of IEM and non-IEM intrahepatic neonatal cholestasis patients is shown in Table 1.

Plasma amino acid analysis was performed in 74 patients. There were 21 patients with a diagnosis of IEM and 53 patients with a diagnosis of non-IEM. In the IEM group, 11 patients (52.38%) had elevated plasma tyrosine (Tyr), four patients (19.04%) had low plasma tyrosine, and six patients (28.57%) had normal plasma tyrosine levels. The mean plasma tyrosine levels were 780.18±346.67 µmol/L in patients with elevated Tyr levels and 24.5±4.6 µmol/L in patients with low Tyr levels. Plasma methionine levels were also elevated in eight patients (38.09%), indicating impaired hepatocellular function. Three patients had low methionine levels. Plasma tyrosine and methionine levels were high in patients with not only tyrosinemia type 1 but also galactosemia. When the plasma amino acid results of 53 patients in the non-IEM group were evaluated, high Tyr was found in nine (16.98%) patients, low Tyr in 11 (20.75%) patients, and normal Tyr in 33 (62.26%) patients. The mean plasma tyrosine levels in the OIHNC group were 180.2±42.2 µmol/L in patients with elevated Tyr levels and 11.6±3.4 µmol/L in patients with low Tyr levels. Plasma methionine levels were elevated in two patients (3.77%) in the OIHNC group. Low branched-chain amino acids (one or more from valine, leucine, isoleucine) were detected in nine (42.85%) patients in the IEM group and 13 (24.52%) patients in the non-IEM group. In galactosemia patients, elevations were observed in many amino acids, including Tyr, methionine, and branched-chain amino acids. Hyperaminoacidaemia was transient in galactosemia patients. When liver functions returned to normal, amino acid concentrations returned to normal.

Treatment

Two patients underwent orthotopic liver transplantation. The first patient had tyrosinemia type 1, the other had a bile acid synthesis defect, and both suffered from liver failure. Regarding the outcome, seven patients died in the IEM group. The mean age at death was 6.41±5.74 months (min:1.4- max:18). Therapeutic plasma exchange was performed in two patients with FAO disorders, but had no effect on mortality. The demographic and clinical characteristics of the IEM patients are presented in Table 2.

Table 1. Comparison of the findings of IEM and Non-IEM patients with intrahepatic neonatal cholestasis (OIHNC)

	IEM n=21 (%)	Non-IEM n=135 (%)	p Value
Gender F/M	11/10	72/63	
Consanguinity Rates	19 (90.47%)	34 (25.18%)	p<0.05
Family History	3 (14.28%)	5 (3.7%)	p>0.05
Prematurity rate	0	30 (22.22%)	p<0.05
Birth asphyxia	0	16 (11.85%)	p>0.05
The mean age at initial findings	38.61±28.38	26.42±14.25	p>0.05
Jaundice	14 (66.66%)	125 (%92.5)	p>0.05
Hepatomegaly	11 (52.38%)	28 (20.74%)	p<0.05
Hypotonia	6 (28.57%)	11 (8.14%)	p>0.05
ALT (IU/L)	449.95±512.41	672.3±324.44	p>0.05
AST (IU/L)	628.38±896.63	976.18±726.	p>0.05

Table 2. Demographic, clinical, and molecular characteristics of IEM patients

P	Diagnosis	Sex	Consang.	Family history	Age at Diagnosis	Age at initial Symptom	Initial Symptom	HMG	Hypotonia	Acute Liver Failure	ET	Coag.	Initial Plasma Tyrosine Levels (µmol/L, N:31-108)	Outcome at last visit
P1	Tyrosinemia Type 1	M	Y	N	19	12	ET	Y	N	Y	Y	Y	774	Alive at 2 years of age, under diet and medication
P2	Tyrosinemia Type 1	F	Y	N	22	19	ET	N	N	Y	Y	Y	842	OLT at 5 months of age. Alive at 3 years of age.
P3	Tyrosinemia Type 1	F	Y	Y	19	14	Jaundice	N	N	N	Y	Y	695	Alive at 1 year of age, under diet and medication
P4	Tyrosinemia Type 1	F	Y	N	29	17	Jaundice, elevated Phe levels	N	N	N	Y	Y	554	Alive at 8 months of age, under diet and medication
P5	Galactosemia	F	Y	N	11	7	Jaundice, PC	N	N	Y	Y	Y	856	Alive at 1 year of age, under diet
P6	Galactosemia	M	Y	N	17	11	Jaundice	N	N	Y	Y	N	1108	Alive at 9 months of age, under diet
P7	Galactosemia	F	Y	N	13	9	Jaundice, vomiting	N	N	Y	Y	N	1255	Alive at 8 months of age, under diet
P8	Galactosemia	F	N	N	12	8	Jaundice, ET	N	N	Y	Y	Y	672	Alive at 14 months of age, under diet
P9	Niemann Pick Type A/B	F	Y	N	102	82	AD	Y	N	N	N	Y	28	Deceased at 18 months
P10	Niemann Pick Type A/B	F	Y	N	55	45	Jaundice, hypotonia	Y	Y	N	N	Y	30	Deceased at 92 days of age.
P11	Niemann Pick Type A/B	M	Y	N	72	72	AD, Jaundice	Y	Y	Y	Y	Y	61	Alive at 10 months of age with tracheostomy and gastrostomy

P: patient, F: female, M: male, Consang.: Consanguinity HMG: Hepatomegaly, Coag.: Coagulopathy, ET: elevated transaminases, GSD: Glycogen storage disease, FAO: fatty acid oxidation disorders, Phe: Phenylalanine, PC: poor condition AD: Abdominal distension, OLT: Orthotopic liver transplantation.

Table 2. Continued

P	Diagnosis	Sex	Consang.	Family history	Age at Diagnosis	Age at initial Symptom	Initial Symptom	HMG	Hypotonia	Acute Liver Failure	ET	Coag.	Initial Plasma Tyrosine Levels (µmol/L, N:31-108)	Outcome at last visit
P12	GSD III	F	Y	N	106	84	Hypoglycemia, ET	Y	N	N	Y	N	50	Alive at 1 year of age
P13	GSD III	M	Y	N	109	72	AD, ET	Y	N	N	Y	N	61	Alive at 14 months of age
P14	Peroxisomal Disorders	M	Y	N	69	41	Hypotonia, jaun-dice	Y	Y	N	Y	N	46	Deceased at 5 months of age
P15	Peroxisomal Disorders	M	Y	N	76	17	Jaundice, hypotonia	Y	Y	N	Y	N	71	Deceased at 12 months of age
P16	FAO	F	Y	N	79	61	ET, jaundice	N	N	Y	Y	Y	19	Deceased at 3 months of age due to cardiac arrhythmia
P17	FAO	M	Y	Y	76	63	ET, PC, hypotonia	Y	Y	Y	Y	Y	21	Deceased at 78 days of age
P18	Mitochondrial disease	M	Y	N	37	7	Jaundice, PC, Hypotonia, ET	Y	Y	Y	Y	Y	1342	Deceased at 40 days old.
P19	Citrin Deficiency	F	Y	N	40	20	Jaundice	N	N	N	Y	N	327	Alive at 10 months old
P20	Niemann Pick Type C	M	N	Y	112	89	Jaundice	Y	N	N	N	N	63	Alive at 12 months of age and under medication
P21	Bile acid synthesis disorder	M	Y	N	90	45	Jaundice	N	N	Y	Y	Y	157	OLT at 6 months of age. Alive at 17 months of age.

P: patient, F: female, M: male, Consang.: Consanguinity HMG: Hepatomegaly, Coag.: Coagulopathy, ET: elevated transaminases, GSD: Glycogen storage disease, FAO: fatty acid oxidation disorders, Phe: Phenylalanine, PC: poor condition AD: Abdominal distension, OLT: Orthotopic liver transplantation.

Table 3. Molecular analysis of the IEM patients

Patient	Diagnosis	Gene	Zygosity	Molecular Analysis
P1	Tyrosinemia Type 1	FAH	Homozygous	c.441_448delGGTGATGC
P2	Tyrosinemia Type 1	FAH	Homozygous	c.1062+5G>A (IVS12+5G>A)
P3	Tyrosinemia Type 1	FAH	Homozygous	c.315-3C>G (IVS3-3C>G)
P4	Tyrosinemia Type 1	FAH	Homozygous	c.456-1G>T (IVS6-1G>T)
P5	Galactosemia	GALT	Homozygous	c.563A>G (p.Gln188Arg)
P6	Galactosemia	GALT	Homozygous	c.563A>G (p.Gln188Arg)
P7	Galactosemia	GALT	Homozygous	c.563A>G (p.Gln188Arg)
P8	Galactosemia	GALT	Compound heterozygous	c.563A>G (p.Gln188Arg)/c.958G>A (p.Ala320Thr)
P9	Niemann Pick Type A/B	NA		
P10	Niemann Pick Type A/B	SMPD1	Homozygous	c.967A>C (p.Ser323Arg)
P11	Niemann Pick Type A/B	SMPD1	Homozygous	c.416T>C (p.L139P)
P12	GSD III	AGL	Homozygous	c.500dupG (p.Leu168fs*3)
P13	GSD III	AGL	Homozygous	c.1694delA (p.Asn565MetfsTer12)
P14	Peroxisomal Disorders	PEX	Homozygous	PEX2:c.355C>T (p.Arg119*)
			Homozygous	PEX5:c.159del (p.Glu54Argfs*18)
P15	Peroxisomal Disorders	PEX	Homozygous	PEX1 c.274G>C, p.(Val92Leu)
P16	FAO	ACADVL	Homozygous	c.623G>A (p.Gly208Glu)
P17	FAO	NA		
P18	Mitochondrial disease	TRMU	Homozygous	c.835G>A (p.V279M)
P19	Citrin Deficiency	SLC25A13	Homozygous	c.1793T>G (p.L598R)
P20	Niemann Pick Type C	NPC1	Compound heterozygous	c.2842G>A (p.Asp948Asn)/c.2009G>T (p.Cys670Phe)
P21	Bile acid synthesis defect	AKR1D1	Homozygous	c.148C>T (p.Arg50*)

Molecular analysis

The diagnoses were confirmed by molecular analysis in all IEM patients, presented in Table 3. We studied single gene analysis in 12 (63.15%) patients and multigene panels in seven (36.84%) patients. While single gene sequence analysis was performed in biochemically diagnosed conditions, the multigene panel was preferred when more than one disease was present in the pre-diagnosis. The molecular analysis could not be performed in two IEM patients. P9 was diagnosed by sphingomyelinase enzyme analysis, and P17 was diagnosed by clinical and diagnosed sibling history.

DISCUSSION

Evaluation of patients with neonatal cholestasis is difficult due to the variety of cholestatic syndromes and non-specific clinical findings. Inborn errors of metabolism disorders can produce all the major manifestations of liver dysfunction, such as jaundice, hepatosplenomegaly, coagulopathy, ascites, and encephalopathy. Family and personal medical details should be collected in children with prolonged jaundice and neonatal cholestasis. It is extremely important to take a detailed history and perform a complete physical and neurological examination to formulate possible differential diagnoses. Pregnancy and perinatal history are very important in identifying factors associated with some multifactorial, transient forms of cholestasis, such as low birth weight, prematurity, asphyxia, sepsis, and total parenteral nutrition. Patients with neonatal cholestasis have some markers for diagnosis in their medical history, physical examinations, or basic laboratory tests. Red flags suggesting IEM as the cause of the NC include similar family history, deceased sibling, parental consanguinity, atypical facial appearance, failure to thrive, nystagmus, cataracts, acute or recurrent liver failure, severe hepatomegaly, splenomegaly, cardiomyopathy, dysrhythmia, acute encephalopathy, hypoglycemia, hyperammonemia, rhabdomyolysis, and elevated AFP without hepatocellular carcinoma.[3,7]

Considering the etiology of 253 patients with neonatal cholestasis in our study, intrahepatic cholestasis was detected in the vast majority of cases (68.77%), most of which were infection-related cholestasis (24.13%). Consistent with the literature, the etiology of NC was determined as 60-70% intrahepatic cholestasis. Infection and TPN-related cholestasis constitute the majority of intrahepatic cholestasis cases.[7,8] As a result of clinical and molecular developments in recent years, the frequency of diagnosis of idiopathic neonatal hepatitis has decreased.[3] In the literature, the frequency of NC due to infections has been reported as 7.7%, 2.6%, and 11.5%.[7,9] Consistent with the literature, the most common cause was CMV infection. In Gottesman et al.'s study, the frequency of IEM in the etiology of NC was found to be 4.4%.[7] In the study of Sağ et al., conducted in Türkiye, the frequency of IEM etiology was determined as 12.1%.[9] In our cohort, the frequency of the IEM patients with NC was 8.3%. The higher incidence of IEM can be explained by the fact that consanguineous marriages are more common in Türkiye than in the USA and European countries. Consistent with the literature, the most common causes were galactosemia and HT-1.[7,9]

Sag et al. reported that the frequency of parental consanguinity was 32.8%.[9] In our cohort, the frequency of parental consanguinity was 25.18% in the OIHNC group and 90.47% in the IEM group. The frequency of parental consanguinity was significantly higher in NC patients with IEM etiology. The family history rate was 14.28% in IEM patients, while it was 3.7% in OIHNC patients. If there is consanguinity and/or similar family history in a patient with neonatal cholestasis, it should be carefully evaluated for IEM. The frequency of prematurity was significantly higher in OIHNC patients.

According to the study by Moreira-Silva et al. in 2019, the mean age at presentation of NC patients with only IEM etiology was reported to be 3.5 weeks.[8] According to the study by Sağ et al. in 2013, when all extrahepatic and intrahepatic etiologies were examined, the mean age at presentation in NC patients was reported to be 45±41.3 days.[9] Consistent with the literature, the mean age at first presentation of NC patients with IEM etiology in our study group was 38.61±28.38 days. There was no difference in the mean age at presentation between the patients with IEM etiology and the other groups. Even if NC is a manifestation of liver disease, other systemic diseases and IEMs involving the liver may also present with cholestasis. For this reason, it is recommended to investigate other system involvements. Central nervous system findings and renal pathologies may accompany metabolic diseases.

It is recommended in the NC guidelines to perform metabolic workup, including the second-line workup, in patients suspected as a result of a careful clinical evaluation and initial workup.[10] Second-line workup for IEM can include plasma amino acids, acylcarnitine profile by Tandem Mass Spectrometry, urinary organic acids, and very long-chain fatty acids.[11] Morgan et al. reported significant changes in plasma amino acid concentrations in patients with severe or minimal liver dysfunction.[12] Infants with liver dysfunction usually have low plasma branched-chain amino acid concentrations (valine, leucine, isoleucine) but high phenylalanine, tyrosine, and methionine concentrations.[12-14] Approximately 40% of patients with citrine deficiency have elevated plasma galactose, methionine, and/or phenylalanine concentrations in neonatal screening.[15] However, elevated plasma tyrosine is not common. When the plasma amino acid results of both groups were examined, high Tyr and methionine levels were more common in patients with IEM, in our cohort. Elevated plasma Tyr levels were found in 52.38% of the IEM group and 16.98% of the OIHNC group. Mean plasma tyrosine levels were higher in the IEM group than in the OIHNC group. Plasma tyrosine and methionine levels were high in patients with not only tyrosinemia type 1 but also galactosemia. Hyperaminoacidaemia was transient in galactosemia patients. The frequency of the low branched-chain amino acids was higher in the IEM group than in the OIHNC group. However, the primary factor determining the changes in plasma amino acids is the diagnosis of the disease.

The diagnosis of a treatable IEM causing NC reduces mortality and morbidity. It also helps in genetic counseling, prenatal diagnosis for future pregnancies and clinicians should be alert to the potential associated risk of liver failure and acute metabolic events.

In recent years, NGS-based assays have been developed allowing the simultaneous analysis of multiple genes.[16,17] It has been reported in the literature that NGS-based tests are a promising tool for distinguishing different causes of intrahepatic cholestasis, if the parameters of a reasonable turn-around time, sufficient expertise in the interpretation of results and quality are met and can be considered as a second-line evaluation after exclusion of surgical and infectious etiologies.[10] In our study, we applied single gene analysis in 12 of 19 patients. A specific diagnosis was made with specific biochemical markers and clinical evaluation in 12 patients and the diagnosis was confirmed by single gene analysis. Since there is more than one type and/or gene that causes the disease in patients with peroxisomal disease (2), FAO (1), GSD (2), a disease-associated multigene panel was

performed. However, there were no specific markers in patients with mitochondrial DNA depletion syndrome and even bile acid synthesis defect, the diagnosis was made by clinical exome analysis.

Efficacy data are not available for ursodeoxycholic acid in most of these diseases. However, to promote biliary flow, UDCA was usually prescribed to patients with neonatal cholestasis at doses of 15-20 mg/kg/day. UDCA was generally well tolerated without significant adverse effects. From the early stage of neonatal cholestasis, patients were supplemented with fat-soluble vitamins (vitamins A, D, E, K) to prevent and treat deficiencies. Most of the patients with galactosemia, HT-1, and citrine deficiency responded well to specific treatments. Two patients with FAO, two patients with peroxisomal disorders, two patients with NP-A, and one patient with TRMU died despite supportive treatment due to the lack of effective treatment of the diseases. The diagnosis of a treatable IEM causing NC reduces mortality and morbidity.

Limitations

Since the cases with suspected extrahepatic cholestasis were referred to another center, we did not have information about their etiology. Although there are many studies on the better-known causes of neonatal cholestasis, to the best of our knowledge, this is the first clinical study conducted on the metabolic etiologies of neonatal cholestasis in Türkiye.

CONCLUSION

In the presence of cholestatic jaundice, severe liver dysfunction, acute liver failure, hepatomegaly with hypotonia, and hepatosplenomegaly, careful evaluation for IEM is essential. In conclusion, IEMs are observed more frequently in the etiologies of neonatal cholestasis in Türkiye due to high parental consanguinity and inadequate newborn screening programs. Clinicians should be aware that serious but treatable conditions such as HT1 and galactosemia may present with NC. Consider treatable disorders early, as therapeutic interventions can be lifesaving early in the disease course. It also helps in genetic counseling, prenatal diagnosis for future pregnancies and clinicians should be alert to the potential associated risk of liver failure and acute metabolic events.

Ethical approval

This study has been approved by the Diyarbakir Gazi Yaşargil Research and Training Hospital Clinical Research Ethics Committee (approval date 02/07/2021, number 819). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: AEB, FDA, ATÜ; Concept: AEB; Design: AEB; Data Collection or Processing: AEB, FDA, ATÜ, İT, HB; Analysis or Interpretation: AEB; Literature Search: AEB; Writing: AEB, ATÜ. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Supplementary 1

Detailed description of IEM patients

Patients 1-4: Patients presented with neonatal cholestasis and liver dysfunction during the first month of life. Elevated plasma tyrosine levels, and high urinary succinyl acetone suggested the diagnosis of tyrosinemia type 1, confirmed by *FAH* gene analysis in patients. The mean diagnosis age was 28.5±4.27 days and the mean age of initial findings was 19.5±6.57 days. P4 was admitted to the hospital because of high Phe detection in newborn screening. When the patient's Tyr level was high and the conjugated bilirubin was also found to be high. Two patients had generalized aminoaciduria and phosphaturia due to tubulopathy. A Nitisinone and Tyr-Phe restricted diet was administered to the patients. However, P2 underwent OLT at the age of five months despite treatment.

Patients 5-8: These patients presented with a similar presentation of neonatal cholestasis at newborn period. At first admission, raised plasma amino acid levels (particularly Phe, Tyr, and methionine) were remarkable. The diagnosis of galactosemia was confirmed by enzymatic assay of blood cells after a positive Benedict test in urine. All patients received diagnostic confirmation by molecular analysis of *GALT* gene. The mean age of diagnosis and initial findings was 13.25±2.27 days and 8.75±1.47 days, respectively. Liver disease resolved under galactose restriction.

Patients 9-11: Three patients were admitted to the outpatient clinic with organomegaly and jaundice. Two patients had a 'cherry-red spot' in the eye and hypotonia. A rapid progressive course was observed in all NP-A patients. P11 had an acute liver failure at the age of three months. He was alive at 10 months old with poor condition with tracheostomy and gastrostomy. P9-P10 died due to respiratory problems at 18 months and three months of age, respectively.

Patients 12-13: P12-13 were investigated for elevated transaminases. During the examinations, cholestasis, hypoglycemia, and hypertriglyceridemia were detected. Hepatomegaly, found in both cases, ranged from mild to moderate. Based on the present findings, glycogen storage disease was considered in the patients. NGS panel of glycogen storage diseases was studied. P12 was found to have c.500dupG (p. Leu168fs*3) homozygous variant and p13 was found to have c.1694delA (p. Asn565MetfsTer12) homozygous variant in *AGL* gene. The fasting tolerance of the patients with hypoglycemia responded to frequent feeding and modified cornstarch therapy.

Patients 14-15: In the examination of the patients, who presented with cholestasis and severe hypotonicity, dysmorphological findings (high forehead, large fontanelles, flattened face, broad nasal bridge, dolichocephaly) were found. C26:0 (P14: 4.28 µmol/L, P15: 3.75µmol/L N:0,6-1,3) and C26/C22 (P14: 0.28, P15:0.31 N: 0,011-0,026) values were significantly increased in very long-chain fatty acids in plasma. Phytanic acid and pristanic acid were normal. In both cases, the diagnosis of Zellweger syndrome was confirmed. P14 was found to have two different homozygous pathogenic variants in PEX genes (*PEX2*:c.355C>T (p.Arg119*) and *PEX5*:c.159del (p.Glu54Argfs*18)). The parents, who were first-degree cousins, were found to be carriers for both variants. P14 died at the age of five months with acute liver failure and respiratory problems due to severe hypotonia. P15 had c.274G>C, p.(Val92Leu) homozygous variant in the PEX1 gene. Both parents were found to be carriers for the same variant in segregation analysis. P15 died at the age of 12 months due to aspiration pneumonia. Cholic acid therapy was not used in patients with advanced liver disease as it may be harmful.

Patients 16-17: P16 presented with tachycardia, acute liver failure, cholestasis, and rhabdomyolysis. C14-carnitine, C14:1-carnitine, C16-carnitine, C18-carnitine, C18:1-carnitine values were increased, and C0-carnitine (3.77 µmol/L, N:8-20) was decreased in Tandem-MS analysis. Echocardiography revealed hypertrophic cardiomyopathy. The patient had dysrhythmia with various conduction abnormalities and arrhythmias. Sudden cardiac arrest occurred at three months of age. NGS panel of genes associated with fatty acid oxidation revealed homozygous c.623G>A (p.Gly208Glu) variant in *ACADVL* gene. At 2 months of age, P17 presented with hepatic failure, cholestasis, metabolic acidosis, and hyperammonemia that developed during acute bronchiolitis. Fatty acid oxidation defect was considered because the patient had a history of sibling death with the diagnosis of medium-chain acyl-CoA dehydrogenase deficiency (MCAD). A marked increase was found in the concentration of C8-carnitine with the help of tandem mass spectrometry (MS/MS) profile. However, the molecular analysis could not be performed due to healthcare insurance problems. Carnitine supplementation (50 mg/kg/day), liver protective drugs, high dextrose infusion, and ammonia scavengers were initiated. Therapeutic plasma exchange was applied to both patients.

Patients 18: 12 days of age female neonate, was admitted to the hospital in poor condition. Blood tests showed acidosis (pH 7.21), hyperlactacidemia (lactate 5.3 mmol/L), hypoglycemia, and coagulopathy and raised tyrosine and methionine. By the age of 40 days, she developed cholestatic liver disease, hypotonia, and rotational nystagmus. The genetic study confirmed the diagnosis

of mtDNA depletion syndrome with homozygous mutation c.835G>A (p.V279M) in the *TRMU* gene. She died at 3 months old due to acute-on-chronic liver failure.

Patients 19: 2-month-old female patient was admitted to the hospital to investigate the prolonged jaundice and failure to thrive. Elevated transaminases, cholestasis, high levels of alpha-fetoprotein (AFP), and elevated plasma galactose were observed. Enzymatic analysis of blood cells for galactosemia was normal. The diagnosis was confirmed by the detection of a homozygous c.1793T>G (p.L598R) mutation in the *SLC25A13* gene. The patient, who is 10 months old, is under control with lactose-free and MCT-enriched therapeutic formulas.

Patients 20: 89 days old male patient admitted to the hospital because of prolonged jaundice. Liver disfunction, cholestasis and hepatosplenomegaly were detected. Plasma amino acid, carnitine-acylcarnitine, and urinary organic acid analysis were unremarkable. The patients' chitotriosidase activity was high and Sphingomyelinase and beta-glucocerebrosidase enzyme analyses were normal. P20 was found to have compound heterozygous c.2842G>A (p. Asp948Asn) and c.2009G>T (p. Cys670Phe) variants in the *NPC1* gene. The patient was alive at 12 months old and under medication with miglustat.

Patients 21: 45 days old male patient admitted to the hospital with cholestasis. Elevated transaminases, increased AFP, conjugated hyperbilirubinemia, elevated plasma tyrosine, and methionine were detected. Abdominal ultrasonography revealed multiple millimetric calcifications in the liver parenchyma. c.148C>T (p. Arg50*) homozygous variant was detected in the *AKR1D1* gene in multigene panel. The patient had orthotopic liver transplantation at 6 months of age. The 17-month-old patient is being followed up with a mild developmental delay.

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Original Article

The prevalence, results, and treatments of the patients followed up with a diagnosis of metabolic disease in the pediatric intensive care unit: A single-center experience

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ABSTRACT

Objective: Inborn errors of metabolism (IEM) are a rare, inherited, heterogeneous group of diseases that are mostly symptomatic in the pediatric age group. Late diagnosis and delays in intervention can result in acute metabolic decompensation, progressive neurological damage, or death. IEM patients are responsible for significantly increased morbidity and mortality in intensive care units. Rapid, aggressive, and supportive treatment in pediatric intensive care units can reduce morbidity and mortality in IEM patients.

Method: Patients diagnosed with IEM and/or diagnosed during hospitalization in the tertiary Pediatric Intensive Care Unit (PICU) between February 2021 and November 2022 were retrospectively analyzed. During this period, 962 hospitalized patients were screened and patients with a diagnosis of IEM were included in the study. Demographic data, laboratory analysis, treatment characteristics, PICU, and length of hospital stay were recorded retrospectively.

Results: Twenty-three patients diagnosed with IEM were included in the study. The mean age of the patients was 48 months, and the majority of participants were female. 5/23 patients were followed up with the diagnosis of intoxication type, 10/23 patients with energy metabolism disorder type, and 8/23 patients with complex molecule disorder type. The median lactate level was (6.7 mmol/L, range: 0.8-32) higher in patients (7/23) who died in the PICU than in those who survived (p=0.016). Continuous renal replacement therapy was used in 6/23 (26%) patients, and invasive mechanical ventilation was applied to 3/23 (56.5%) patients.

Conclusion: IEM patients are challenging for pediatric intensive care professionals at the diagnostic and therapeutic levels. Undiagnosed patients at the time of admission to the PICU require a high degree of suspicion for prompt diagnosis and treatment. It is thought that the newborn screening program should be expanded. Aggressive and supportive treatment and specific metabolic disease treatment can be lifesaving, but these patients still have a high mortality rate.

Keywords: Inborn errors of metabolism, pediatric intensive care unit, continuous venovenous hemodiafiltration, invasive mechanical ventilation

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INTRODUCTION

Inborn errors of metabolism (IEM) are a rare, inherited, heterogeneous group of diseases that are mostly symptomatic in the pediatric age group. Although they are seen as rare as 1:100.000 births one by one, their incidence is 1:800-1:2500 births when considered as a group.[1] IEMs result from a deficiency or abnormality of an enzyme or cofactor, or a transport defect. In general, it leads to an accumulation or deficiency of metabolite.

IEM can be classified into three subgroups according to their physiological characteristics: 1- Intoxication type (urea cycle disorders, amino acidopathies, organic acidurias), which occurs with metabolic crises due to the damage in the metabolic pathway causing the accumulation of toxic metabolites; 2- Energy metabolism disorders (mitochondrial disorders, glycogen metabolism disorders, fatty acid oxidation defects), which result from insufficient energy production, involving organs with higher energy needs such as muscles and the brain; and 3- Complex molecule type (lysosomal and peroxisomal storage diseases) with an accumulation of complex molecules in solid organs due to enzyme deficiency.[2] In IEM patients, especially those with intoxication type and energy metabolism disorders, the acute metabolic crisis is observed when energy insufficiency occurs. Late diagnosis and delayed intervention can result in acute metabolic decompensation, progressive neurological damage, or death. IEM patients are responsible for significantly increased morbidity and mortality in intensive care units. Generally, IEM patients with complex molecule type also need intensive care for organ failures, such as congestive heart failure, respiratory failure due to organ system involvement, or severe infections. The most common causes of hospitalization in IEM patients are metabolic decompensations, septicemia, and respiratory problems. Rapid, aggressive, and supportive treatment in pediatric intensive care units can reduce morbidity and mortality in IEM patients.

In our study, we aimed to describe the demographic, clinical, and laboratory characteristics, causes of hospitalization, and mortality rate of patients with a diagnosis of IEM in the tertiary pediatric intensive care unit.

MATERIAL AND METHOD

In our study, patients diagnosed with IEM and/or diagnosed during hospitalization in the tertiary PICU of Manisa City Hospital between February 2021 and November 2022 were retrospectively analyzed.

The study protocol was approved by the local ethics committee of Bakırçay University. Children, aged between 1 month and 18 years, who presented to the PICU with a metabolic emergency and were diagnosed with IEM, were included in the study conducted between February 2021 and November 2022. We included children diagnosed with IEM for the first time on admission to the PICU and children diagnosed with metabolic disease in the neonatal period or on their previous admission. Children without a diagnosis of IEM, with missing data, and without a definitive diagnosis at discharge or death were excluded from the study.

Demographic data (age, gender, and cause of hospitalization), PRISM score, laboratory analysis (liver function tests, renal function tests, hemogram, infection parameters, blood gas parameters), culture results (urine, blood culture), treatment characteristics, PICU and length of stay (LOS) were retrospectively recorded. All patients were followed up until discharge or death.

The patients were divided into three groups: Intoxication types (amino acidopathies, organic acidurias, urea cycle defects, carbohydrate intolerances, metal disorders, and porphyrias), energy metabolism disorders (Glycolysis, glycogenosis, gluconeogenesis defects, creatine pathway, pentose phosphate pathway defects, mitochondrial disorders), and complex molecule type (lysosomal storage diseases, peroxisomal disorders, congenital disorders of glycosylation, and cholesterol synthesis defects).

All samples were analyzed by one laboratory with the same technique. Plasma amino acid levels were determined by the LC-MS/MS kit (Shimadzu LCMS-8040 Liquid Chromatography Mass Spectrometer, ImmuChrom GmbH kit). DBS were pre-processed following the instruction of NeoBaseTM non-derivatized MS/MS kit (PerkinElmer, MA, United States), using 1525u high-performance liquid chromatography (HPLC) (Waters Technologies, Milford, MA, United States) and ACQUITY TQD mass spectrometer (Waters, Milford, MA, USA) for quantitative analysis. The analytes included 11 amino acids and 31 acylcarnitine. Urinary organic acid analysis was performed by modifying the method described by Christou et al. Analysis was performed on GC-2010 Plus Gas Chromatography System, Shimadzu Manufacturing Co, Japan. Four-phenylbutyric acid was used as an internal standard, and ethyl acetate was used to extract the organic acids. The organic acids were derivatized using the N, O-Bis(trimethylsilyl) trifluoroacetamide, and trimethylsilyl chloride. Creatinine was measured according to the Jaffe method.[3]

Statistical analyses

Statistical analysis was performed using SPSS software version 22.0 (SPSS, Chicago, IL) for Windows. The distribution of data was evaluated using the Kolmogorov-Smirnov test. We used the one-way ANOVA test to compare more than two groups with normal distribution and homogenous variance and the Kruskal-Wallis test for non-normally distributed data. To compare categorical data, Fisher's exact test with Monte Carlo simulation was used. We presented the descriptive results with normal-distributed data as mean ± standard deviation and skewed data as median (interquartile range (IQR) 25/75). Categorical data were expressed as frequency (%), while numerical data were expressed as mean ± standard deviation. In all statistical tests, p-values<0.05 were considered significant.

RESULTS

Between February 2021 and November 2022, 962 pediatric patients were followed up in the pediatric intensive care unit. Of these, 23 (2.4%) were followed up with a diagnosis of IEM. Five (21.7%) patients were followed up with a diagnosis of intoxication type, 10 (43.5%) patients with an energy metabolism disorder type, and 8 (34.8%) patients with a complex molecule disorder type (Figure 1). Of these 23 patients, seven (30.4%) were diagnosed during hospitalization. The median age of IEM patients was 48 months (IQR, 9-86) and 52.2% were female, while the median age of non-IEM patients was 26 months (IQR, 12-124) and 51% were female. The etiology of PICU hospitalization of IEM patients was metabolic decompensation in 8 (34.8%), respiratory failure in 8 (34.8%), severe sepsis in 5 (21.7%), and cardiovascular failure in 2 (8.7%) patients. There was a history of consanguinity in 17 (73.91%) patients. Thirteen (56.5%) patients in the IEM group and 320 (34%) patients in the non-IEM group were followed up with invasive mechanical ventilation. Mortality was 7 (30.4%) in IEM patients and 62 (6.6%) in non-IEM patients. The median lactate level was (6.7 mmol/L, range: 0.8-32) higher in patients (7/23) who died in the PICU than the patients who survived (p=0.016). The demographic and clinical characteristics of the IEM and non-IEM patients were presented in Table 1.

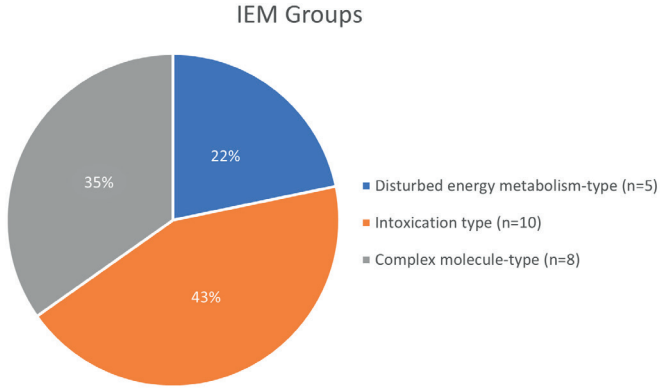

Figure 1. Inborn errors of metabolism Etiology

There was no significant difference in the mean ages between disease groups. Respiratory supportive treatments, such as invasive mechanical ventilation, were most commonly required in patients with complex molecule disorder type (p=0.022).

Table 1. Demographic and clinical characteristics of the IEM and non-IEM patients

Parameters	IEM patients (n=23) n, %	Non-IEM patients (n=939) n, %
Gender M/F	11/12 (47.8/52.2)	453/480 (48/51)
Age (month)*	48 (9-86)	26 (12-124)
Consanguinity rate	17 (73.91)	80 (8.51)
Death sibling history	4 (17.39)	17 (1.81)
PRISM III score*	6 (2-12)	5.6 (1-23.2)
Respiratory Support	13 (56.5)	320 (34)
Duration of mechanical ventilation*	3 (0-8)	9 (3-21)
Lactat level mmol/L*	6.7 (0.8-32)	2.0 (1.3-3.1)
Length of PICU stay (days)*	7 (5-22)	15 (3-101)
Length of hospital stay (days)*	11 (8-22)	22 (4-166)
Mortality in PICU	7 (30.4)	62 (6.6)

PICU: Pediatric Intensive Care Unit, IEM: Inborn Errors of Metabolism, PRISM III score: Pediatric Risk of Mortality III score.
* Median, IQR (Interquartile range)

Table 2. Demographic and clinical characteristics of patients according to disease groups

Parameters	Intoxication-type n=5	Disorders of disturbed energy metabolism-type n=10	Complex molecule-type n=8	p
Age (month) median, (IQR)	47 (14.5-58.5)	42.5 (6.5-97)	63.5 (23.2-150)	0.487
Gender M/F n	2/3	4/6	5/3	0.624
PRISM III score median, (IQR)	2 (2-12)	7 (2-12)	7 (2.25-10)	0.739
Treatment n (%)				
Metabolic Arrangements	1 (20)	4 (40)	5 (62.5)	0.341
RBC Transfusion	2 (40)	5 (50)	2 (25)	0.594
FFP	0	3 (30)	1 (12.5)	0.350
Platelet Transfusion	1 (20)	4 (40)	1 (12.5)	0.429
CRRT n (%)	1 (20)	3 (30)	2 (25)	0.924
Diagnosed in PICU n (%)	1 (14.3)	5 (71.4)	1 (14.3)	0.518
Respiratory Support n (%)	1 (20)	5 (50)	7 (87.5)	0.022
Duration of mechanical ventilation, median (IQR)	0 (0-1.5)	3 (0-8)	9 (2.5-22.5)	0.392
Length of PICU stay (days), median (IQR)	6 (3-14)	9 (5.7-16.7)	15 (5.2-33)	0.359
Length of hospital stay (days), median (IQR)	12 (5.5-16.5)	10.5 (7.7-19)	17 (8.5-33)	0.487
Mortality n (%)	1 (20)	4 (40)	2 (25)	0.702

M: Male, F: Female, RBC: Red blood cell, FFP: Fresh Frozen Plasma, PRISM III score: Pediatric Risk of Mortality III score.

Although the length of stay in the PICU was longer in the complex molecule disorder type, this was not statistically significant. Mortality rates were higher in the energy metabolism disorder type, however, it did not differ significantly between disease groups. CRRT was performed in 6 (26.1%) patients. Although mortality was higher in patients who underwent invasive mechanical ventilation (p=0.022), there was no statistically significant relationship with the duration of mechanical ventilation (p=0.392). The median length of stay in the PICU was longer in patients who died, but this was not statistically significant. The clinic, laboratory, and treatment characteristics by disease groups are presented in Table 2. IEM patients followed in the PICU are shown in Table 3.

DISCUSSION

Five million people in Türkiye and 350 million people in the world have a rare disease.[4] Approximately 50% of the patients are children. 30% of children with rare diseases do not reach the age of 5 years. Inborn errors of metabolism are rare diseases; however, as a group, they are relatively more common. Their incidence in the community varies depending on the consanguineous marriage rates, newborn screening programs, developing technology, ethnicity, and level of awareness. It is estimated that the incidence of IEM is higher in countries where consanguineous marriages are more common, such as Türkiye.[5] IEM can present at any stage of life. Neonatal screening programs and their scope differ by country. In Türkiye, screening for phenylketonuria and congenital hypothyroidism was started in 2006, screening for biotinidase deficiency in 2008, screening for cystic fibrosis in 2015, and screening for congenital adrenal hyperplasia in 2022. Since extended newborn screening is not performed in our country, patients whose clinical findings start after the neonatal period need PICU care. In addition, the need for intensive care is more frequent in IEM patients due to metabolic decompensation episodes, multisystem involvement, secondary immunodeficiency, and progressive course.

In the literature, the frequency of IEM in the PICU was reported as 2.6% by Kamate et al.[6], 2% by Lipari et al.[7], and <1% by Ruttiman et al.[8] In our study, 962 patients were followed in the PICU between February 2021 and November 2022, 939 patients with non-IEM and 23 patients with IEM, aged 0-18 years. We focused on those with a confirmed diagnosis of IEM. The incidence of metabolic disease was 2.39%, which is consistent with the literature. This frequency is similar to the malignancy (3.3%) and septic shock (2.4%) incidences in the PICU reported in other studies.[9] The consanguinity rate was 8.51% in non-IEM

Table 3. Patients' diagnosis and demographic characteristics (n=23)

	Patient	Gender	Age at admission (month)	Consang. (Yes/No)	Diagnosis	Intervention	Outcome
Intoxication type (n=5)	P1	M	9	Yes	MSUD	Metabolic decompensation, CVVHDF	Alive
	P2	F	69	Yes	GA-1	Acute encephalopathyc crisis	Alive
	P3	F	20	Yes	Hereditary Fructose Intolerance	Metabolic acidosis	Alive
	P4	M	48	No	NAGS	Metabolic decompensation	Alive
	P5	F	47	Yes	MMA	Metabolic decompensation, IMV	Decesead
Disturbed energy metabolism-type (n=10)	P6	F	33	Yes	Dopamine transporter deficiency	IMV	Alive
	P7	F	7	Yes	Mitochondrial DNA depletion syndrome	Severe lactic acidosis, IMV	Decesead
	P8	M	203	Yes	MNGIE	Sepsis, CVVHDF, IMV	Decesead
	P9	M	2	Yes	MCAD	Metabolic decompensation, CVVHDF, IMV	Decesead
	P10	F	8	No	Mitochondrial DNA depletion syndrome	Severe lactic acidodis	Alive
	P11	F	5	Yes	Congenital lactic acidosis	Severe lactic acidodis, CVVHDF, IMV	Decesead
	P12	F	86	Yes	Pyruvate carboxylase deficiency	Metabolic decompensation	Alive
	P13	M	52	Yes	GSD III	Acute liver failure	Alive
	P14	F	84	Yes	Ketolysis defect	Metabolic decompensation	Alive
	P15	M	130	Yes	GSD IX	Rhabdomyolisis	Alive
Complex molecule-type (n=8)	P23	F	156	No	MPS type I	IMV	Alive
	P16	M	19	No	MPS type II	IMV	Alive
	P22	F	36	Yes	MPS type III	IMV	Alive
	P17	M	175	Yes	MPS type IV	IMV	Alive
	P18	M	9	Yes	Mucolipidosis (I-cell)	CVVHDF, IMV	Decesead
	P21	M	67	No	Gaucher's disease I	IMV	Alive
	P19	F	60	No	Tay-Sachs Disease	IMV	Alive
	P20	M	132	Yes	CDG	Sepsis, CVVHDF, IMV	Decesead

M: Male, F: Female, Consang.: Consanguinity, MSUD: Maple Syrup Urine Disease, GA-1: Glutaric aciduria type 1, NAGS: N-Asetil glutamate Sentetase Deficiency, MMA: Methyl malonic acidemia, MNGIE: Mitochondrial Neruogastrointestinal encephalomyopathy, MCAD: Middle chain Acetil CoA Dehydrogenase deficiency, GSD: Glycogene Storage disease, MPS: Mucopolisacaridosis, CVVHDF: Continuous Venovenous Hemodiafiltration, IMV: Invasive mechanical ventilation.

patients and 73.91% in IEM patients hospitalized in the PICU. There was a history of sibling death in %1.81 of non-IEM patients and 17.39% of IEM patients. Therefore, clinicians should be careful about IEM if patients have a history of consanguineous marriage or sibling death. IEM patients are mostly diagnosed before 1 year of age, except for those with lysosomal storage disease. Dionisi-Vici et al. reported in a large-scale study that 59% of IEM patients were diagnosed before the age of three years.[10] Considering all patient populations admitted to the PICU, Edae et al. reported a mean age of 48.13 ± 53.65 months.[11]

Lipari et al. reported that the median age at admission to PICU for IEM patients was 36 months.[7] In our study group, the median and mean age of the IEM patients at first admission to the PICU was 48 months and 63.35 months, respectively. The median and mean age of the non-IEM patients was 26 months and 22.3±64.1 months (min:1-max:204), respectively. The lack of standardization between studies, the differences in the number of patients, the types of IEM, and the differences in the socio-economic levels of the countries may cause variations.

In a study conducted in a tertiary PICU in Portugal, intoxication-type metabolic diseases were the most common IEM.[7] The metabolic disease type most frequently observed in the NICUs is usually the intoxication type IEM. Amino acidopathies and organic acidurias were the most frequently diagnosed IEM in the population on PICU admission[12], however, energy metabolism disorders were observed more frequently in our study. Intoxication type and disturbances in energy metabolism disorders were diagnosed earlier than the other types of IEM.[10] These differences between studies may be because our study was conducted in a single center within a limited time frame, and/or the lack of newborn screening in Türkiye.

Most IEM patients admit to the PICU with metabolic acidosis, encephalopathy with or without seizures, hepatic presentation, and cardiac presentation.[13] The studies reported that the most common admission etiology of IEM was metabolic decompensation due to infections in 70.4% and elective procedure in 29.5%. The most common clinical presentation was respiratory failure in 34.1%.[6,14] Consistent with the literature, the most common clinical presentation was metabolic decompensation and respiratory failure. These were followed by infections and congestive heart failure. In our study group, 30% of the patients were not diagnosed with IEM prior to admission to our PICU. In these clinical conditions, such as metabolic acidosis, respiratory failure, multisystem involvement, and encephalopathy, simple laboratory tests (ammonia, lactate), neuroimaging and first-line metabolic workup (Tandem MS/MS, urine organic acid analyses) tests should be studied in PICU patients. Patients diagnosed in the PICU highlight the lack of awareness among pediatricians and the non-specific presentation of IEM.

Treatment of IEM generally includes the removal of toxic metabolites, elimination of energy deficit, specific nutrition management, and supportive treatment in the intensive care unit. In a multicenter study, the need for mechanical ventilation in patients admitted to the PICU was 35%.[15] In our study group, the need for mechanical ventilation in all patients was 14.35% and 56.52% in IEM patients. The need for mechanical ventilation was significantly higher in IEM patients. We thought this was due to multisystem involvement and poor condition. Sivaraman et al. reported the mortality rate as 83.3% in patients who needed mechanical ventilation. Accordingly, mechanical ventilation treatment was found to be associated with mortality.[16] In our study group, the mortality rate was 53.86% in patients who needed invasive mechanical ventilation and 83.33% in those who needed invasive mechanical ventilation (p=0.007). The need for extracorporeal therapy need was 26.08%. The mortality rate was %83.33 in patients who needed extracorporeal therapy in our study group. Mortality rates due to metabolic disease in the PICU vary. In developed countries, the IEM-related mortality rate in the PICU was reported as 36% by Kamate et al.[6] and 28.6% by Jouvet et al.[17] In our study, the mortality rate was 30.4% in IEM patients and 6.6 % in non-IEM patients. A retrospective study in Italy reported an IEM-related mortality rate of 25.2%, with specific mortality rates up to 48.7% for primary lactic academia.[10] Consistent with the literature, when we compared disease groups in our study, the highest mortality was found for the energy metabolism disorder at 40%. Kamate et al. attributed the high mortality to less use of extracorporeal therapy, but the use of extracorporeal therapy was higher in our study group compared to other studies.[6] Despite this, our mortality rate was high. The reason for the increased use of extracorporeal therapy may be due to the presence of intoxication type and energy metabolism disorder (going with severe lactic acidosis) in a significant proportion of these patients. Lipari et al. reported that the median LOS in PICU was 1-2 days among metabolic disease groups, whereas complex molecule type had the longest LOS with 35 days.[7] In our study, the longest LOS was seen in the complex molecule type and the median LOS in the PICU was 15 days, and it was not statistically significant according to groups. The median LOS in the PICU was longer for patients who died, but this was not statistically significant.

Optimal outcomes in IEM depend on early recognition of symptoms and signs, rapid evaluation, and aggressive treatment. Variabilities can be moderated by early diagnosis and treatment via newborn screening in the country. Inadequacy of newborn screening tests, acute metabolic decompensation due to diagnostic delay, progressive course, delayed diagnosis, and delayed treatment have an impact on the high mortality. When the mean lactate levels of non-IEM-related deceased patients were compared with the IEM-related deceased patients, the median lactate was significantly higher in the IEM group. It may be due to the fact that it constitutes the majority of patients with

energy metabolism disorder including congenital lactic acidosis and intoxication type IEM. We thought that the reason might be due to the poor prognosis of IEM type (energy metabolism disorders) and late diagnosis (due to lack of newborn screening). Rapid and aggressive PICU management, including mechanical ventilation and extracorporeal therapy, is effective in reducing mortality.

This study has some limitations. This study was retrospective, conducted in a single center with small sample size and difficulties in accessing some laboratory tests.

CONCLUSION

These patients are challenging for pediatric intensive care professionals at the diagnostic and therapeutic levels. Undiagnosed patients at the time of admission to the PICU require a high degree of suspicion for prompt diagnosis and treatment. Metabolic decompensation and deterioration due to organ dysfunction are more common in children with a pre-existing IEM. A multicenter approach will be necessary to obtain comprehensive information It is thought that neonatal screening programmes should be expanded, particularly for intoxication-type IEM, considering the timing of symptom onset and presentation. Aggressive and supportive treatment and specific metabolic disease treatment can be lifesaving, but these patients still have a high mortality rate.

Ethical approval

This study has been approved by the İzmir Bakırçay University Non-invasive Clinical Research Ethics Committee (approval date 30/11/2022, number 792). Written informed consent was obtained from the participants.

Author contribution

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

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Intended versus delivered parenteral nutrition in the pediatric intensive care units: A multi-center survey

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ABSTRACT

Objective: Prevention and management of malnutrition are important in critically ill children. Parenteral nutrition (PN) is considered for patients who cannot tolerate enteral feeding. There are many reasons why PN cannot be delivered in the prescribed amount. We aimed to evaluate whether PN is delivered as prescribed in the pediatric intensive care units and to reveal the reasons for failure.

Method: Demographics, pediatric risk of mortality (PRISM) III scores, predicted death rates (PDR), indications for PN, duration of PN, vascular access site, daily amount of prescribed and delivered PN, reasons for not receiving PN as prescribed, and whether renal replacement therapy (RRT) was received were noted. The delivered/prescribed PN volume ratio was compared by gender, age, PRISM III score, PDR, indications for PN, duration of PN, and vascular access site.

Results: The most common indication for PN was failing to meet the targeted energy enterally (n=51, 69.9%). The duration of PN was ≤ 7 days in 40 (54.8%) patients and the type of vascular access was jugular venous catheter in 46 (63%) patients. 16 (21.9%) patients received RRT. PN was administered for 906 PN-days and the patients received the prescribed volume on 698 PN-days (77%). The most common reasons for not receiving the PN volume as prescribed were volume restrictions (n= 29, 39.7%) and electrolyte imbalance (n=13, 17.8%). Age, gender, weight, duration of PN, vascular access site, receiving RRT, PRISM III score, and PDR were not associated with receiving more than 0.8 of the prescribed PN volume. All gastrointestinal surgery patients received more than 0.8 of the prescribed amount.

Conclusion: In about a quarter of PN-days, the prescribed volume could not be delivered, often due to volume restrictions in the pediatric intensive care units. Setting the correct nutritional targets, individualizing nutritional support, and preventing and overcoming obstacles on the way to the targets may improve outcomes.

Keywords: Critically ill, malnutrition, outcomes, parenteral nutrition, pediatric intensive care

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INTRODUCTION

Prevention, early detection, and management of malnutrition are important issues in critically ill children.[1] Malnutrition is associated with prolonged duration of ventilation, prolonged hospital stay, and increased risk of infection and mortality.[1-3] All pediatric intensive care unit patients should have a nutrition plan, which include the nutrition route and administration time, the amount of the macro and micronutrients, and the energy to be provided, and it should be updated according to the changing clinical conditions.[1] Parenteral nutrition (PN) can be total PN or supplemental PN. Enteral nutrition (EN) is a priority for critically ill children.[1] In these patients, EN is frequently delayed or interrupted due to gastrointestinal dysfunction, so PN is considered since the resulting nutritional deficiency is associated with adverse outcomes.[1,4] Optimizing energy provision with supplemental PN in critically ill patients receiving inadequate EN has been associated with fewer hospital infections, antibiotic use, and shorter duration of mechanical ventilation.[5] There is no consensus on the timing of initiating PN.[4,6-11] According to current guidelines, PN is not recommended in the first 24 hours, and the waiting period may be extended in children in whom EN can be started and gradually increased.[1] The waiting period can be extended up to one week for patients with a good nutritional status, but it is recommended to start PN in the first week in patients with malnutrition.[1]

There are many reasons why PN cannot be delivered in the targeted and prescribed amount in pediatric intensive care units. Lack of appropriate vascular access, interactions with other drugs, electrolyte disturbances, abnormalities in kidney and liver tests, and volume restrictions are some of these reasons. In the presented study, we aimed to evaluate whether PN was delivered as planned and prescribed in the pediatric intensive care units participating in the study and to reveal the reasons for failure.

MATERIAL AND METHODS

Study design

The data of 5 tertiary hospitals in Türkiye that agreed to participate in this multi-center retrospective study were evaluated. All patients aged between 1 month and 18 years, who were hospitalized in the pediatric intensive care units and received total or supplemental PN between July 2018 and January 2019, were included. The characteristics of the pediatric intensive care units participating in the study are described in Figure 1.

Variables and measurements

Demographics, pediatric risk of mortality (PRISM) III scores, predicted death rates (PDR), indications for PN, duration of PN,

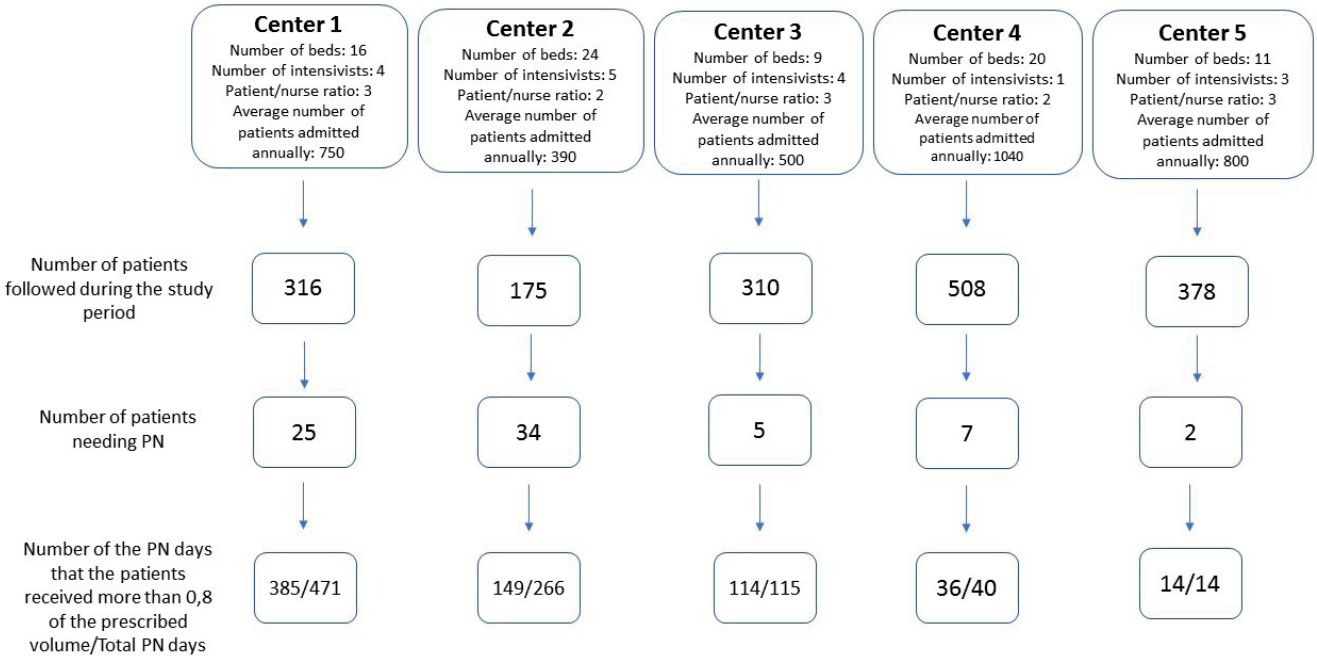

Figure 1. Characteristics and patient numbers of the pediatric intensive care units participating in the study.
PN: Parenteral nutrition

vascular access site, daily amount of prescribed and delivered PN, reasons for not receiving PN as prescribed, and whether patients received renal replacement therapy (RRT) and/or extracorporeal membrane oxygenation (ECMO) support were noted. The patients were divided into two groups: those who received the prescribed PN volume on more than 0.8 of PN days and those who did not. The received/prescribed PN volume ratio was compared by gender, age, PRISM III score, PDR, indications for PN, duration of PN, and vascular access site.

Indications for parenteral nutrition

Indications for PN include failure to meet the targeted energy enterally, gastrointestinal surgery/bleeding, and inborn errors of metabolism/metabolic crisis.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics (version 22.0.0; IBM Co., Armonk, NY, USA), and p-values <0.05 were considered statistically significant. The normal distribution of variables was analyzed visually (histogram and probability graphs) and statistically (Kolmogorov-Smirnov test). Data were presented as medians (25th-75th percentiles) for continuous variables and as numbers of cases and percentages (%) for categorical variables that did not fit a normal distribution. Chi-square or Fisher's exact test was used to compare differences between frequencies. The Mann-Whitney U test was used to compare numerical variables without normal distribution.

Ethical approval

Ethical approval was obtained from the ethics committee of the hospital where the study was conducted (Approval number: E-21/11-237). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

RESULTS

Seventy-three patients (41 males, 56.2%) were included in the study. The median age was 17 (5-66) months, and the median body weight was 10 (5.3-17.2) kg.

PN was given to patients with sepsis/multi-organ failure (26%), gastrointestinal surgery/bleeding/obstruction (21.9%), inborn errors of metabolism/chronic diarrhea (16.4%), respiratory diseases/infections (15.1%), congenital heart disease (8.2%), malignancy (6.8%), and immunodeficiency (5.5%).

The most common indication for PN was failing to meet the targeted energy enterally (n=51, 69.9%) (Table 1). The duration of PN was ≤ 7 days in 40 (54.8%) patients and the vascular access type was jugular venous catheter in 46 (63%) patients (Table 1). 16 (21.9%) patients received RRT and 5 (6.8%) received ECMO (Table 1). PN was administered for 906 PN-days and the patients received the prescribed volume only on 698 PN-days (77%) (Fig. 1). The most common reasons for not receiving the PN

Table 1. Demographic and clinical characteristics of the patients

Demographic Characteristics	n (%)
Gender	
Male	41 (56.2)
Female	32 (43.8)
Age, months	17 (5-66)
Body weight, kg	10 (5.3-17.2)
Indications for PN	
Failure to meet the targeted energy enterally	51 (69.9)
Gastrointestinal surgery	9 (12.3)
Inborn errors of metabolism/metabolic crisis	8 (11.0)
Gastrointestinal bleeding	5 (6.8)
Duration of PN (days)	
≤7	40 (54.8)
8-30	26 (35.6)
>30	7 (9.6)
Vascular access site	
Jugular	46 (63.0)
Femoral	16 (21.9)
Subclavian	5 (6.8)
Peripheral	6 (8.2)
RRT	16 (21.9)
CRRT	14 (19.2)
IHD	2 (2.7)
ECMO	5 (6.8)
Reason for not receiving PN as prescribed	
Volume restriction	29 (39.7)
Electrolyte imbalance	13 (17.8)
Delay for preparing the PN solution	3 (4.1)
Cholestasis	1 (1.4)
PRISM III (n=66)	12.0 (7.8-18.0)
PDR (n=66)	8.00 (4.2-21.3)

Data are presented as n (%) or median (25^{th} and 75^{th} percentiles).
CRRT: continuous renal replacement therapy, ECMO: extracorporeal membrane oxygenation, IHD: intermittent hemodialysis, PDR: predicted death rate, PN: parenteral nutrition, RRT: renal replacement therapy.

volume as prescribed were volume restrictions (n= 29, 39.7%) and electrolyte imbalance (n=13, 17.8%) (Table 1).

Age, gender, body weight, duration of PN, vascular access site, receiving RRT and ECMO, PRISM III score, and PDR were not associated with receiving more than 0.8 of the prescribed PN volume (Table 2). All gastrointestinal surgery patients received more than 0.8 of the prescribed amounts of PN (Table 2).

DISCUSSION

The nutritional status of critically ill children is associated with the outcomes.[1] The nutritional status of the patients should be evaluated within the first 48 hours after hospitalization and an appropriate nutritional plan should be made.[1] Energy, protein, and other macro- and micronutrient needs should be correctly determined and optimally provided.[1] Interruptions in nutrition for various reasons or failure to deliver the targeted volume are usually ignored, and this adversely affects the outcomes. These patients often receive inadequate nutrition, and their nutritional status gradually deteriorates during their stay in the pediatric intensive care units.[2,8] In an international multicenter study that included 31 pediatric intensive care units in eight countries, 30% of the patients had severe malnutrition, 38% of the daily energy target and 43% of the daily protein target were achieved, and the mortality was lower in children who received more energy via EN.[2]

Only a few studies have evaluated the amount of enteral or parenteral nutrition delivered/prescribed in pediatric intensive care units. Moreover, the appropriate method to assess whether parenteral nutrition is delivered as intended in critically ill children needs to be clarified. A study on enterally fed critically ill children reported that the daily caloric intake was about 60% of the calorie requirement and 85% of the prescribed calories.[12] In another study conducted on pediatric patients admitted to intensive care units, the estimated energy requirement, the prescribed calories, and the delivered calories were 90 kcal/kg/day, 75 kcal/kg/day, and 58 kcal/kg/day, respectively. The ratio of calories delivered/prescribed was 77%.[13] In a prospective survey conducted by De Jonghe et al.[14], 78% of the mean caloric requirement was prescribed, and 71% was actually delivered. The amount of calories actually delivered compared with the amount prescribed was significantly lower in enteral than in

Table 2. Factors associated with the received/prescribed parenteral nutrition volume ratio

Variables	Patients received ≥0.8 of prescribed PN (n=32)	Patients received <0.8 of prescribed PN (n=41)	p value
Age, months	17.5 (4.0-67.5)	16.0 (5.5-71.5)	0.894
Gender, Male	19 (59.4)	22 (53.7)	0.625
Weight, kg	10.0 (5.3-17.3)	10.0 (5.4-17.8)	0.697
Indications for PN			
Failure to meet the targeted energy enterally	25 (78.1)	26 (63.4)	0.174
Gastrointestinal surgery	0 (0.0)	9 (22.0)	0.004
Metabolic crisis	5 (15.6)	3 (7.3)	0.287
Gastrointestinal bleeding	2 (6.3)	3 (7.3)	1.000
Duration of PN, days			
≤7	21 (65.7)	19 (46.3)	0.100
8-30	9 (28.1)	17 (41.5)	0.238
>30	2 (6.3)	5 (12.2)	0.456
RRT (n=16)	9 (28.1)	7 (17.1)	0.257
CRRT	8 (25.0)	6 (14.6)	0.264
IHD	1 (3.1)	1 (2.4)	1.000
ECMO	1 (3.1)	4 (9.8)	0.377
PRISM III (n=66)	11 (7-17)	15 (8-18)	0.382
PDR (n=66)	8.0 (4.9-21.3)	9.4 (2.9-22.5)	0.683

Data are presented as n (%) or median (25^{th} and 75^{th} percentiles).
CRRT: continuous renal replacement therapy, ECMO: extracorporeal membrane oxygenation, IHD: intermittent hemodialysis, PDR: predicted death rate, PN: parenteral nutrition, RRT: renal replacement therapy.

parenteral administration (86.8% vs. 112.4%). In summary, the delivered/prescribed amount of nutrition was 85%, 77%, and 86.8% in these three studies. Based on these studies, we determined a similar cut-off value of 80% and divided patients into two groups: those who received the prescribed volume of PN on more than 80% of PN days and those who did not. Another point worth noting is that the reasons for the interruption of EN were airway management, digestive intolerance, diagnostic procedures, and mechanical problems. Therefore, PN may provide an advantage in patients whose EN is interrupted.

We saw that we could not give the targeted volume of PN to a significant proportion of the patients included in the study. This was mainly due to hypervolemia and electrolyte imbalance. The interruption of PN for a single reason also interrupts the provision of all energy, macro, and micronutrients. Therefore, dynamically arranging the PN solution to the current clinical condition without disrupting the overall nutrition can prevent such problems. For patients with volume restriction and/or metabolic imbalance, individually prepared PN solutions in the hospital allow for a more appropriate composition in the proper volume. However, in patients with electrolyte imbalance, preparing and administering electrolytes and minerals separately from PN may prevent interruption of PN due to electrolyte and mineral imbalances. Although all patients in the study used individual PN solutions prepared with a compounder, the patients could not reach the nutritional target.

We think that RRT may be advantageous in patients with volume restriction. The present study included patients receiving intermittent hemodialysis and continuous RRT. Especially in patients receiving CRRT, the amount of ultrafiltration can be dynamically regulated so that volume restriction will not be necessary, so the nutrition of the patient can be brought closer to the optimum level. In the present study, there was no relationship between receiving RRT and receiving the PN volume effectively. This relationship should be investigated in studies with a larger patient population.

In a small number of our patients, the delay in the preparation of the PN solution resulted in the target volume not being delivered to the patients. Although individualized PN solutions prepared in the hospital provide an advantage in patients with metabolic imbalance and volume restriction, the disadvantage is that it takes time to prepare and requires teamwork and appropriate equipment.

Establishing a standard nutrition protocol with a high compliance rate for pediatric intensive care units is difficult. Compliance with the nutritional recommendations was evaluated in a prospective cohort that included 158 adult intensive care units from 20 countries, and although there was a high rate of compliance with some recommendations, such as the priority of EN, it was found that there was no compliance with the recommendations in many subjects.[3] We think it's worth trying to at least ensure that feeding is not interrupted for a preventable reason. As seen in our study, nutrition may not be given as intended in pediatric intensive care units in Turkey. If the composition of PN solutions is regulated appropriately, this problem can be overcome.

Age, gender, body weight, duration of PN, vascular access site, receiving RRT and ECMO, PRISM III score, and PDR were not associated with receiving more than 0.8 of the prescribed PN volume. We think that the heterogeneity in the patient population may have made it difficult to find an associated factor. Interestingly, however, all patients who underwent gastrointestinal surgery received all the prescribed PN volume.

This study has several limitations. It is a retrospective study with a limited number of patients, which was carried out with the participation of 5 hospitals in Türkiye. Therefore, its capacity to represent the whole country is limited. There was no written protocol on enteral and PN in the centers participating in the study. The presence of different nutritional practices in the different hospitals caused difficulties in the evaluation of the results. In the study, we presented the PRISM III and PDR scores; however, organ failure scores were not noted. Given these limitations, we invite readers to interpret the results carefully.

CONCLUSION

The intended and prescribed volume could not be delivered in about a quarter of PN-days, often due to volume restriction in critically ill children. The patient population in pediatric intensive care units is heterogeneous. Setting the correct nutritional targets, individualizing nutritional support, and preventing and overcoming obstacles on the way to the targets may improve outcomes.

Ethical approval

This study has been approved by the Dr. Sami Ulus Gynecology, Child Health and Diseases Training and Research Hospital Clinical Research Ethics Committee (approval date 17/11/2021, number E-21/11-237). Written informed consent was obtained from the participants.

Author conribution

Surgical and Medical Practices: ZÖ, ST, EK, DY, MK, MÇ, EÇD, BB; Concept: ZÖ, BB; Design: ZÖ, BB; Data Collection or Processing: ZÖ, ST, EK, DY, MK, MÇ; Analysis or Interpretation: ZÖ, BB; Literature Search: ZÖ; Writing: ZÖ, BB. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Intrahospital transport practices of pediatric intensive care units and adverse events experienced during transport process in Türkiye

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ABSTRACT

Objective: The purpose of this study was to identify the intrahospital transport practices of pediatric intensive care units and the adverse events that occurred during intrahospital transport in Türkiye.

Method: In this descriptive study, a questionnaire with 22 questions was used, which was created by the researchers based on the relevant literature. The questionnaire was filled out electronically.

Results: The study included 26 centers from 13 different provinces. In terms of intrahospital transport practices, 53.8% of the units lacked a written protocol for patient transport, and 92.3% did not utilize a transport preparation checklist. It was determined that in 65.4% of the units, a nurse accompanied a physician during transport. Examining the adverse events during intrahospital transport, findings reveal that 96.2% of the units reported a decrease in oxygen saturation, 80.8% hypotension, 73.1% hypothermia, 61.5% unplanned extubation, and 61.5% cardiac arrest. It was found that 7.7% of the units had an accident with mortality during transportation.

Conclusion: As a result of our study, it has been determined that many of the measures recommended in the literature to ensure the safe transport of intensive care patients are implemented at varying rates, and adverse events occur during intrahospital transport. In pediatric intensive care units, it is crucial to utilize a written in-hospital transport protocol when transporting pediatric patients and to enhance monitoring procedures during transportation.

Keywords: Pediatric intensive care, intrahospital transport, patient safety, nursing

INTRODUCTION

Pediatric patients of all ages are treated in pediatric intensive care units (PICUs), typically with one or more organ failures and a broad diagnostic spectrum. Also, intensive care hospitalizations may necessitate the use of diagnostic and therapeutic techniques for critically ill patients.[1-4] Depending on the capabilities of the hospital where they are treated, critically ill patients require a range of procedures. These procedures are sometimes performed at the patient's bedside (echocardiography, abdominal ultrasound, etc.) in the unit they are in, and sometimes in the service where the procedure is performed [abdominal computed tomography (CT) in the radiology service, laparotomy in the operating room, etc.].

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Patients should be transported from the intensive care unit to the appropriate service in this instance. Additionally, transport within the hospital is required for transferring patients from the Pediatric Emergency Care Unit to the PICU.[1,2,4]

Transporting gravely ill children into or out of the hospital has the potential to have severe negative effects and even be life-threatening.[5-7] According to studies, transporting critically ill children carries a greater risk of morbidity and mortality.[2,8,9] The mortality rate for patients who are transported is 17% higher than that of those who are not transported in the same condition, even when the transport conditions are optimal.[9] Among the risks associated with transport are respiratory decompensation, equipment failures, and ineffective team communication. The majority of critically ill children may experience a change in vital signs during transport, and more serious adverse events, such as death and severe injury, have also occurred.[2-4] The most clinically applicable definition of an adverse event is an incident that necessitates a change in therapy while being transported. It is essential to remember that accidents can occur directly or indirectly. Numerous observational studies have focused on the incidence or types of adverse events associated with intrahospital transport. In studies examining the effects of intensive care unit (ICU) transport on patients, the incidence of adverse events related to in-hospital transport ranges from 0.11 percent to 75 percent.[2-4,10-15]

Due to the limited resources available that may be used for patient monitoring and necessary interventions, the patient is perceived by healthcare professionals as more vulnerable during the patient's transfer from the ICU. Transporting a critically ill patient outside the intensive care unit is therefore a very challenging and stressful situation, even for the most experienced intensive care nurses.[7-12] To avoid any negative outcomes for the patient or a healthcare provider during the transport of an intensive care patient, effective management of all procedures before and during intrahospital transport is crucial.[11] To ensure the safe mobility of intensive care patients inside the hospital, it is recommended that procedures be established that include requirements for transport planning, staffing, organization, and equipment. The use of checklists, stabilizing the patient before transport, securing patient devices, checking the necessary equipment, and having qualified nurses and doctors present are all advised in order to ensure patient safety during all transport processes.[3,10,14,16-20]

However, little is known about the transport practices used in PICUs across Türkiye, the adverse events that can happen during transport, and how the PICU healthcare team members respond to serious events that occur. Intrahospital transport of critically ill children is a high-risk procedure. The purpose of this study was to identify the intrahospital transport procedures used by pediatric intensive care units and the adverse events that have occurred during intrahospital transport in Türkiye.

MATERIALS AND METHODS

Institutions (university, research and training, and private hospitals) that offer specialized intensive care for children and were willing to take part in the study were included. Hospitals that provided intensive care interventions to children in other intensive care units (such as internal medicine, coronary, and anesthesiology intensive care units) were excluded from the study. This descriptive study employed a questionnaire comprising 22 questions to assess intrahospital transport practices and the occurrence of adverse events during the intrahospital transport process. This questionnaire was distributed to the participating institutions in 2021. The questionnaire was developed by the researchers based on the relevant literature and provided to the attending nurses and physicians of the units that agreed to take part in the study. The questionnaire asks about the characteristics of the participating units, intrahospital transport preparations, applications made during the transport process, and whether the participants have encountered unexpected events that took place during the transportation process in their previous experiences. The data were collected online using the Redcap (Research Electronic Data Capture) software, which can be accessed online at "redcap.deu.edu.tr". The data was analyzed using the IBM SPSS Statistics 21.0 (Chicago, IL) software package. Numbers, percentages, the mean, standard deviation, and median (minimum-maximum) values were used to present descriptive characteristics.

Approval from the Non-Interventional Research Ethics Committee was obtained before the study began. In addition, the necessary institutional approvals were obtained to conduct the research. Since our study was descriptive and we received no information about the patients, we did not request informed consent from the children and parents.

RESULTS

The questionnaire was sent to 28 centers; 26 centers in 13 provinces participated in the study. The units that participated in our study had an average of 10.6 ± 4.6 beds (minimum = 6, maximum = 24, median = 10). Among the PICUs, 69.2% were training and research hospitals, 23.1% were university hospitals, and 7.7% were private hospitals. It was determined that 34.6% of these units had 6–10 intrahospital transports in the previous week, while 26.9% had 11–15 intrahospital transports.

Table 1. Reasons and frequency for intrahospital transport of patients in PICU (n=26)

Reasons*	n	%
Computed tomography (CT)	24	92.3
Magnetic resonance imaging (MRI)	24	92.3
Surgical procedure	23	88.5
Angiography	9	34.6
Transport to another intensive care unit	6	23.1
Electroencephalography	5	19.2
Ultrasonography	1	3.8
Bronchoscopy	1	3.8
Frequency (In a Week)		
5 and less	7	26.9
6-10 times	9	34.6
11-15 times	8	30.7
16-20 times	2	7.7

* Multiple choices were selected

Table 2. Equipment and monitoring methods used in the transport of intubated patients in Pediatric Intensive Care Units (n=26)

Equipment Used in The Transport of Intubated Patients*	n	%
Oxygen cylinder	26	100
Manual resuscitator	26	100
Emergency medicine and supplies	26	100
Pulse oximeter device	26	100
Laryngoscope Set	25	96.2
Transport bag	19	73.1
Monitor	17	65.3
Transport ventilator	12	46.2
Portable aspirator	8	30.1
Monitoring Methods Used in Transporting The Intubated Patient*		
Electrocardiography	24	92.3
Oxygen saturation	24	100
End-tidal carbon dioxide	8	30.1
Invasive blood pressure	9	34.6
Noninvasive blood pressure	9	34.6
Central venous pressure	1	3.8
Body temperature	4	15.3

* Multiple choices were selected

Table 3. The findings of the intrahospital transport procedures in Pediatric Intensive Care Units (n=26)

Availability of Written Intra-Hospital Transport Protocol	n	%
The protocol exists	12	46.1
No protocol	14	53.8
Use of Transport Preparations Checklist		
Using checklist	2	7.7
No checklist	24	92.3
Medical Record Keeping Status During Transport		
Medical record is kept	7	26.9
No record	19	73.1
Medical Team Members Accompanying the Transport*		
Pediatric intensive care specialist	6	23.1
Assistant physician	24	92.3
Pediatric intensive care nurse	17	65.3
Paramedic	20	76.9
Support staff	3	11.5

* Multiple choices were selected

The most common reasons for intrahospital transport of patients were computed tomography (CT) and magnetic resonance imaging (MRI) scans (Table 1). During intrahospital transport, the majority of units were found to utilize only a single monitoring method (ECG or oxygen saturation). At least 50% of PICUs monitored SpO2 and ECG during the transport of intubated patients; 30% of PICUs used portable aspirators, and 46% of PICUs used transport ventilators (Table 2). According to the findings, a significant proportion of Pediatric Intensive Care Units (PICUs), specifically 53.8%, did not possess a documented protocol for patient transport. Furthermore, a substantial majority of PICUs, approximately 92%, did not adhere to the practice of utilizing a checklist for intrahospital transport preparation. Additionally, a considerable percentage of PICUs, specifically 73.1%, failed to maintain records during the patient transport process. It was determined that 34.7% of PICU patients were transported without a pediatric intensive care nurse (Table 3). It was determined that units participating in the study frequently experienced device- and equipment-related adverse events. All twelve units using a transport ventilator for intrahospital transport reported experiencing adverse events related to the transport ventilator during previous transports. At least 15 out of 17 PICUs that utilized monitors during transport reported at least one monitor or battery failure in the past. Shortage of health care professionals and communication issues were the most common system-related issues encountered by

pediatric intensive care units, while more than half of the units reported unfavorable outcomes due to inadequate preparation prior to transport. In these circumstances, more than half of the PICUs reported experiencing life-threatening adverse events, while two units experienced an event resulting in mortality during transport (Table 4).

Table 4. Adverse Events Experienced in Previous Transport Experiences in Pediatric Intensive Care Units (n=26) *

Patient-Related Adverse Events	n	%
Oxygen desaturation	25	96.2
Hypotension	21	80.8
Hypothermia	19	73.1
Unplanned extubation	16	61.5
Cardiopulmonary arrest	16	61.5
Dislocation/occlusion of the vascular access or central venous catheter	9	34.6
Falling of the patient	2	7.7
Death	2	7.7
Device and Equipment-Related Adverse Events		
End of the oxygen cylinder	18	69.2
Monitor malfunction/out of battery	15	57.7
Transport ventilator failure / out of battery	12	46.2
Infuser failure / out of battery	12	46.2
Manual resuscitator failure	10	38.5
System-Related Adverse Events		
Shortage of health care professionals	21	80.8
Lack of communication with the unit where the patient is transported	19	73.1
Problems in accessing the elevator	18	69.2
Starting the transport without making adequate preparations	15	56.7

* Multiple choices were selected

DISCUSSION

Intrahospital transport poses a substantial risk to patient safety and is associated with a high incidence of complications and adverse events that have a significant impact on clinical outcomes. The intrahospital transport of critically ill children requires extensive labor, care, and logistical support, but even the most critical patients can be transported safely in the hands of trained professionals.

This study represents the first investigation of the intrahospital transport protocols employed by pediatric intensive care units in Türkiye. The findings of our study indicate that the implementation rates of measures outlined in the existing literature to ensure the safe transport of pediatric intensive care patients vary significantly. Furthermore, adverse events occur during intrahospital transport in Türkiye. Even though patient transport is often needed in pediatric intensive care units in Türkiye, it has been found that major improvements are required in terms of equipment, training, guidelines, and preparing checklists to keep patients safe and avoid complications during transport.

It is strongly recommended to use checklists for pretransport and intrahospital transport preparation, to carefully plan and organize the timing of intrahospital transport, to provide adequate equipment for transport, and to train PICU team members to standardize transport practices.[16-22] In Türkiye, there are deficiencies in maintaining patients' medical records during intrahospital transport, reviewing the preparation procedures with a checklist for safe transport, beginning transport only when preparations are completed, and using a written protocol to standardize these processes. Studies examining adverse events during intrahospital transport have identified, inadequate protocols, inadequate equipment, shortage of trained health workers, inadequate patient preparation, and communication problems as situations posing a threat to transportation safety.[5,6,11,12,14] In this study, deficiencies of this sort were found to be prevalent during the transportation process in many intensive care units, indicating the need for significant improvements in this area in Türkiye.

The transport team must have the necessary technical skills and knowledge to transport patients.[23] Our research shows that there is a severe shortage of qualified transportation professionals and support staff in Türkiye. Therefore, the duration of transport can be prolonged, and patients can spend more time outside the intensive care units as a result of the insufficient availability of qualified support staff. The physical demands involved in tasks such as lifting and pulling patients, particularly when relocating them for diagnostic examinations, can pose a potential threat to the health of medical professionals, including doctors and nurses.

Diagnostic tests are often performed outside of the ICU, which increases the risk of complications without the proper support. Adverse events during intrahospital transport are caused by logistical issues and the relative instability of patients.[24] These complications prolong the extremely dangerous transport time of the critically ill child. Institutions are required to provide a

supportive and sustainable transport environment with fewer transport-related risks, develop a streamlined process, and make all the necessary arrangements to minimize the time a patient spends outside the intensive care unit.[23,25]

The adverse events experienced during in-hospital transports in pediatric intensive care units in Türkiye are comparable to those described in the literature. Numerous studies examining adverse events that occurred during intrahospital transport of critically ill patients have found that equipment-related adverse events and significant changes in at least one physiologic variable are the most prevalent.[2,13,15,16,26-28] However, the results of our study showed that most pediatric intensive care units in Türkiye were not able to utilize the monitoring technologies that are necessary for patient transport. The fact that more than half of the pediatric intensive care units in Türkiye do not monitor end-tidal carbon dioxide during transport and that these centers have experienced cardiopulmonary arrest during transport in the past demonstrates the critical importance of advanced monitoring techniques during transport.

The study had some limitations. First, the study did not examine the relationship between potential complications and adherence to transport guidelines in the ICUs, the presence of health care workers during transport, or the monitoring techniques used during transport. Second, the study design required the participation of a single physician or nurse from each institution. This implies that the collected data may have been influenced by the subjective experiences of the respondent. It is essential to recognize that the findings may not be representative of the overall practices observed in each PICU. It is crucial to consider these limitations when interpreting the data, and it is recommended that further studies should aim to objectively evaluate the standard practices of the participating healthcare facilities and the challenges encountered during transport.

CONCLUSION

Our study revealed that approximately 50% of the units did not adhere to the established written protocol for patient transfer. Furthermore, the majority of these units neglected to utilize the prescribed checklist to prepare for intrahospital transport. In these instances, it was observed that nurses were primarily accompanied by physicians during the transport process, yet there was a notable deficiency in the utilization of advanced monitoring techniques. To increase the safety of critically ill children during intrahospital transport, it is essential to develop intrahospital transport procedures, guidelines, and checklists for transport readiness based on the most recent evidence. To ensure full adherence to national recommendations in PICUs, it is essential to ensure the provision of proper equipment and the maintenance of an adequate number of skilled medical experts. To prevent any potential problems that may arise during transportation, it is imperative to enhance the utilization of modern monitoring tools.

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Ethical approval

This study has been approved by the Dokuz Eylül University Non-interventional Clinical Research Ethics Committee (approval date 08/09/2016, number 2016/24-38). Written informed consent was obtained from the participants.

Author contribution

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

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Symptoms, clinical profile and management of pediatric hereditary angioedema: A single-centre experience

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ABSTRACT

Objective: Hereditary Angioedema (HAE) is a rare but life-threatening disease. It is aimed to present data on the clinical characteristics of our pediatric patients with HAE, whose symptoms usually start in childhood, but the delay in diagnosis is still a serious problem.

Method: Clinical and laboratory findings, family histories, and clinical characteristics of 14 patients with HAE diagnosed in our clinic between 1998-2019 were analyzed.

Results: Half of our patients diagnosed with HAE were girls, 78.5% of them were diagnosed with HAE type 1, and 21.4% were HAE type 2. All our patients had a family history, and 10 of them were diagnosed based on their family history. The mean age at diagnosis was 9.7±4.4 years and the mean age at the onset of the first angioedema symptom was 5.3±1.8 years. The delay in diagnosis was 4.4±4.1 years. The swollen areas included extremities (78.5%), abdominal attacks (71.4%), facial edema (57.1%), and laryngeal edema (21.4%). C4 levels were low in all patients. The mean C1 esterase inhibitor level was 0.69±0.08 g/l for HAE type 2 and 0.08±0.04 g/l for HAE type 1. The mean C1 esterase inhibitor functional activity level was 18.6±10.4% in HAE type 2.

Conclusion: Early diagnosis of the disease is critical for reducing morbidity and mortality due to attacks. There are very few studies in Türkiye that focus exclusively on pediatric HAE patients. Sharing our patients' clinical findings and treatment plans for this rare disease is crucial for bringing the disease to light and raising awareness.

Keywords: Hereditary angioedema, pediatric, clinical trial

INTRODUCTION

Hereditary Angioedema (HAE) is an autosomal dominant, life-threatening disease characterized by recurrent swelling of the skin and mucous membranes without pruritus or urticaria.[1] Although the real prevalence of HAE is unknown, the probable prevalence calculated by dividing the number of patients diagnosed in some European countries by the general population is 1/10000-1/50000.[2] Attacks can start at any age, but the first symptom usually appears in childhood and adolescence.

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In a large series of HAE patients, the first episode occurs in approximately 90% of patients by the age of 20.[3] HAE has been reported in both genders in all races.[4]

The main pathophysiological mechanism in HAE is the level or functional deficiency of the C1-inhibitor (C1-INH) glycoprotein. This protein has an inhibitory function in the plasma contact system, kallikrein-kinin system, coagulation system, and complement system.[5] Bradykinin is the primary mediator responsible for the clinical findings in HAE.[6] As a result of the numerical and functional deficiency of C1-INH protein, inhibition of the contact system cannot be achieved, and bradykinin formation increases. The bradykinin B2 receptor is constitutively expressed in vascular endothelial tissues, activation of this receptor loosens adherent junctions between endothelial cells that limit vascular permeability, and subsequently, increase pore sizes between endothelial cells by contraction of the intra-endothelial actin cytoskeleton resulting in angioedema.[7] The SERPING-1 gene, which codes for C1-INH, is found on chromosome 11.[8]

Three HAE variants have been identified: Type 1 HAE is the most common form of HAE associated with C1-INH deficiency, accounting for up to 85% of cases. The expression of the C1-INH protein is low as a result of mutations in the relevant gene, and its function is inadequate. Type 2 HAE is defined as HAE caused by C1-INH dysfunction. Although the C1-INH level is normal in this group, which accounts for 15% of cases, the functional activity of the protein is low.[9] The third group consists of HAE cases with normal C1-INH (nC1-INH-HAE), whose clinical and treatment responses are compatible with HAE despite normal C1-INH levels and function, and was first introduced in 2000.[7]

In this study, we aimed to shed light on the childhood data of this rare disease by analyzing the demographic and clinical data of the HAE patients followed in our clinic.

MATERIAL AND METHODS

Between 1998 and 2019, all patients with HAE diagnosed in Pediatric Immunology Clinic in Dr Behcet Uz Children's Education and Research Hospital were evaluated. The study excluded patients with ACEI/NSAI-related (Angiotensin-converting enzyme inhibitors/non-steroidal anti-inflammatory drugs) angioedema, angioedema associated with chronic spontaneous urticaria, and acquired angioedema.

Clinical and demographic data of the patients were gathered retrospectively from hospital records and out-patients' records. Age, gender, disease type, family history, consanguinity, blood count at admission, biochemical and immunological examinations, treatments, frequency of angioedema attacks, localization of angioedema, family history of angioedema, age of symptom onset, age at diagnosis, and delay in diagnosis were evaluated. The delay in diagnosis was defined as the time between the onset of the symptoms and the patient's diagnosis.

Immunonephelometry (Siemens, Marburg, Germany) was used to determine the levels of C4 (reference range: 10–40 mg/dL) and C1-INH antigen (reference range: 21–39 mg/dL), and a chromogenic assay (Berichrom Siemens, Marburg, Germany) was used to determine the levels of functional C1-INH (reference range: 70%–130%).

The data were analyzed using SPSS18 (Statistical Package for Social Sciences). Descriptive analysis was used, and categorical variables were expressed in numbers and percentages. The chi-squared test was used for comparisons between groups of qualitative variables. The Mann-Whitney U test, which is a nonparametric hypothesis, was used to compare two independent groups. A p-value <0.05 was considered statistically significant.

Study design and ethical approval

This retrospective cross-sectional study was approved by SBU Izmir Dr. Behcet Uz Education and Research Hospital Clinical Research Ethics Committee in 2021 (Decision No:2021/15-15).

RESULTS

Fourteen patients who were followed up in our clinic with the diagnosis of HAE were included in the study (Table 1). Fifty percent of them were female. The mean age at diagnosis was 9.7±4.4 years (min:3, max:10). The mean age at the onset of the first angioedema symptom was 5.3±1.8 years (min:1, max:9.1). The time between the onset of symptoms and the patient's diagnosis is referred to as the delay in diagnosis. The mean delay in diagnosis was 4.4±4.1 years for our patients (min:0, max:13.7). Three of our patients were diagnosed with HAE type 2, and the others with HAE type 1. There was no patient diagnosed with HAE type 3 among our patients. The results of the detailed demographic, clinical, and laboratory analysis are shown in Table 2. The frequency of the attacks varied from almost one week to 1-2 times per year in each patient. When the patients were evaluated based on the swelling patterns, the number of patients and areas of swellings were as follows: extremities in 11 (78.5%); abdominal attacks in 10 (71.4%); facial edema in 8 (57.1%); and laryngeal edema in 3 (21.4%) patients. One patient also had genital edema. All the patients had relatives who had

Table 1. Clinical and demographic characteristics of our patients diagnosed with HAE		
	n (%)	**(min-max)**
Gender		
Female	7 (50%)	
Male	7 (50%)	
Mean diagnosis age (year)	9.7±4.4	(3-10)
Mean first symptom age (year)	5.3±1.8	(1-9.1)
Delay between first symptoms and diagnosis (year)	4.4±4.1	(0-13.7)
Family history	14 (100%)	
Diagnosis based on family history	10 (71.4%)	
Consanguinity between parents	1 (7.1%)	
Swelling patterns		
Laryngeal	3 (21.4%)	
Facial	8 (57.1%)	
Abdominal	10 (71.4%)	
Extremities	11 (78.5%)	
Type of HAE		
HAE Type 1	11 (78.5%)	
HAE Type 2	3 (21.4)	
Mean C4 level (mg/dl)	6.6	
Mean C1 esterase inhibitor level (g/l)		
HAE Type 1	0.08	(0.03-0.15)
HAE Type 2	0.69	(0.60-0.76)
Mean C1 esterase inhibitor functional activity level in HAE Type 2 (%)	18.6	(7-27)
Number of patients who underwent acute attack treatment		
C1 inh (Berinert®/Cetor®/Cinryze®)	8 (57.1%)	
Ecallantide (Kalbitor®)	3 (21.4%)	
Ikatibant (Firazyr®/Icatin®/Heact®)	7 (50%)	
Number of patients who received short-term prophylaxis		
C1 inh (Cetor®/Cinryze®)	2 (14.2%)	
Number of patients who received long-term prophylaxis before		
Tranexamic acid (Transamin®)	7 (50%)	
Androgens (Danazol®/Stanazolol®)	4 (28.5%)	
C1 inh (Cetor®/Cinryze®)	2 (14.2%)	

either been diagnosed with HAE or had similar complaints, as determined after the detailed patient interviews. Nine patients were diagnosed based on one or more cases of HAE in their family, and the appearance of symptoms in the patient. One patient with no symptoms was diagnosed using scanning after the diagnosis of her siblings. Thus, a total of ten patients were diagnosed based on their family history (71.4%).

Table 2. The results of the detailed demographic, clinical and laboratory analysis

	Gender	Type of HAE	Symptom onset age (year)	Diagnosis age (year)	Delay on diagnosis (year)	Diagnosis based on family history	Average attacks per year	Involved sites during the attacks				C4 level (mg/dl)	C1 esterase inhibitor level (g/l)	C1 esterase inhibitory functional activity (%)	Genetic Analysis	Family History
								Larynx	Face	Abdomen	Extremity					
P1	F	Type 2	5	13	8	No	10		+		+	5.8	0.6	7		The grandmother's undiagnosed swellings+ (sudden death)
P2	F	Type 2	1	3	2	No	12		+	+	+	6.8	0.76	22		Father's similar symptoms +
P3	M	Type 1	6	14	8	Yes	*			+		6.9	0.06	-		Father, uncle, aunt, cousins with diagnosis HAE
P4	F	Type 1	-	12	0	Yes	*					6.9	0.08	-		Sibling with diagnosis HAE (diagnosis by scanning)
P5	F	Type 1	6	14	8.5	Yes	50		+	+	+	5.9	0.05	7		Mother, grandmother, aunt with diagnosis HAE +
P6	F	Type 1	7	14.5	7	Yes	12		+	+	+	7.9	0.15	-		Mother's similar symptoms +
P7	M	Type 1	5	12	7.2	Yes	12	+	+	+	+	6.6	0.03	-		Father, grandmother, paternal grandmother, uncle with diagnosis HAE
P8	M	Type 2	4	4.5	1	Yes	1				+	6.6	0.72	27	c.1396C>T	Father's similar symptoms +
P9	M	Type 1	5	6.9	2	Yes	3	+	+	+		6.2	0.13	-	c.431delA	Father with diagnosis HAE+ 1 uncle (53 years), 1aunt (33 years) Larynx edema (death)
P10	M	Type 1	4	17.7	13.7	Yes	6			+	+	6.6	0.08	-		Father, grandmother, paternal grandmother, uncle with diagnosis HAE
P11	F	Type 1	4	4.6	1	No	50			+	+	6.8	0.05	14.3		The grandfather's undiagnosed swellings+ (sudden death), Sibling with diagnosis HAE (diagnosis by scanning)
P12	F	Type 1	9.1	10	1	No	40	+	+	+	+	5.5	0.08	8.7		The grandfather's undiagnosed swellings+ (sudden death)
P13	M	Type 1	5	5	0	Yes	3				+	7.3	0.04	-		Father's similar symptoms +
P14	M	Type 1	5	8	3	Yes	36		+	+	+	7.1	0.14	30	c.1397G>T	Mother with diagnosis HAE, mother's cousin (20 year) sudden death, The grandfather's undiagnosed swellings+ (sudden death

P3 and P4; P11 and P12 are siblings. * Average attacks per year are unknown because because patients were not followed up.

C4 levels were low in all patients. The mean C4 level was 6.6±0.6 mg/dl. The mean C1 esterase inhibitor level was 0.69±0.08 g/l in HAE type 2 patients and 0.08±0.04 g/l in HAE type 1 patients. The mean C1 esterase inhibitor functional activity level in HAE type 2 patients was 18.6±10.4%.

When HAE type 1 and HAE type 2 were compared according to the age at symptom onset, age at diagnosis, delay in diagnosis, levels of C4, and the amounts of functional C1-INH, no significant difference was found between the two groups. When the same criteria were analyzed by gender, there was no significant difference between the two genders. Girls experienced statistically considerably more angioedema attacks annually than boys (p=0.04).

Eight of the patients (57.1%) underwent acute attack treatment with C1-INH, 3 (21.4%) with Ecallantide, and 7 (%50) with Icatibant. Short-term prophylaxis with C1-INH was performed for 2 patients. Tranexamic acid was used in 7 patients (50%), androgens were used in 4 patients (28.5%), and C1-INH in 2 patients (14.2%) for long-term prophylaxis. Androgen prophylaxis was used only in patients whose pubertal stage was Tanner stage 4. Tranexamic acid was preferred when long-term prophylaxis was required in the younger age group.

Genetic analysis was performed in 3 patients. Genetic analysis was not planned for the other patients because they were diagnosed by clinical laboratory results and family history. Patients 1 and 2 had intermittent urticaria accompanied by angioedema. Patient 5 (P5) also had the MEFV R202Q mutation and patient 9 (P9) was also diagnosed with Marfan syndrome.

DISCUSSION

Although HAE attacks can occur at any age, it usually manifests in childhood. In our study, the mean age of symptom onset was 5.3±1.8 years. Except for patient 4 (P4), the first symptom appeared in the first decade. P4 was a screening case diagnosed after her sibling, and she had no symptoms until the time of diagnosis. The median age of symptom onset in a study of pediatric HAE patients in Cincinnati was 5.7 years, which was similar to our findings.[10] The median age of first symptom onset was 12 years in a European study that included patients with HAE type 1 and 2[11] and in a previous pilot study in Türkiye, the mean age of onset of angioedema was found to be 12.5±9.2 years.[12] Symptom onset was under 5 years for 4 patients in our study. Even though it is a hereditary mutation, it is uncommon in infancy and the neonatal period. The first attack, however, was seen in a 4-week-old baby, according to reports.[13]

Suspicion of the illness is the key to the diagnosis of HAE. Mortality from exacerbations is 24 times higher in undiagnosed patients than in diagnosed patients.[14]

In studies, the term “diagnostic delay” refers to the period between the onset of symptoms and the patient’s diagnosis. In our study, the median age at diagnosis was 10.9 years. In our study, the delay in diagnosis was 4.4±4.1 years, which is much lower than the value reported in the literature. The delay in diagnosis, which has been found to range from 8.5 to 16.5 years in recent studies, is still quite long and is not at an acceptable level, even though it has been claimed that this period has shortened recently compared to previous years.[15] In the TURHAPS study conducted in Türkiye, the interval between the onset of symptoms and diagnosis was determined as 26±14.4 years.[12] In the European study, the median age at diagnosis was 24.3 years, and the median delay in diagnosis was 8.5 years in type 1 and type 2 HAE patients.[11] According to this study, the diagnostic delay varied significantly between countries, ranging from 2.0 years (Germany) to 15.0 years (Italy).[11] The difference in diagnostic delay between countries, however, was not statistically significant. When the literature was reviewed, it was stated that the median delay in the diagnosis was 3 years, which was close to our study, according to the Hungarian experience.[16]

Although 20% of cases may occur as a result of sporadic mutations[17], there are cases with similar clinical findings or a family history of HAE when questioned in detail, owing to the autosomal dominant inheritance pattern. Ten of our patients (74.1%) were diagnosed based on the family history of an individual with HAE and when questioned in detail, it was learned that all patients had individuals with HAE or similar symptoms in their families. The rate of patients diagnosed based on family history was 73% in a Hungarian study, similar to our study.[16]

The frequency and severity of HAE symptoms vary from person to person and may even differ between different members of the same family. Extremity edema (90%) and abdominal pain (80-90%) are defined as the most common findings in studies[18], and as in our study, patients most frequently reported experiencing extremity swelling (78.5%) and abdominal attacks (71.4%). The majority of abdominal attacks do not appear to be associated with concurrent skin edema.[13] This situation directs the focus on more common etiological reasons such as surgical causes such as appendicitis, or other causes such as FMF, which is very common in Türkiye, and causing the diagnosis of HAE to be delayed. However, in addition to the diagnosis of HAE, one of our patients (patient 5) had a genetic mutation related to FMF and had been treated with colchicine for several years. Laryngeal edema is

the most detrimental and life-threatening attack. In an adult study evaluating 55 patients with HAE, laryngeal attacks were reported in 19 patients (34.5%).[19] If untreated, the risk of death from airway obstruction is estimated to be 30%.[13] Additionally, 3 of our patients (21.4%) had laryngeal attacks.

HAE is classically defined as an angioedema attack without urticaria. This is a crucial distinction from histaminergic angioedema in terms of clinical presentation. Urticaria is very rare, even though erythema marginatum may occasionally be present in patients as a prodromal finding prior to an attack. Intermittent urticaria, on the other hand, was present in two of our patients. Recurrent urticaria was reported in 7.3% (n = 3) of patients in the HAE group in a study comparing the clinical characteristics of hereditary angioedema and histaminergic angioedema.[20] In the foreground, this was thought to be an incidental histaminergic urticaria.

A study reported that the gender of pediatric patients changed the clinical presentation of the disease but there was no significant difference between the genders in terms of the age of onset of the first symptoms, similar to our study.[21] According to this study, HAE attacks in places other than genitals were reported more frequently in girls than in boys.[21]

The C4 (complement 4) level is the first laboratory parameter to be examined in suspected cases. The diagnosis of type 1 and type 2 HAE is ruled out by a normal C4 level during attacks, despite the fact that it may be normal in a very small percentage of cases (2%) between attacks.[1] As a result, a screening test for type 1 and type 2 HAE can be performed by measuring the C4 level during an attack. In our study, it was found that all the patients had low C4 levels.

Genetic analysis is not mandatory to diagnose HAE type 1 and type 2. The diagnosis can be made by evaluating the C1 esterase inhibitor levels and functional activity in the presence of clinical findings. If necessary, the diagnosis can be supported by genetic analysis. HAE type 1 and type 2 are associated with mutations in the SERPING1 gene. Mutations in the SERPING1 gene were identified in 3 of our patients. In HAE type 3, the diagnosis can only be made by demonstrating the mutation with genetic analysis in patients with clinical findings of HAE, although the C1 esterase level and functional activity are at normal levels.

Since HAE patients were evaluated over a period of 20 years, the type of drugs used in the treatment of acute attacks and prophylaxis varied according to their availability in our country, Türkiye. For the treatment of acute attacks, 57.1% of the patients received C1-INH concentrate, 50% Icatibant, and 21.4% Ecallantide. Two patients received C1-INH concentrate as short-term prophylaxis prior to the intervention. Tranexamic acid was used in 50% of the patients for long-term prophylaxis. Androgens were used in 4 (28.5%) patients in the post-pubertal period. C1-INH concentrate was preferred for long-term prophylaxis in 2 patients.

CONCLUSION

Early diagnosis and rapid treatment of this disease, which is lifesaving, is the most important step of the disease. The possibility of HAE should be considered if a patient has a family history of similar symptoms, experienced the onset of symptoms during childhood or adolescence, suffers from recurrent and painful abdominal attacks, generally lacks urticaria, exhibits accompanying prodromal symptoms, and has angioedema that does not respond to antihistamine, steroid, or adrenaline treatments. The delay in diagnosis between the onset of symptoms and the diagnosis of patients is still quite long in recent studies. Therefore, the awareness of physicians and patients with HAE about this disease should be increased.

Ethical approval

This study has been approved by the İzmir Dr. Behçet Uz Education and Research Hospital Clinical Research Ethics Committee (approval date 07/10/2021, number 2021/15-15). Written informed consent was obtained from the participants.

Author contribution

Concept: SÖB, FG, NG; Design: SÖB, FG, NG; Data Collection or Processing: SÖB, ÖA, İT, İAH, MSK, FCC, ÖS, CŞK, NG, FG; Analysis or Interpretation: SÖB, FG, NG; Literature Search: SÖB, ÖA, İT, İAH, MSK, FCC, ÖS, CŞK, NG, FG; Writing: SÖB, FG. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Evaluation of troponin T levels and cardiac findings of the children in pediatric intensive care with high proBNP levels

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ABSTRACT

Objective: Pro-B type brain natriuretic peptide (proBNP) is released from cardiac ventricular myocytes as a result of increased volume and pressure. Troponin T plays a role in the contraction process. Both proteins may be elevated in many cardiac and non-cardiac conditions. Our aim is to evaluate troponin T values and cardiac findings of the patients in pediatric intensive care unit (PICU) with elevated proBNP levels.

Method: Patients with high proBNP values who were admitted to the PICU between January 2022 and January 2023 were included in the study. The clinical diagnoses, proBNP, and troponin T values were recorded. Information about the presence of heart disease and the status of systolic functions were obtained from echocardiographic examination reports.

Results: One hundred and ten patients were included in the study. Mean age of the patients was 2.48±3.41 years. Among the patients hospitalized in the pediatric intensive care unit, 41% had lower respiratory tract infections, and 20% had heart disease. The mean proBNP values were 11827.06±12652.82 ng/l, and troponin T was 201.41±737.74 ng/l. Ejection fraction (EF) was normal in 75% of the patients. The mean values of proBNP and troponin T in the patients with normal EF were 7284.74±8437.16 ng/l and 49.67±73.15 ng/l while the mean values of proBNP and troponin were 25129±13659.24 ng/l and 645.8±1380.74 ng/l in the patients with decreased EF ($p<0.05$, for both). ProBNP and troponin T values of the patients with decreased EF accompanied with or without heart disease were higher than those in the group with normal EF without existing heart disease ($p<0.0001$, for all). It was observed that decreased EF value was more common in cases who have proBNP>16314 ng/l and troponin T >114 ng/l ($p=0.0031$, $p<0.0001$, respectively).

Conclusion: ProBNP and troponin T values increase in many cardiac and non-cardiac diseases. However, quite high values of the parameters help to distinguish the patients with cardiac systolic dysfunction.

Keywords: Children, Pro-B type natriuretic peptide, systolic function, Troponin T

INTRODUCTION

NT-proBNP is an important marker in the diagnosis, evaluation, and treatment of heart failure.[1] NT-proBNP is a diuretic peptide released from ventricular myocytes as a result of increased volume and pressure load as a preprohormone (preproBNP). Then, it is converted to proBNP. ProBNP consists of N-terminal proBNP (NT-proBNP) which is biologically inactive, and biologically active form called BNP. Afterward, the N-terminal region separates from the prohormone and the active form which

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is called BNP stays in circulation. Both serum BNP and NT-proBNP levels are used to determine cardiac involvement and to evaluate the prognosis of the patients with congestive heart failure.[2-5] This peptide causes vasodilatation, natriuresis, inhibition of renin-angiotensin-aldosterone, and vasopressin release. The functions become apparent in target cells by receptors leading to the formation of cyclic guanosine monophosphate (cGMP). The receptors are present in the blood vessels, the kidney, the brain, the adrenal gland, the testis, the lung, and in ventricular myocytes in much lower concentrations.[6-9] They are inactivated by endopeptidase which is present in the lung and kidney.[1,10] BNP has a half-life of 22 minutes and can respond quickly to changes. The half-life of NT-proBNP is 2 hours, serum levels are relatively higher, and it is not disturbed in the serum sample. The concentrations of BNP and NT-proBNP are nearly similar in circulation. Therefore, NT-proBNP concentrations are used to evaluate pressure or volume overload to the ventricles. The clearance of NT-proBNP depends on renal function.[1,10]

Troponin T and troponin I called cardiac troponins were used for screening and detecting cardiac injury.[1,11] Troponin T is a protein involved in contraction by regulating the interaction of actin and myosin. Most of the troponins are present in the cardiac sarcomere, but 3-8% of troponin is present in the cytoplasmic form.[12] The plasma half-life of cardiac troponin is approximately 2 hours. Although the exact mechanism by which troponin is eliminated from the body is not fully known, it is hypothesized that renal reticulo-endothelial system plays role in the clearance of the protein.[12]

Both proteins may be elevated in some non-cardiac conditions besides cardiac conditions.[13] NT-proBNP increases in heart muscle diseases, arrhythmia, renal dysfunction, anemia, sepsis, burns, lung diseases, and pulmonary hypertension.[13] Troponin increases in coronary syndromes, inflammation, kidney failure, exercise, myocarditis, drugs, metabolic conditions, and sepsis.[2] Our aim is to evaluate troponin T values and cardiac findings in the patients with elevated NT-proBNP levels who were treated in ourpediatric intensive care unit.

MATERIAL AND METHODS

Patients with high NT-proBNP values who were admitted to the pediatric intensive care unit between January 2022 and January 2023 were included in the study. The clinical diagnoses, NT-proBNP, and troponin T values of the patients were examined retrospectively. Presence of heart disease and cardiac functions were recorded according to echocardiographic evaluations. M-mode and 2D measurements were made according to the recommendations of the American Society of Echocardiography.[14,15] The ejection fraction (EF) of the left ventricle was calculated with the modified Simpson method. Decreased EF was defined when it was<55%.[14,15]

The patients were also grouped according to the presence or absence of heart disease (HD) into four groups. Group 1- Decreased EF with the presence of HD: dilated cardiomyopathy (DCMP), noncompaction cardiomyopathy, hypertrophic cardiomyopathy (HCMP), operated complex congenital HD with significant hemodynamic residual cardiac findings; Group 2-Decreased EF with no HD: sepsis, renal pathologies, lower respiratory tract infection, asphyxia; Group 3- Normal EF with the presence of HD: complete atrioventricular septal defect (AVSD), pulmonary hypertension (PHT), large patent ductus arteriosus (PDA) and large ventricular septal defect (VSD), operated congenital HD with hemodynamically significant residual findings, functional single ventricle; Group 4- Normal EF with no HD: normal echocardiographic findings, mild valve insufficiency without hemodynamic significance, small atrial septal defect and ventricular septal defect.

Statistical analyses

Statistical analyses were performed using the SPSS software version 23 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.). Categorical data are presented as numbers and percentages, and numerical data are presented with mean ± standard deviation if normally distributed, medium (minimum-maximum) if non-normally distributed. Kolmogorov-Smirnov test was used to determine the normal distribution of numerical variables. Kruskall-Wallis H test was used in the comparison of two independent groups. Bonferroni correction was used to determine the significance level of pairwise comparisons. Receiver operating characteristic (ROC) curve analysis was used to predict the presence of heart disease by troponin and proBNP measurements. The analysis of the ROC curve was performed using MedCalc version 20.0 software. The cut-off value was calculated and the sensitivity, and specificity values were determined. A p-value<0.05 was considered statistically significant.

Ethical approval

The study was approved by the Ethics Committee of the University of Health Sciences, Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision number: 2023-04-12, date: 20.02.2023). Informed consent was obtained from all the patients and their parents.

RESULTS

The mean age of the patients was 2.48±3.41 years. 66 patients were male, and 44 patients were female (Table 1). 41% of the patients had lower respiratory tract infections and 20% had congenital heart disease (Table 2). Patients were grouped according to EF as the patients with decreased EF and the patients with normal EF. Patients with decreased EF included DCMP, non-compaction cardiomyopathy, and myocarditis and accounted for 25% of the patients. Patients with normal EF included left to right shunted diseases, pulmonary hypertension, single ventricle, and valvular insufficiencies (Table 3). NT-proBNP value was 7284.7± 8437.1 ng/l and troponin T value was 49.6 ± 73.1 ng/l in the patients with normal EF, while the mean NT-proBNP value of the patients with decreased EF was 25129 ± 13659.2 ng/l, and the mean troponin T value was 645.8 ± 1380.7 ng/l in the patients with decreased EF (p<0.001, for both) (Table 4). When we grouped the patients according to EF status and presence of HD, NT-proBNP and troponin T values were higher in the patients with low EF and presence of HD (group 1) and low EF without HD (group 2) than the group with normal EF without HD (group 4) (p<0.0001, for all). In addition, troponin T value was also higher in the patients with decreased EF accompanied by HD (group 1) than in the patients with normal EF accompanied by HD (Table 5).

Table 1. Demographic and laboratory findings of the patients

	PATIENTS n =110 (mean ± sd)
Age (year)	2.48 ± 3.41
Gender (M/F)	66/44
NT-proBNP (ng/l)	11827.06 ± 12652.82
Troponin T (ng/l)	201.41± 737.74

Table 2. Diagnoses of the patients

	(%)
Lower tract respiratory infections	41
Heart diseases	20
Renal diseases	12
Intracranial diseases	7
Sepsis	6
Dehydration	4
Ischemia	5
Metabolic disorder	5

Table 3. Distribution of cardiac diseases

DECREASED EF (%25)	NORMAL EF (%75)
Dilated cardiomyopathy	Left to right shunted diseases
Noncompaction cardiomyopathy	Pulmonary Hypertansion
Myocarditis	Single Ventricle
	Valvular insufficiencies

EF: Ejection fraction

Table 4. Laboratory parameters according to ejection fraction

	NORMAL EF (n=82) Mean ± sd	DECREASED EF (n=28) Mean ± sd	*p
NT-proBNP (ng/l)	7284.7± 8437.1	25129 ± 13659.2	<0.001
Troponin T (ng/l)	49.6 ± 73.1	645.8 ± 1380.7	<0.001

*Mann Whitney U test

Table 5. Laboratory parameters related with EF status and presence of HD

	Decreased EF, With HD (n=14) mean ± sd GROUP 1	Decreased EF , Without HD (n=14) mean ± sd GROUP 2	Normal EF, With HD (n=10) mean ± sd GROUP 3	Normal EF, Without HD (n=72) mean ± sd GROUP 4	*p
NT-proBNP (ng/l)	22454.7 ± 14834.4	27804.4 ± 12330.1	15713.8 ± 12768.8	6114.1 ± 7010.5	<0.0001
Troponin T (ng/l)	1042.2 ± 1890.1	249.4 ± 220.1	67.3 ± 64.8	47.2 ± 74.3	<0.0001

EF: Ejection fraction, HD: Heart disease.
*Kruskal Wallis H test

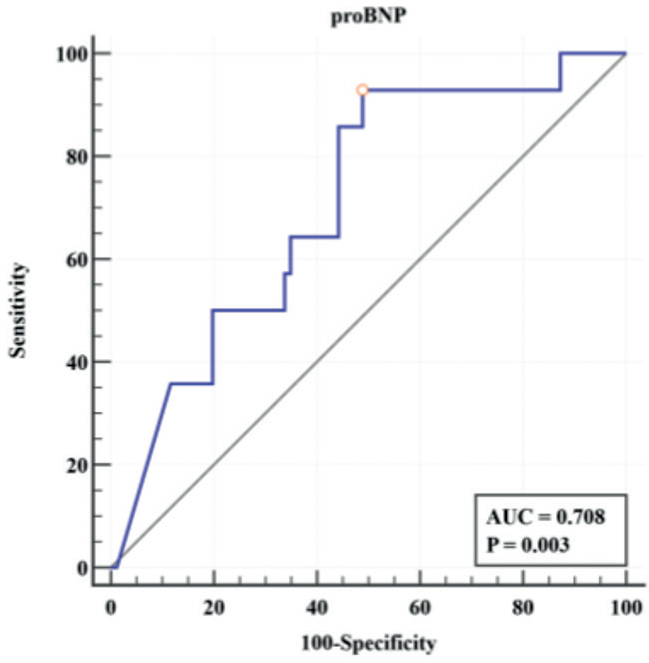

Figure 1. proBNP level in predicting left ventricular dysfunction

p=0.031 (sensitivity 71.4%, specifity 90.24%)

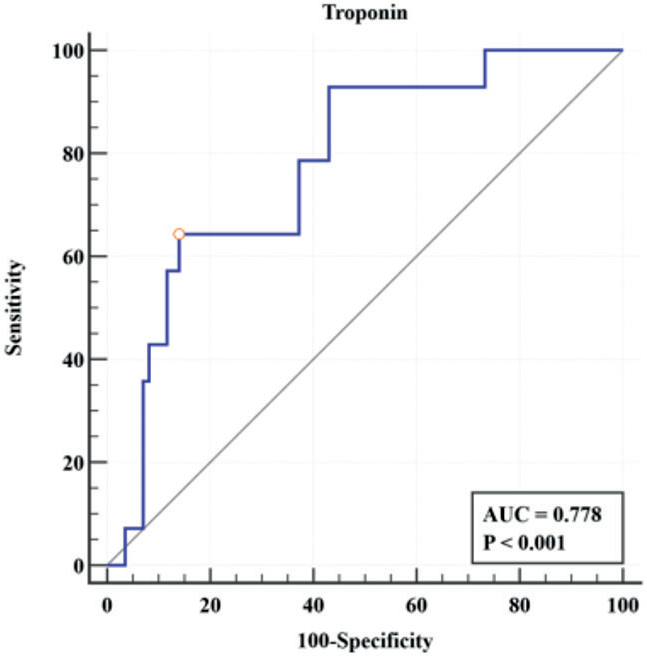

Figure 2. Troponin T level in predicting left ventricular dysfunction

p<0.001 (sensitivity 71.4%, specifity 93.9%)

The cut-off value for NT-proBNP was 16314 ng/l (p=0.0031, sensitivity 71.4%, specificity 90.24%), and for troponin T was 114 ng/l (p<0.0001, sensitivity 71.4%, specificity 93.9%) to predict decreased EF (Figure 1 and Figure 2).

DISCUSSION

In the literature, different reference intervals were defined for NT-proBNP and Troponin T levels.[2,13,16] These studies indicate that the reference values of these variables can differ according to age and sex. Most of the studies state that levels of these variables are at their maximum ranges at birth, afterward a prominent decline occurs during the first months of life with slight decreases during childhood.[2,13,16] Also, it was shown that the levels of NT-proBNP and troponin T showed a positive correlation with each other.[2] Studies have reported increased levels of these parameters in many cardiac pathologies, but also in many non-cardiac pathologies. The most prevalent causes of non-cardiac pathologies are lower respiratory tract infections, sepsis, renal diseases, and intracranial pathologies.[2] In our study, the patients with high NT-proBNP had lower respiratory tract infections, congenital heart diseases, renal pathologies, intracranial pathologies, sepsis, dehydration, ischemia, and metabolic diseases. Increases of the parameter in many non-cardiac conditions may be the result of the widespread presence of the receptors in the related tissues.

Yang et al.[17] performed a study on newborns and divided them into three groups: the first group comprised of patients with cardiovascular disease and sepsis, the second group consisted of patients with sepsis only, and the third group consisted of controls. The first group had the highest proBNP and troponin levels, followed by the second group and both groups had higher levels of these parameters than the controls. The study also declared a threshold of NT-proBNP of 12291.5 pg/ml (80% sensitivity and 79% specificity) to predict newborn sepsis. Favory et al.[18] stated that patients with sepsis accompanied by left ventricular dysfunction had higher NT-proBNP levels, but Klouche et al.[19] stated that patients without left ventricular dysfunction also had increased proBNP levels. Inflammation, endotoxins, endothelial damage, direct cardiac damage, excess volume in the ventricles, and low blood pressure cause an increase of this parameter. One of the other most prevalent cause of increased levels of these parameters is renal disease. Jones et al.[20] indicate that acute renal failure increases the levels of NT-proBNP and troponin. Nalcacioglu et al.[21], suggested that chronic renal failure also causes increased NT-proBNP levels as a result of volume excess, hypertension, left ventricular hypertrophy, and congestive heart failure.

There are many studies supporting that both parameters mostly increase in cardiac diseases.[2] Also, it was shown that different cardiac diseases act differently over NT-proBNP level. NT-proBNP is used to distinguish acute heart failure and chronic heart failure.[22] The increase is more prominent in acute left ventricular dysfunction. Congenital HD including pressure overload increases NT-proBNP levels more than volume overloading pathologies.[23] The patients in our study who were evaluated in the pediatric intensive care unit mostly had normal ejection fraction accompanied by left to right shunted diseases, pulmonary hypertension, single ventricle, and valvular insufficiencies. Patients with decreased ejection fraction include patients with dilated cardiomyopathy, non-compaction cardiomyopathy, and myocarditis. Lv et al.[24] conducted a study on patients with myocarditis and showed that the increase in NT-proBNP was apparent in 3-7 days of the disease and showed regression during the first month. Another study revealed that NT-proBNP values were significantly higher in children with myocarditis, predicting the early and late outcomes of the disease with similar troponin T levels. They also reported that NT-proBNP levels higher than 2000 pg/ml predict left ventricular dysfunction.[25] In our study, we found NT-proBNP level to be 7284.7 ± 8437.1 ng/l in the patients with normal EF, while it was 25129 ± 13659.2 ng/l in the patients with decreased EF. Consistent with these findings, the mean value of troponin T levels was 49.6 ± 73.1 ng/l, while it was 645.8 ± 1380.7 ng/l in the participants with decreased EF, supporting the idea that even though both groups had HD, the patients with decreased EF had the prominent increases in these parameters.

Soongswang et al.[26] stated that troponin values were found to be higher in the patients with acute myocarditis, compared to the patients with dilated cardiomyopathy and the group including large ventricular septal defect with congestion findings. This study also supported the importance of EF in determining the level of troponin. The threshold value for troponin T in acute myocarditis was found to be 0.052 ng/ml.[26] Dionne et al.[27] declared 0.045 ng/ml as a threshold value for troponin T in children <3 months, and 0.005 ng/ml for children ≥3 months for differentiating the diseases as cardiac and non-cardiac. When we evaluated the patients according to EF status and the presence of HD, we found that both the first and second groups had higher NT-proBNP levels and troponin T levels than the fourth group, supporting that having low EF demonstrates high serum parameters independent of the presence of HD. Higher troponin T levels in the first group, compared to the third group, also supported the idea that even though both groups had HD, the patients with decreased EF levels had higher levels of troponin T.

Sugimoto et al.[28] stated different cut-off values in the patients with heart failure according to heart failure stage and age. Lin et al.[29] stated the threshold values for NT-proBNP suggestive of heart failure according to age and it was 502 ng/l for 0-1 years old, 456 ng/l for 1-3 years old, 445 ng/l for 4-7 years old, 355 ng/l for 8-14 years old. NT-proBNP was 438.4 pg/ml in stage 2 while it was 7733.5 pg/ml in stage 4 under 3 years of age. The cut-off value was 295.2 pg/ml in stage 2 and 3617 pg/ml in stage 4 older than 3 years of age. El-Amrousy et al.[30] showed that values >10 pg/ml for troponin T indicate acute heart failure with 100% sensitivity and 85% specificity. This study also supported the increased mean values of troponin T according to heart failure stage which is 55.35±10.25 pg/ml in stage 2 and 92.35±14.52 pg/ml in stage 4. In our study, the threshold values for predicting decreased EF were >16314 ng/l for NT-proBNP (sensitivity 71.4%, specificity 91.24%) and >114 ng/l for troponin T (sensitivity 71.4%, specificity 93.9%). These increased values in our study also supported the studies in the literature.

CONCLUSION

NT-proBNP and troponin T values also increase in the presence of non-cardiac reasons besides cardiac causes. However, the values of NT-proBNP and troponin T levels were found to be quite high, especially in the patients with cardiac systolic dysfunction defined by low EF. Regardless of the diagnosis, patients with high NT-proBNP values and high troponin values should be evaluated for cardiac reasons.

Ethical approval

This study has been approved by the University of Health Sciences, Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (approval date 20/02/2023, number 2023-04-12). Written informed consent was obtained from the participants.

Author contribution

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

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Original Article

Assessment of risk factors for congenital heart disease through prenatal fetal echocardiography and the correlation with postnatal diagnoses

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ABSTRACT

Background: Congenital Heart Disease (CHD) constitutes a significant cause of morbidity and mortality in newborns. Identifying CHD prenatally and understanding associated risk factors can aid in early diagnosis, intervention, and postnatal management. This study aims to assess risk factors for CHD using prenatal fetal echocardiography (FE) and investigate their correlation with postnatal diagnoses.

Patients and Methods: In this study, we included 993 pregnant women presenting to the pediatric cardiology outpatient clinic between December 2018 and December 2020, considered at risk for CHD. We retrospectively evaluated the cases' postnatal echocardiography data with detected CHD during fetal echocardiography.

Results: The average age of the patients was 29.8±5.7, and the mean gestational week was 23.61±3.9. Among the pregnant women, 253 (25.47%) were primiparous, 740 (74.53%) were multiparous, 103 cases (9.32%) involved multiple pregnancies, and 259 (26.08%) had chronic diseases. The most common reason for fetal echocardiography referral was the suspicion of CHD in fetuses with dysmorphic findings detected during obstetric ultrasonography. Among the cases, 329 (33.1%) were classified as low-risk, while 664 (66.9%) as high-risk. Among all patients, the most commonly observed prenatal CHD were Ventricular Septal Defects (VSD) (8.2%), Hydrops Fetalis (6.1%), and large Atrial Septal Defects (ASD) (3.9%). The overall prevalence of CHD was 31.6%. The accuracy of postnatal echocardiography in confirming the diagnoses made with fetal echocardiography was 94%.

Conclusion: Prenatal diagnosis of congenital heart diseases is crucial for planning prenatal and postnatal management and providing families with the option of pregnancy termination in severe anomalies. Fetal echocardiography has shown significant potential for early diagnosis of CHD, even in low-risk fetuses, and its inclusion in routine prenatal screenings by increasing the number of experienced specialists and centers could play a crucial role in reducing CHD-related mortality and morbidity rates.

Keywords: Fetal echocardiography, congenital heart diseases, prenatal diagnosis, high risk pregnancy

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INTRODUCTION

Congenital Heart Diseases (CHDs) constitute a significant portion of congenital anomalies worldwide and are a leading cause of neonatal mortality and morbidity.[1] CHD is observed in approximately 0.8% of live births. A large portion of congenital heart diseases occur due to polygenic multifactorial causes. CHD accounts for a considerable proportion of mortality among children with congenital malformations.[2,3]

Fetal echocardiography (FE) is a reliable and non-invasive method used to diagnose and evaluate structural heart diseases in the prenatal period.[4] Fetal echocardiography, particularly in high-risk pregnancies, enables early detection of structural heart diseases and determines appropriate treatment approaches. The early diagnosis of structural heart disease during pregnancy can significantly impact the baby's quality of life and health outcomes.[5,6] The increasing experience in fetal echocardiography is vital for making accurate diagnoses in the early stages, providing families with the option of terminating the pregnancy in case of severe anomalies, and optimizing the timing of surgical interventions and treatments in the postnatal period.[7] Using fetal echocardiography helps families and healthcare professionals make informed decisions during the prenatal and postnatal periods.[8]

In this study, we aim to investigate the indications for the referral of pregnant women to our clinic for fetal echocardiography, early diagnosis of structural heart abnormalities with prenatal and postnatal fetal echocardiography, and the examination of risk factors. Additionally, we aim to evaluate the accuracy and correlation of fetal echocardiography results during the prenatal and postnatal periods.

PATIENTS AND METHODS

This study included 993 pregnant women referred from the Department of Obstetrics and Gynecology to the Department of Pediatric Cardiology Dokuz Eylül University Hospital between December 2018 and December 2020, considered at risk for CHD. We collected the pregnant women's demographic information, pregnancy history, parity, multiple pregnancies, consanguineous marriage status, maternal chronic diseases (diabetes mellitus, phenylketonuria, Lupus and Sjögren's syndrome, hypothyroidism, vitamin D deficiency), medication use, smoking, alcohol, and substance use, as well as the results of prenatal screening tests (2nd and 3rd-trimester screenings), and karyotype results if amniocentesis performed. We retrospectively evaluated the postnatal echocardiography data of cases with detected CHD during fetal echocardiography.

Inclusion criteria

We included pregnant women with a gestational age of 18 weeks or more who agreed to participate and divided them into two groups according to their risk factors.

High-risk group

The maternal factors were diabetes, medication use, advanced maternal age (>40 years), presence of CHD, TORCH infection, and presence of collagen vascular disease.

The fetal factors were polyhydramnios/oligohydramnios, increased nuchal translucency, fetal anomalies, arrhythmia, immune/non-immune hydrops, and chromosomal anomalies presence.

The hereditary factors were the previous history of fetal anomalies in previous pregnancies or the family history of CHD.

Low-risk group

The low-risk group comprised pregnant women who voluntarily sought medical attention, had suspicions of CHD, or had inadequate fetal ultrasound evaluation in the second trimester. Exclusion criteria

We excluded pregnant women with a gestational age below 18 weeks, cases requiring termination of pregnancy before delivery, and those who refused to participate.

Ethics

The study received ethical approval from the Dokuz Eylül University Non-Interventional Clinical Research Ethics Committee (approval date 08/05/2019, number 2019/12-19).

Fetal echocardiography

A team of pediatric cardiology specialists experienced in this field performed the fetal echocardiography examinations, conducting the fetal cardiac evaluations using a high-resolution ultrasound system (Philips Affiniti 50c System, Philips, Netherlands, C; 5-1 MHz transducer). They employed standard techniques to determine the fetal position and cardiac axis and to obtain Doppler and M-mode measurements. The team assessed structural anomalies using 2D echocardiographic images while evaluating rhythm problems using M-mode and Doppler techniques.[5]

Statistical analysis

We performed the statistical analyses using SPSS Statistics V 26.0 (IBM Corp., Armonk, New York, USA). Our team examined the distribution and frequencies of the data and analyzed continuous or categorical variables to determine statistically significant differences between groups. We presented the parametric test results as mean and ± standard deviation and used percentages to categorize pregnant women and risk factors. Our team used the Chi-square test to compare parametric values between groups while using the Student's T-test for non-parametric data. A p-value of <0.05 was considered statistically significant for indicating differences.

RESULTS

We included 993 pregnant women in the study, with a mean age of 29.8±5.7 years and an average gestational age of 23.61±3.9 weeks. Among the participants, 253 (25.47%) were primiparous, 740 (74.53%) were multiparous, 103 (9.32%) had multiple pregnancies, 259 (26.08%) had chronic diseases, and 128 (12.9%) reported consanguineous marriages. The demographic characteristics of the pregnant women are present in Table 1. The most common reasons for fetal echocardiography referrals were the evaluation of suspected CHD in fetuses with dysmorphic findings during obstetric ultrasonography (16.46%), seeking a second opinion from another center (15%), and multiple pregnancies (9.32%) (Table 2). We classified 329 (33.1%) of the cases into the low-risk group and 664 (66.9%) into the high-risk group. The most commonly detected prenatal CHD anomalies were Ventricular Septal Defects (VSDs) (8.2%), Hydrops Fetalis (6.1%), and large Atrial Septal Defects (ASDs) (3.9%). In the postnatal group, the anomaly rates we observed were VSD (7.3%), isolated Hydrops Fetalis (5.9%), and large ASD (4.5%).

Table 1. Demographic characteristics of pregnant women

Age, year (*mean ± SD, min-max*)	29.8±5.7 (17-51)
Gestational week (*mean ± SD, min-max*)	23.61±3.9 (18-39)
Primipar, n (%)	253 (%25.47)
Multipar, n (%)	740 (%74.53)
Multiple pregnancy, n (%)	103 (%12.8)
High risk pregnancy, n (%)	664 (%66.9)
Low risk pregnancy, n (%)	329 (%33.1)
Maternal chronic disease, n (%)	259 (%26.08)
Consanguineous marriage, n (%)	128 (%12.9)

Table 2. The indications for pregnant women's referrals for fetal echocardiography

Reason for referral	n	(%)
Dysmorphic features in the fetus	163	16.4
Secondary consultation	149	15.0
Multiple pregnancy	127	12.8
Maternal chronic disease	75	7.6
Inadequate evaluation on obstetric USG	73	7.4
Hyperechoic focus in fetal heart	66	6.6
Increased risk in screening	60	6.1
History of CHD in a previous pregnancy	48	4.8
Maternal History of CHD	45	4.6
Advanced maternal age	29	2.9
Maternal medication use	26	2.6
Hydrops fetalis	23	2.3
Rhythm disorder in baby	17	1.7
Genetic pathology in previous pregnancy	4	0.4
Other reasons	87	8.8

The prevalence of CHD detected with fetal echocardiography was 27.12% in the high-risk group and 4.92% in the low-risk group. Among all cases, normal findings were observed in 68.4% of patients, while the overall prevalence of CHD was 31.6%. We performed postnatal echocardiography in 53.8% of the cases, and while 66.6% of them had no abnormal results, 172 patients received a diagnosis of CHD. Our outpatient clinic's accuracy in diagnosing CHD with fetal echocardiography was 94%. We presented the CHD cases detected by prenatal and postnatal echocardiography in Table 3.

Three patients diagnosed with Atrioventricular Septal Defect (AVSD) had Down syndrome. A patient with pulmonary stenosis was diagnosed with Williams syndrome, and another with a large ASD was diagnosed with Holt-Oram syndrome during the postnatal period. Four of the 17 fetuses referred for suspected rhythm disorders in the high-risk group were diagnosed with supraventricular tachycardia and three with complete atrioventricular block. In the low-risk group, we observed four fetuses with atrial premature contractions. A fetus with an atrioventricular block was diagnosed with Sjögren's syndrome when anti-Ro and anti-La autoantibodies tested positive in the mother. Another mother in the low-risk group was diagnosed with Systemic Lupus Erythematosus.

Table 3. Congenital heart diseases detected in prenatal and postnatal echocardiography

	Prenatal (n:993) (n/%)	Postnatal (n:534) (n/%)
Congenital heart diseases	313/31.6	172/33.4
Ventricular septal defect	82/8.2	39/7.3
Hydrops fetalis	61/6.1	32/5.9
Large atrial septal defect	39/3.9	24/4.5
Pulmonary stenosis	36/3.6	19/3.5
Hyperechoic focus	34/3.4	16/2.9
Tetralogy of Fallot	15/1.5	8/1.49
Atrioventricular septal defect	9/0.90	7/1.31
Great artery transposition	7/0.70	6/1.12
Coarctation of the aorta	5/0.50	4/0.74
Aortic stenosis	4/0.40	5/0.93
Tricuspid atresia	4/0.40	3/0.56
Pulmonary atresia	4/0.40	3/0.56
Double outlet right ventricle	3/0.30	3/0.56
Truncus arteriosus	2/0.20	2/0.37
Hypoplastic left heart syndrome	2/0.20	2/0.37
Other	6/0.60	5/0.92

DISCUSSION

Congenital heart diseases are predominantly multifactorial and rank first as the most common congenital anomaly worldwide.[1] Fetal echocardiography performed by experienced individuals is highly valuable for detecting structural cardiac anomalies. In pregnancies considered at risk for CHD, fetal echocardiography should be part of the prenatal screening between the 18th and 22nd weeks.[5] Although the mean gestational week in our study was 23 weeks, we evaluated most of the cases during the period of optimal imaging. Maternal, fetal, and familial risk factors constitute the three main categories for fetal echocardiography indications.[9] According to the American Heart Association's Fetal Heart Disease Diagnosis and Treatment Guidelines in 2014, a risk of CHD above 2% is considered high-risk, a risk between 1% and 2% low-risk, and a risk of CHD at 1% or below imposes no indication.[10] During routine practice, pregnant women in the high-risk group are usually referred by obstetricians for fetal echocardiography evaluation. However, studies evaluating pregnant women without any risk factors or with low-risk factors have found cardiac anomalies in the range of 2.7% to 4.9%.[5,11,12] In our series, 4.92% of cases were diagnosed with CHD in the low-risk group, consistent with the literature. The most commonly observed cardiac anomaly in both high and low-risk groups in prenatal evaluations is VSD.[7-8,13] In our study, VSD prevalence was 8.2%, similar to the literature. Early diagnosis of patients with a large VSD can benefit surgical planning. Maternal chronic or systemic diseases increase the fetal anomaly risk, leading to a higher prevalence of CHD.[14] The diagnosis of complete AV block in one fetus and Sjögren's syndrome in the mother of another fetus after the diagnosis of complete AV block support this observation. Both fetuses underwent epicardial pacemaker implantation in the postnatal period. In the study by Özbarlas et al., metabolic disorders in the mother, the presence of CHD in previous pregnancies or children, and non-cardiac fetal anomalies were the most common risk factors.[11] In our research, among the risk factors, the presence of chronic diseases in the mother, dysmorphic findings and hyper-echoic foci in the heart, and a history of CHD in the mother or previous pregnancies were the most common. Boughman et al.'s study showed that although different types of CHD vary, families with CHD history have a higher risk for children with CHD than the general population.[15] Among 2102 infants with cardiovascular disease, 13% had reported chromosomal abnormalities. In another study, 28% of cases with detected cardiac anomalies during the intrauterine period had co-existing chromosomal anomalies, which increased in cases with non-cardiac anomalies.[16,17] In our study, three of the cases with karyotype examination had Trisomy 21 (Complete AVSD), two had 22q11 micro-deletion (Di George syndrome; tetralogy of Fallot), and one had a 7q11.23 deletion with Williams syndrome. Some medications used by pregnant women pose a risk for the development of CHD.10 In particular, a pregnant woman using an ACE inhibitor (enalapril) had a fetus with a large secundum ASD and a large PDA with accompanying hydronephrosis. Additionally, approximately 70% of all CHD consists of cardiac anomalies that do not have a syndromic clinic alone, confirming that the etiopathogenesis is multifactorial in a genetic cause absence.[18] In our study, isolated cardiac malformations were found in 7% of patients diagnosed with CHD in the postnatal period. According to data from the European Surveillance of Congenital Anomalies and Twins (EUROCAT) between 2004 and 2010, in 16,791 patients with isolated CHD, 30.3% had isolated CHD.[19] In the study by Best et al., 82.5% out of 5070 patients had isolated CHD, 5.7% had structural abnormalities with accompanying cardiac anomalies, and 11.9% had genetic or chromosomal abnormalities.[20]

CONCLUSION

We conclude that significant cardiac anomalies, while surely may be present in pregnancies deemed high-risk by the perinatology department, can also present in low-risk fetuses that raise suspicion for CHD in the second trimester.

Our study's results are consistent with the literature, demonstrating that fetal echocardiography has significant potential for early diagnosis of CHD, and increasing the number of experienced experts and centers that include fetal echocardiography in routine prenatal screenings will play a substantial role in reducing mortality and morbidity rates related to CHD.

Limitations

The most significant limitation of our study is the limited sample of patients at one center, which may limit the generalizability of these results. Different results are possible in diverse geographical locations or with other patient groups. Multi-center studies with extensive case series and increased availability of postnatal echocardiographic evaluations will play a crucial role in the early detection of accurate diagnoses through fetal echocardiography, leading to reduced mortality and morbidity rates.

Ethical approval

This study has been approved by the Dokuz Eylül University Non-Interventional Clinical Research Ethics Committee (approval date 08/05/2019, number 2019/12-19). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: KY, MK, NÜ; Concept: CKZ, OT; Design: KY, CKZ; Data Collection or Processing: OT, HZG, VÇ, YSB; Analysis or Interpretation: HEB, YDA, HB; Literature Search: HEB, YDA, YSB; Writing: KY. All authors reviewed the results and approved the final version of the article.

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The authors declare that there is no conflict of interest.

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Original Article

Four years of surveillance data on healthcare-associated infections in high-risk newborns

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ABSTRACT

Objective: Healthcare-associated infections (HAIs) are a major issue in neonatal intensive care units (NICUs). The characteristics of HAIs and the distribution of pathogens might also vary. HAI surveillance is important for infection control to determine HAI rates and pathogen characteristics. The purpose of this study was to assess the rates of HAIs, distribution of HAI types, characteristics of the pathogens, and antibiotic susceptibility in the first four years of a newly opened NICU.

Method: In the NICU of Marmara University Pendik Training and Research Hospital, the infection control team identified HAIs and recorded the National Hospital Infection Surveillance Network in accordance with the standards of the Centers for Disease Control and Prevention throughout the period of four years after the unit's opening. All patients in the first four years of the NICU were included in the study. The capacity of the NICU is 16 incubators and the average nurse/neonate ratio was 1/3 in this period.

Results: During the 4-year study period, 1301 patients were hospitalized in the NICU and 378 HAIs were detected. The overall HAI rate was 29.1% and the density was 21.8 per 1000 patient days. Neonatal groups with birth weights of 750 grams and 751–1000 grams had the highest rates and incidence density of HAIs. The most common HAI pathogens were *Klebsiella* spp. (27.8%), *Staphylococcus* spp. (26.2%), *Acinetobacter baumannii* (5.8%), and *Escherichia coli* (5.8%).

Conclusion: The risk of HAIs was found to be higher in neonates with a birth weight <1000 grams. In places where HAI rates are high such as NICUs, analyzing the characteristics of HAIs with active surveillance data is an essential component of infection control. This could enhance patient care and increase the survival of preterm infants with low birth weight.

Keywords: Healthcare-associated infections, neonate, surveillance, Türkiye

INTRODUCTION

Healthcare-associated infections (HAIs) are common in neonatal intensive care units (NICUs), but the patterns of infection and distribution of pathogens may vary. Neonates are especially vulnerable to HAIs due to the immature host immune defense, invasive devices that penetrate skin and mucosal surfaces, frequent use of antibiotics that disrupt the microbiome, and the necessity for prolonged hospitalization.[1] HAIs are one of the major causes of mortality and morbidity in newborns with a birth

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weight of less than 1500 grams in neonatal intensive care units (NICUs). The incidence of HAIs in NICUs is higher than in other hospital wards and it has been reported to increase up to 30% in preterm infants.[2,3] Moreover, HAIs are also associated with high mortality, increased length of stay, high healthcare costs, and adverse neurodevelopmental outcomes.[2,3] Monitoring HAI rates is considered crucial to the quality of care in the NICU. The infection rate can be reduced through effective infection control measures. The routine and orderly data collection based on defined case criteria is known as surveillance. It provides information for important precautions of infection control.[4] The necessity of active HAI surveillance has been stressed in recent years to increase patient safety, particularly for critically ill patients in intensive care units.

The purpose of this study was to assess the rates of HAIs, distribution of HAI types, characteristics of the pathogens, and antibiotic susceptibility in the first four years of a newly opened NICU.

MATERIALS AND METHODS

The retrospective surveillance study was conducted in the NICU at Marmara University Hospital for four years following its opening. The Level III severely ill newborns, extremely low birth weight premature infants, neonates requiring pre- or postoperative management, and newborns with congenital anomalies requiring multidisciplinary follow-up are all treated in the NICU, which has 16 incubators and a 100% occupancy rate. During the study period, the average nurse-to-baby ratio was one-third. The nurse in charge of infection control performed active surveillance information of HAIs. Laboratory and medical records-based HAI surveillance was conducted prospectively from 1 January 2011 to 31 November 2014.

UHESA, the National Hospital Infections Surveillance Network, was established in 2008.[5] HAI-related information was collected prospectively according to the standard protocols of the UHESA. HAIs were defined using the criteria of the Centers for Disease Control and Prevention (CDC-2008) for children <1 year of age.[6] HAI was described as an infection that occurred 48 hours after admission or ten days after hospital discharge. HAIs were analyzed according to the birth weight of the neonates. Cerebrospinal fluid (CSF), urine, sputum, endotracheal aspirate, or wound specimens were collected based on symptoms. The Clinical and Laboratory Standards Institute (CLSI) criteria's breakpoints of resistance were utilized for the evaluation of the susceptibility results.[7]

The following formulas were used to calculate healthcare-associated infection rates[8]:

HAI rate: Number of healthcare-associated infections/number of hospitalized patients) ×100

HAI incidence density: Number of healthcare-associated infections/patient days) ×1000

The extra length of stay was the difference between the length of stay of patients with HAIs and the length of stay of patients hospitalized in the NICU during that period who did not acquire a device-associated (DA)-HAI.[9, 10] All information was recorded by a certified infection control nurse after clinical findings and culture results were discussed with the consultant neonatologist and pediatric infectious disease specialist. The Marmara University Clinical Research Ethics Committee approved the study (Date: 09.08.2023, No: 09.2023-1107).

RESULTS

The total number of inpatients during the study period was 1301, while 6401 live births and 378 HAIs were identified. Based on the surveillance data, the annual HAI rates for 2011-2014 were 23.7%, 36.2%, 24.9%, and 29.6%, respectively. The incidence density for HAIs was 21.8 per 1000 patient days, and the overall HAI rate was 29.1 per 100 admissions (Table 1). The incidence density and infection rate of neonatal HAIs were highest in the < 750 g group and the 751-1000 g group by birth weight. The distribution of the neonates with HAI based on birth weight is shown in Table 2.

Regardless of the surveillance year, bloodstream infections (BSIs), pneumonia (24.4%), and urinary tract infections (UTIs) (12.7%) were the three most common HAI types. In the first three years, BSI was the most prevalent type of HAI. In 2014, pneumonia was the most prevalent HAI type, while it was the second most common HAI type in 2012 and 2013. The distribution of the HAI types for each year is shown in Table 3. A total of 39 DA-HAIs were detected in the first three years. The overall rate of DA-HAIs was calculated to be 3.6 per 1000 ICU days and 5.3 per 1000 device days. The total number of urinary catheter, ventilator, and central line days was 405, 2407, and 4509, respectively. The average rates of ventilator-associated pneumonia (VAP), catheter-associated urinary tract infection (CAUTI), and central line-associated bloodstream infection (CLABSI) were 13.7, 7.4, and 0.6 per 1000 device days, respectively.

Table 1. The HAIs characteristics by year

	2011	2012	2013	2014	Total
Number of HAIs	68	151	97	62	378
Number of patients	286	417	389	209	1301
Total patient days	2763	5131	5489	3985	17368
Rate of HAIs(%)	23.7	36.2	24.9	29.6	29.1
Incidence Density (per 1000 patient-days)	24.6	29.4	17.7	15.6	21.8

Table 2. The HAIs characteristics by birth weight

	Number of HAIs	Number of patients	Total patient days	Rate of HAIs (%)	Incidence Density (per 1000 patient-days)
<750 g	65	46	2069	141.3	31.4
751-1000 g	56	38	2370	147.3	23.6
1001-1500 g	79	97	3414	81.4	23.1
1501-2500 g	83	273	3796	30.4	21.9
>2500 g	95	847	5719	11.2	16.6
Total	378	1301	17368	29,1	21.8

Table 3. The distribution of HAIs types

Types of HAIs	Years				
	2011 n (%)	2012 n (%)	2013 n (%)	2014 n (%)	Total n (%)
BSI*	24 (35.3)	48 (31.8)	43 (44.3)	10 (16.2)	125 (33.1)
Pneumonia	12 (17.6)	40 (26.5)	15 (15.5)	25 (40.3)	92 (24.4)
UTI†	14 (20.6)	13 (8.6)	8 (8.2)	13 (21)	48 (12.7)
GISI‡	5 (7.4)	14 (9.3)	7 (7.2)	1 (1.6)	27 (7.2)
SSTI§	5 (7.4)	11 (7.3)	4 (4.1)	2 (3.2)	22 (5.8)
CNSI‖	1 (1.4)	7 (4.6)	4 (4.1)	4 (6.4)	16 (4.2)
SSI¶	0 (0)	0 (0)	1 (1)	0 (0)	1 (0.2)
CVSI**	0 (0)	0 (0)	1 (1)	0 (0)	1 (0.2)
OI††	7 (10.3)	18 (11.9)	14 (14.4)	7 (11.3)	46 (12.2)
Total	68 (100)	151 (100)	97 (100)	62 (100)	378 (100)

*BSI: Bloodstream infection, †UTI: Urinary tract infection, ‡GISI: Gastrointestinal system infection, §SSTI: Skin and soft tissue infections, ‖CNSI: Central nervous system infections, ¶SSI: surgical site infection, **CVSI: Cardiovascular system infection, ††OI: Other infection.

One hundred seventy-two pathogens were isolated from 378 HAIs. *Klebsiella spp.* accounted for 27.8% of all strains and were the most common cause of HAIs, followed by S*taphylococci* (26.2%), *Acinetobacter baumannii* (5.8%), and *Escherichia coli* (5.8%) (Table 4). When we analyzed the antibiotic susceptibility of isolated pathogens we found that the methicillin resistance rates were 29.4% and 25% for *Coagulase-negative staphylococci* and *Staphylococcus aureus*, respectively. Thirty-two (66.6%) isolates of *Klebsiella* spp. and six (60%) *Escherichia coli* strains produced ESBL. Ampicillin and vancomycin resistance were calculated at 37.5% and 37.5% of *enterococci,* respectively. Carbapenem resistance rates were 70% and 62.5% for *Acinetobacter baumannii* and *Pseudomonas aeruginosa* strains, respectively (Table 5).

Table 4. The distribution of pathogens

Pathogens of HAIs	Years				
	2011 n (%)	2012 n (%)	2013 n (%)	2014 n (%)	Total n (%)
Klebsiella spp.	6 (23.1)	17 (28.3)	7 (17.1)	18 (40)	48 (27.8)
Klebsiella pneumoniae	5 (19.3)	15 (25)	6 (14.7)	18 (40)	44 (25.6)
Klebsiella oxitoca	0 (0)	2 (3.3)	1 (2.4)	0 (0)	3 (1.6)
Other Klebsiella spp.	1 (3.8)	0 (0)	0 (0)	0 (0)	1 (0.6)
Staphylococcus spp.	10 (38.5)	12 (20)	11 (26.8)	12 (26.7)	45 (26.2)
CoNS	9 (34.7)	12 (20)	9 (22)	11 (24.5)	41 (23.9)
S. aureus	1 (3.8)	0 (0)	2 (4.8)	1 (2.2)	4 (2.3)
Acinetobacter baumannii	1 (3.8)	2 (3.3)	5 (12.2)	2 (4.4)	10 (5.8)
Escherichia coli	2 (7.7)	6 (10)	0 (0)	2 (4.4)	10 (5.8)
Pseudomonas aeruginosa	0 (0)	1 (1.7)	4 (9.8)	3 (6.7	8 (4.7)
Enterococcus spp.	1 (3.8)	3 (5)	1 (2.4)	3 (6.7)	8 (4.7)
Enterococcus faecium	1 (3.8)	1 (1.7)	0 (0)	0 (0)	2 (1.2)
Enterococcus feacalis	0 (0)	2 (3.3)	1 (2.4)	3 (6.7)	6 (3.5)
Other Enterococcus spp.	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Others	6 (23.1)	19 (31.7)	13(31.7)	5 (11.1)	43 (25)
Total	26 (100)	60 (100)	41 (100)	45 (100)	172(100)

Table 5. The distribution of the antibiotic susceptibility patterns

Pathogens of HAIs	Years				
	2011 n (%)	2012 n (%)	2013 n (%)	2014 n (%)	Total n (%)
Klebsiella spp.	6 (12.5)	17 (35.4)	7 (14.6)	18 (37.5)	48 (100)
Presence of an ESBL[†]	4 (8.3)	11 (22.9)	5 (10.4)	12 (25)	32 (66.6)
Absence of an ESBL	2 (4.2)	6 (12.5)	2 (4.2)	6 (12.5)	16 (33.4)
*CoNS**	9 (22)	12 (29.2)	9 (22)	11 (26.8)	41 (100)
Methicillin sensitive	4 (9.7)	11 (26.8)	8 (19.5)	6 (14.6)	29 (70.6)
Methicillin resistance	5 (12.2)	1 (2.5)	1 (2.5)	5 (12.2)	12 (29.4)
Staphylococcus aureus	1 (25)	0 (0)	2 (50)	1 (25)	4 (100)
Methicillin sensitive	1 (25)	0 (0)	1 (25)	1 (25)	3 (75)
Methicillin resistance	0 (0)	0 (0)	1 (25)	0 (0)	1 (25)
Acinetobacter baumanii	1 (10)	2 (20)	5 (50)	2 (20)	10 (100)
Carbapenem resistance	0 (0)	2 (20)	4 (40)	1 (10)	7 (70)
Escherichia coli	2 (20)	6 (60)	0 (0)	2 (20)	10 (100)
Presence of an ESBL	2 (20)	3 (30)	0 (0)	1 (10)	6 (60)
Absence of an ESBL	0 (0)	3 (30)	0 (0)	1 (10)	4 (40)
Pseudomonas aeruginosa	1 (12.5)	1 (12.5)	4 (50)	2 (25)	8 (100)
Carbapenem resistance	0 (0)	0 (0)	3 (75)	2 (100)	5 (62.5)
Enterococcus spp.	1 (12.5)	3 (37.5)	1 (12.5)	3 (37.5)	8 (100)
Ampiciline resistance	1 (100)	1 (33.3)	0 (0)	1 (33.3)	3 (37.5)
Vancomycin resistance	1 (100)	1 (33.3)	0 (0)	1 (33.3)	3 (37.5)

*CoNS: Coagulase negative staphylococcus, [†]ESBL: Extended-spectrum beta-lactamases

DISCUSSION

HAIs continue to have a significant negative impact on healthcare costs, prolonged hospital stays, increased antibiotic use, and cause morbidity and mortality. HAIs are a global public health issue, especially in developing countries.[11,12] HAIs have been reported to occur more frequently in developing countries than in developed countries.[12]

Most of the current HAI literature focuses on adults, and data on NICU-acquired HAIs are limited, especially in developing countries. Although Turkey's national HAI surveillance system has been in effect since 2008, there is a scarcity of published data on infection rates, types of HAI, pathogen distribution, and antibiotic susceptibility rates.[5] We believe that clinicians can find current data, messages, and suggestions about HAIs and HAI control in this study. The other important aspect of this study is that it was conducted in a newly opened NICU. To our knowledge, there is limited data on a newly opened NICU.

The incidence of HAIs in the NICU has been reported to range between 9-50.7%.[3,13-18] The rates of HAIs reported in the literature show a wide range, which may be due to differences in study methods or surveillance, and the conditions of the country. In Türkiye, the National Hospital Infections Surveillance Network (UHESA), was established in 2008.[5] Since its establishment in the 1970s, the National Nosocomial Infections Surveillance System (NNIS) in the USA has helped to reduce the incidence of HAIs by 30–40%.[19,20] In Germany, the incidence of ventilator-associated pneumonia decreased by 24% over three years when the Krankenhaus Infektions Surveillance System (KISS) was implemented.[21] In Europe, surveillance systems for HAIs in NICUs are active in Germany (Germany's Neonatal-Krankenhaus Infektions Surveillance System, NEO-KISS) and England.[22–24] Therefore, HAI surveillance studies, ideally prospective active surveillance, are important for effective infection control. Active surveillance studies can help characterize the epidemiology of HAIs.

In all NICUs, infection prevention must be a major concern. Clinical practices and the patient care environment must be closely monitored to reduce the risk of HAIs.[25] Although the NICU was recently opened, HAI characteristics have varied over the years. The HAI rate was at its lowest in the first year and at its highest in the second year. Although the average HAI rate in Türkiye was higher than the rates in certain industrialized countries, such as the United States, Italy, and China, it was still lower than previous reports from several developing countries, such as Brazil and Indonesia.[13,16,18,26,27] The overall HAI rate was reported to be 23.5%, according to a national point-prevalence survey study conducted in 38 NICUs in Türkiye.[28] The HAI rate in neonatal care has been reported to be between 8.3-23.5 % in Türkiye.[28-32]

The incidence density for HAIs in this series was 21.8 per 1000 patient days, and the overall HAI rate was 29.1%. Our rates were higher than the mean of the recently reported rates in Türkiye.[28-32] The high incidence of HAIs despite modern infrastructure, equipment, and facilities implies that healthcare staff have not followed infection control procedures. One of the reasons for the high rate of HAIs was low HH compliance Other reasons may include staff shortages, poor training, inadequate feedback, and delayed awareness. We looked into how well the medical staff in our neonatal and pediatric intensive care units adhered to HH. The main factor contributing to the high HAI rates was the low overall compliance with HH among physicians and nurses, which was found to be 31.9% and 41.4%, respectively.[33] Regarding HH compliance, we provided input to the NICU and PICU personnel as well as the hospital infection control committee. Training on HH was provided more often. Members of the infection control committee and NICU staff worked harder to reduce HAIs. HH compliance and active surveillance are the two key infection control strategies. To monitor and manage HAIs, we would like to reiterate the value of active surveillance and HH compliance. Therefore, we think that one factor contributing to the high HAI rates in Türkiye is the lack of knowledge about infection control preventive strategies.[34]

Low gestational age with extremely low birth weights (ELBW) infants (≤1000 g) are particularly at risk because they require more intensive care in neonatology units and undergo more invasive procedures.[1] Although all BW classes were affected by HAIs, ELBW neonates were particularly at risk of acquiring HAIs. We found that HAI rates in the <1000 gram groups were very high compared to the other groups by birth weight, which is consistent with the literature.[13-15]

In this study, BSI (33.1%), pneumonia (24.4%), and UTI (12.7%) were the most prevalent HAI types (Table 3). According to recent reports, BSI and pneumonia are the most common HAI types in the NICU.[13-18] Depending on the department, hospital population, and setting, the relative occurrence of different HAI types may vary.

In this study, 172 (45.5%) causative pathogens were isolated in 378 HAIs. The isolation rate for HAIs was reported to be 88% in the USA.[35] Our isolation rate was lower, possibly due to inadequate sampling and technical insufficiencies in the microbiology laboratories. The main pathogens that cause newborn infections vary not only from country to country and

from nursery to nursery, but they also alter over the years in the same location.[36] *K. pneumoniae*, various gram-negative rods, and staphylococci are common infection agents in NICUs, and antimicrobial resistance is a significant issue in developing countries.[37,38] The most frequently isolated pathogen among all HAIs in this study was *Klebsiella spp.*. In the present study, over 60% of *Klebsiella spp.* and *E. coli* isolates were ESBL-positive, which is similar to the rates in 2008–2010 in the former hospital building.[12] An international, multicenter study including Türkiye showed that 78% of *K. pneumoniae* strains produce ESBLs.[39] Susceptibility patterns of *P. aeruginosa* and *A. baumannii* vary over time and in different hospital settings. The prevalence of *P. aeruginosa* and *A. baumannii* infections in NICUs is also rising as a result of the use of broad-spectrum antibiotics.[12] In this study, the overall carbapenem resistance rates were 70% and 62.5% among *A. baumannii* and *P. aeruginosa* isolates. All of the *A. baumannii* strains were susceptible to colistin. Previous national studies have demonstrated that the carbapenem susceptibility rates for *P. aeruginosa* were between 48% and 71%.[11,12,40,41]

We took into account the persistently high rates of resistance caused by inadequate adherence to infection control procedures and inappropriate and prolonged use of broad-spectrum antibiotics in critically ill newborns in the NICU. Active surveillance allows physicians to estimate antibiogram patterns, which may aid in the empirical use of antibiotics. Some pathogenic bacteria are resistant to commonly used antibiotics. They are frequently observed in hospitals and are associated with contaminated water supplies. They can colonize patient mucosa and the surfaces of numerous devices in NICUs. Regular monitoring of water and water-related devices in NICUs could aid infection control measures.

CONCLUSION

We reported a high prevalence of HAIs in a newly opened NICU. The high rates of HAIs with resistant bacteria identified in our study could be attributed to a number of factors, including lack of infrastructure, late adoption of HAI surveillance, lack of infrastructure, and lack of ability to implement HH. This manuscript underlines once again the need to use active surveillance data to analyze the characteristics of HAIs, which can improve the treatment of patients and increase the survival of preterm newborns in developing countries such as Türkiye.

Ethical approval

This study has been approved by the Marmara University Clinical Research Ethics Committee (approval date 09.08.2023, number 09.2023-1107). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: SA, AÇM, EK, YP, HSB, EÖ, AS; Concept: SA, AS; Design: SA, AÇM, AS; Data Collection or Processing: YP; Analysis or Interpretation: SA, AÇM, AS; Literature Search: SA, AÇM; Writing: SA, AÇM, AS. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Case Report

Ceftriaxone induced acute generalized exanthematous pustulosis confirmed with patch test

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ABSTRACT

Background: Acute generalized exanthematous pustulosis (AGEP) is a rare cutaneous drug reaction presenting with rapid-onset sterile pustules on edematous erythema.

Case: A 12-year-old female patient with acute gastroenteritis was consulted with complaints of pruritic erythema and high fever developing with small pustules on the 2nd day of ceftriaxone treatment. Lab tests showed an elevated absolute neutrophil count and lymphopenia. Ceftriaxone was discontinued immediately. The fever went away within 24 hours. According to EuroSCAR, the diagnosis of AGEP was confirmed. The skin biopsy was compatible with AGEP. After 6 weeks, a patch test with ceftriaxone was performed. A strong positive reaction to ceftriaxone was detected. Three months later, amoxicillin, amoxicillin-clavulanate, clarithromycin, and trimethoprim/sulfamethoxazole patch tests were performed, all were negative, and provocation tests were also planned.

Conclusion: AGEP is a severe cutaneous drug reaction. We wanted to emphasize that patch tests help identify the responsible drug and find a safe alternative.

Keywords: Acute generalized exanthematous pustulosis, drug eruption, patch test, severe drug hypersensitivity reactions

INTRODUCTION

Acute generalized exanthematous pustulosis (AGEP) is a rapid-onset cutaneous drug reaction that presents as non-follicular sterile disseminated pustules on an edematous erythematous background. Peripheral blood leukocytosis and fever are frequently seen in patients.[1] Usually drugs, especially antibiotics, cause AGEP and there have been rare cases of viral infections (e.g. enterovirus) and exposure to inorganic compounds (e.g. mercury) or contrast agents.[1-3] Patch testing, a safe and useful in vivo test, is used to find the causative agent.[2] In this report, we present a patient with ceftriaxone-induced AGEP, which was confirmed by patch testing and skin biopsy.

CASE

A 12-year-old girl was admitted to a secondary health care institution due to complaints of vomiting and diarrhea that started one week ago, and fever three days ago. She was diagnosed with acute gastroenteritis and started on parenteral

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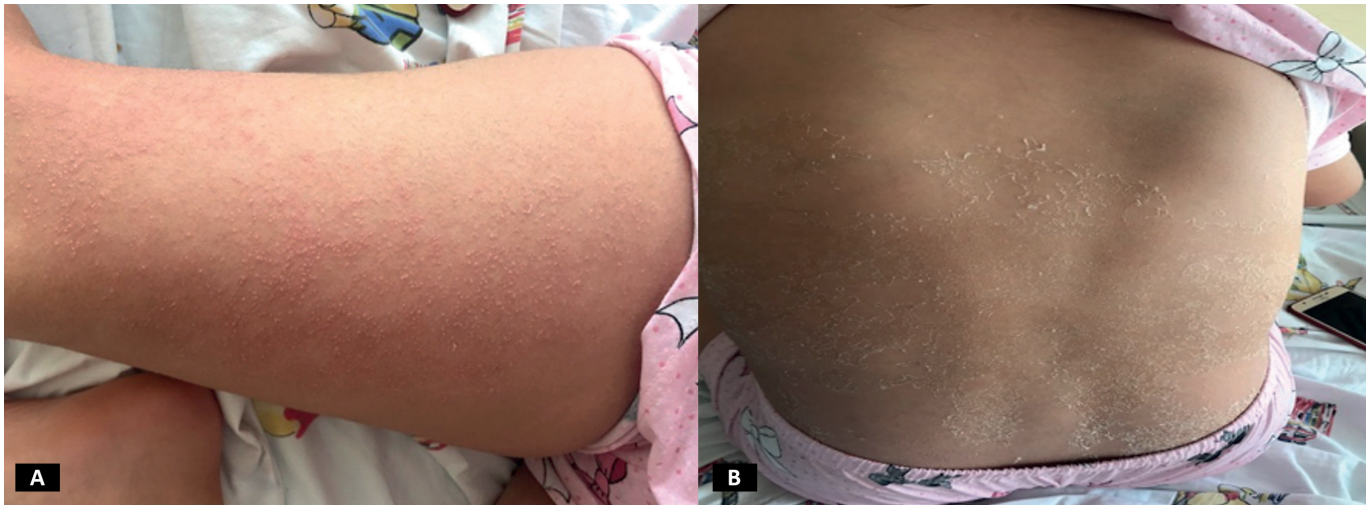

Figure 1. (A) Erythaema with numerous small non-follicular pustules. (B) Desquamation of lesions on the back.

hydration and ceftriaxone. The next day, she was referred to our hospital with prerenal renal failure due to increased urea, creatinine, and uric acid levels. Because of the COVID-19 pandemic, the patient was hospitalized after obtaining a COVID-PCR test, and continued hydration and ceftriaxone treatment. At 48-72 hours of ceftriaxone treatment, she developed pruritic erythema growing with multiple small non-follicular pustules associated with fever (39°C), most commonly in the inguinal and axillary regions, as well as on the trunk, face, and proximal limbs (Figure 1A). The patient's gastrointestinal, respiratory, and lymph node examinations of the patient did not reveal any features, and there was no mucosal involvement. Her personal and family history was unremarkable. Laboratory tests showed leukocytosis (21100/mm^3, absolute neutrophil count: 19200/mm^3) and lymphopenia (800/mm^3 [%6,9]). Urea, creatinine, and uric acid levels improved. An infectious etiology was excluded through PCR test, antibody response (for COVID-19), viral serology (for CMV, EBV VCA, Parvovirus B19, HSV tip1 IgM), and blood and throat swab cultures were all negative. Ceftriaxone was thought to be the culprit drug and was discontinued, and the patient's fever regressed within 24 hours. Desquamation (Figure 1B) started on the 3rd day after ceftriaxone was discontinued, and the skin was completely healed on the 10th day. According to the AGEP scoring system of the EuroSCAR study group, which we performed according to the history, clinical, and laboratory findings, our patient got 11 points (Table 1) and the diagnosis of AGEP was confirmed. We performed a skin biopsy which showed subcorneal, intraepidermal non-follicular pustules containing neutrophils, consistent with AGEP (Figure 2A). The immunohistochemical study revealed accumulations stained with IL 17 (Figure 2B).

Table 1. The patient's EuroSCAR scoring (AGEP validation score)

Morphology	Typical Pustules	2
	Typical Erythema	2
	Distribution pattern Compatible	2
Course	Mucous membrane involvement (No)	0
	Acute beginning (Yes)	0
	Resolution within 15 day (Yes)	0
	Fewer >38 0C (Yes)	1
	Polymorphonucleer cells >7000 /mm3 (Yes)	1
Histology	Involves subcorneal, and/or intraepidermal pustules with papillary edema	3
Total score		11

Six weeks after the reaction, a patch test with ceftriaxone was performed. A drop of ceftriaxone (200 mg/ml) and a drop of normal saline (as negative control) were applied to the skin on the child's upper back using IQ Chambers on 9 mm adhesive tape. The occlusion time was 48 h; 15 min after the removal of the cups and readings were recorded on day two and day four, according to the current guideline.[2] A strong positive reaction (++) to ceftriaxone was documented with infiltrated erythema and pustules (Figure 3).

To determine the safe alternative antibiotic, we performed further patch tests three months after her discharge with beta-lactams such as amoxicillin and amoxicillin-clavulanate (which do not share the same side chain with ceftriaxone) and non-beta lactam antibiotics that are clarithromycin and trimethoprim-sulfamethoxazole. Amoxicillin and amoxicillin-clavulanate

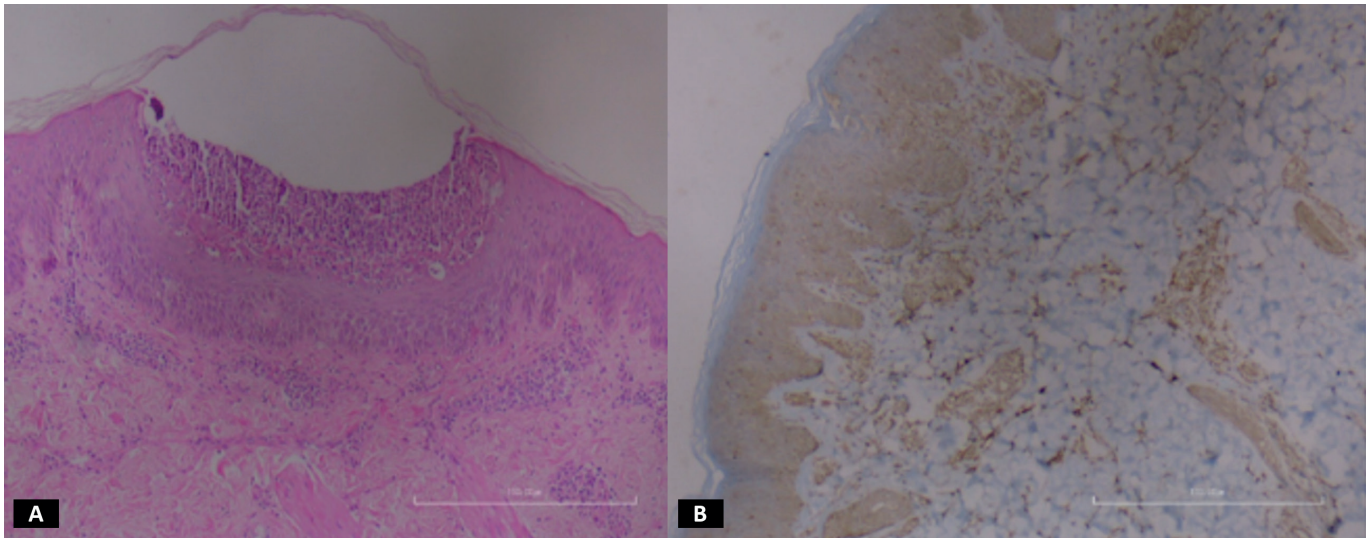

Figure 2. (A) Subcorneal pustule, epidermal spongiosis, neutrophil exocytosis, superficial perivascular mixed inflamation including rare eosinophils. Hematoxylen and eosine x100. (B) Deposits stained with IL-17 in the dermis.

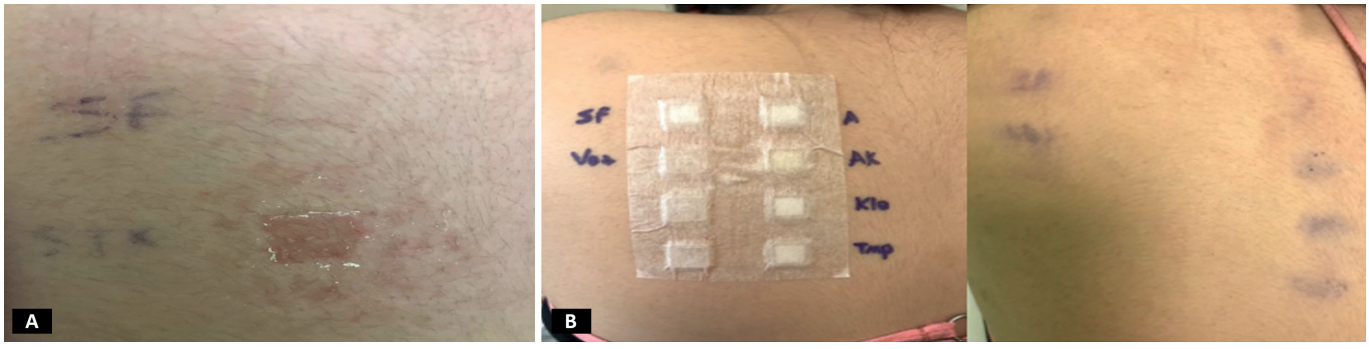

Figure 3. (A) A strong patch test reaction with ceftriaxone on day 2. (B) Negative patch tests with moxicilin, amoxicilin-clavulanate, trimethoprim/sulfamethoxazole, clarithromycin.

tablets were diluted 30% in petrolatum, drops of trimethoprim/sulfamethoxazole (80 mg/ml), and clarithromycin (50 mg/ml). Normal saline and petrolatum were used as negative controls. They were all negative at 48 and 72 hours (Figure 3).

DISCUSSION

AGEP is a rare adverse drug reaction with a frequency of one to five cases per million per year and is a severe pustular reaction characterized by acute onset, non-follicular pustules with high fever and leukocytosis.[1] Mild oral mucosal involvement may occur in about 20 percent of cases with AGEP. Pustules resolve within a few days (average 4-10), followed by post-pustular punctate peeling patches.[4] In a retrospective study of 63 AGEP cases, Roujeau et al.[5] characterized this incidence as drug-induced. Beylot et al.[6] reported that drugs were involved in 90% of cases and antibacterials were the most common triggers. The β-lactam antibiotic group is responsible for the majority of antibiotic-associated AGEP cases[6] as was the case with ceftriaxone in our patient. The period between the start of the drug and the onset of AGEP symptoms varies; 24-48 hours for common causative agents such as penicillin and 10-14 days for other high-risk drugs.[1] The periods between the administration and cessation of ceftriaxone and the onset of symptoms were 2 and 10 days respectively, as reported in the literature.[4]

Generalized pustular psoriasis (GPP), follicular pustular diseases, Drug reaction with eosinophilia and systemic symptoms syndrome (DRESS), Steven-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) should be considered in the differential diagnosis of AGEP. It has been suggested that a mutation in the IL-36RN gene results in a decrease or inefficacy

of the IL-36 receptor antagonist (IL-36Ra) and an uncontrolled increase in IL-36. Increased IL-36 signaling causes IL-1α, IL-1β, IL-6, and IL-8 production and may predispose to pustular formations.[7] Recent studies have identified similarities in the pathogenesis of AGEP and GPP, such as mutations detected in IL-36Ra and increased expression of IL-17 by TH17 cells.[8,9] However, the distinction between the two diseases is based on several specific features. Only a minority of AGEP patients has a history of psoriasis and AGEP has a much shorter course than psoriasis.[1]

AGEP differs from follicular pustular diseases because it is an example of non-follicular pustulosis. Two other follicular pustular diseases to consider in the differential diagnosis are subcorneal IgA dermatoses and Sneddon-Wilkinson disease (subcorneal pustulosis). These two diseases differ from AGEP by the presence of large pustules that occur subacutely.[10]

In distinguishing AGEP from severe cutaneous drug reactions, Dress syndrome has a long latent period, typically 2 to 6 weeks, and an erythematous morbilliform rash is typical. Mucosal and visceral involvement is more common than in AGEP.[11] SJS and TEN are characterized by Nikolsky signs and mucosal involvement. Therefore, it may be difficult to distinguish SJS/TEN from severe AGEP cases with mucous membrane involvement. However, TEN also presents with full-thickness epidermal necrosis and a lymphocytic infiltrate at the dermo-epidermal junction.[12]

Determining the cause of cutaneous adverse drug reactions (CADR), skin tests are helpful in identifying the cause of CADR.[13] Because the patch test shows positive results, AGEP is recognized as a delayed type of hypersensitivity reaction, which is one of the CADRs.[14]

Diagnostic approaches for delayed hypersensitivity reactions include patch testing, delayed intradermal testing (IDT), and drug provocation tests for milder reactions. Unfortunately, guidelines for performing IDTs have not been standardized and have unknown values.[15] Provocation tests should not be performed in severe cutaneous drug reactions such as AGEP.[16] Since re-exposure to the drug may lead to another episode of AGEP, causality assessment after the acute phase is over is a very important procedure.[17] Positive patch test results are more common in AGEP than those in SJS/TEN, usually showing many small sterile pustules at the test site.[14] Patch testing has been reported to be a safe diagnostic method and found to be positive in 58 % of patients with AGEP[2] and we performed it without any problems in our patient.

Patch tests can also help examine the ability of drugs to elicit symptoms due to cross-reactivity, e.g. among beta-lactam antibiotics.[18] Patients with a positive patch test result for cephalosporin should not be tested with another molecule that shares the same side chain due to the higher risk of cross-reactivity.[19] To find a safe alternative antibiotic, we applied a patch test with antibiotics with different side chains that are frequently prescribed by physicians. When choosing medications that can be used safely, a patch test can be done beforehand, and if it is negative, a provocation test is appropriate. Our patient had a history of using amoxicillin-clavulanate and clarithromycin safely. However, we still planned to perform a provocation test with drugs that were positive in the patch test.

CONCLUSION

We emphasize that AGEP should be kept in mind by clinicians since it is a very rare disease. In addition to the frequent occurrence of ceftriaxone as the culprit in the literature, the number of cases confirmed by patch testing in childhood is very low. We also want to emphasize that patch tests are useful not only for defining the culprit drugs in AGEP but also for finding safe alternatives.

Author contribution

Surgical and Medical Practices: ÖTU; Concept: PGÖ; Design: ÖTU; Data Collection or Processing: SKS; Analysis or Interpretation: ÖTU, PGÖ; Literature Search: ÖTU, MY; Writing: ÖTU, NC. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Case Report

A case report of invasive glabrata candidiasis in extremely low birth weight premature twin newborns

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ABSTRACT

The incidence of invasive candidiasis (IC) in neonatal intensive care units (NICUs) has significantly increased. Although C. albicans is still the most common pathogen detected in IC cases (60-75%), the increase in the use of prophylactic antifungal therapies and empirical echinocandin has led to a shift in detected pathogens to non-albicans candida species such as C. glabrata (2-8%). In the past, C. glabrata was considered one of the relatively non-pathogenic saprophytes of the normal flora. However, mucosal and systemic C. glabrata infections have escalated with the increase in the survival rates of premature newborns, prolonged hospitalization, and the widespread use of immunosuppressives and broad-spectrum antibiotics and started to appear more frequently as an important nosocomial pathogen, especially with its natural resistance to the azole antifungals. In this article, we aimed to draw attention to the importance of C. glabrata in NICUs by presenting extremely low-birth-weight premature twins with severe clinical course.

Keywords: Extremely low birth weight, invasive candidiasis, Candida glabrata, sepsis

INTRODUCTION

Invasive candidiasis (IC) infection is an important cause of morbidity and mortality in low-birth-weight premature newborns.[1] Candida albicans is responsible for 60-75% of all cases, whereas Candida glabrata constitutes only 2-3% of candida infections in the neonatal period.[2-4] Definitive diagnosis of IC cases is made by demonstrating Candida species in the culture of sterile body fluid samples such as blood or cerebrospinal fluid (CSF). However, since the sensitivity of blood culture for IC cases is less than 50%, making a definitive diagnosis of Candida meningitis gets more difficult.[5] Normal neuroimaging and CSF findings do not exclude the diagnosis. Since C. glabrata is resistant to the azole group of antifungals, which are the first choice of empirical antifungal therapy when a fungal infection is suspected, this may create a challenge to the treatment.[6] This case report presents premature twin newborns with C. glabrata sepsis who were followed up and treated in the neonatal intensive care unit.

CASE PRESENTATION

A female newborn weighing 800 grams and a male newborn weighing 780 grams, delivered by C/S at the age of 25 1/7 weeks due to fetal distress, were transferred to the neonatal intensive care unit. In prenatal history, two courses of betamethasone and antibiotic treatment for premature rupture of membranes were administered. Both were treated with penicillin-gentamicin for 7 days with the diagnosis of early neonatal sepsis. The female newborn received three doses and the male newborn received

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two doses of surfactant therapy. On the 16th day of the follow-up, the female baby's general condition deteriorated and her activity decreased, immediately after her twin developed similar findings. Blood samples were obtained to evaluate these clinical changes, and laboratory tests showed thrombocytopenia and increased acute phase reactants. Based on these findings, late neonatal sepsis was considered in both twins. Lumbar puncture was also performed to exclude central nervous system involvement. Blood and CSF laboratory findings are shown in Table 1. In light of these findings, the infection was evaluated as a nosocomial infection by the infection committee, and they decided to start broad-spectrum empirical antibiotic treatment and to increase the antifungal treatment from prophylaxis dose to treatment dose. Vancomycin, meropenem, and fluconazole treatments were administered to both patients. At the 48th hour of the treatment, the microbiology laboratory presented the preliminary report that this pathogen could be fungi. Amphotericin B was added to the antifungal treatment. The same agent, Candida glabrata, was isolated from two consecutive blood cultures of the cases. CSF cultures were sterile. Abdominal and transfontanelle ultrasonography, echocardiography, and eye examinations were normal. After the first negative blood culture was obtained, antifungal treatment was continued for another 2 weeks and then discontinued. The female newborn was discharged on postnatal day 76, however, her twin died on postnatal day 136 while being followed up on mechanical ventilation with a tracheostomy, with the diagnosis of severe bronchopulmonary dysplasia and severe pulmonary hypertension.

DISCUSSION

The incidence of invasive candidiasis in neonatal intensive care units has escalated with the increase in the survival rates of extremely low birth weight premature newborns and prolonged hospitalization.[7,8] Although C. albicans is still the most common pathogen detected in IC cases (60-75%), the increase in the use of prophylactic antifungal therapies and empirical echinocandin has led to a shift in detected pathogens to non-albicans candida species such as C. tropicalis, C. parapsilosis, C. krusei and C. glabrata, which are more likely to be resistant to the azole group of antifungals.[9,10] Since this condition changed treatments and prognosis, identifying the type of the pathogen has become more important in cases with candidemia. C. glabrata as a

Table 1. Blood and CSF laboratory findings of patients

	Female Newborn	**Male Newborn**
Complete Blood Count Results	**WBC:** 18.66 x10^3/uL **Hb:** 9.7 g/dL **Thrombocyte:** 13 x10^3/uL	**WBC:** 24.99 x 10^3/uL **Hb:** 10.5 g/dL **Thrombocyte:** 109 x10^3/uL
CRP	1.89 mg/dl	2.39 mg/dL
CSF Results	**Glucose:** 70 mg/dL **Protein:** 189,00 mg/dL **Culture:** No growth.	**Glucose:** 65 mg/dL **Protein:** 187,00 mg/dL **Culture:** No growth.
Blood Culture	1. *Non-albicans Candida spp.* 2. *Candida Glabrata*	1. *Non-albicans Candida spp.* 2. *Candida Glabrata*
Urine Culture	No growth.	No growth.
Antifungal Sensitivity Results	***Candida Glabrata***	***Candida Glabrata***
Antifungal agent *Amphotericin B *Anidulafungin *Caspofungin *Fluconazole *Flucytosine *Itraconazole *Micafungin *Posaconazole *Voriconazole	**Resistant/MIC*** (1 µg/mL) Sensitive (0.06 µg/mL) Sensitive (0.06 µg/mL) (16 µg/mL) Sensitive (<=0.06 µg/mL) (0.5 µg/mL) Sensitive(<=0.008 µg/mL) (1 µg/mL) Sensitive (0.5 µg/mL)	**Resistant/MIC** (1 µg/mL) Sensitive (0.12 µg/mL) Sensitive (0.06 µg/mL) (16 µg/mL) Sensitive (<=0.06 µg/mL) (0.5 µg/mL) Sensitive (<=0.008 µg/mL) (1 µg/mL) Sensitive (0.25 µg/mL)

*MIC: minimum inhibitory concentration.

non-albicans Candida, which was isolated in our case, accounted for approximately 2-3% of IC cases.[2-4] In the study of Chen et al. published in 2022, it was reported that C. glabrata constitutes 7.9% of IC cases.[11] It is known that C. glabrata can be transmitted horizontally from the hospital environment as well as vertically from the mother.[12] As in other IC cases, C. glabrata cases usually present with sepsis findings. Since it can spread to other organs and systems by hematogenous and/or septic embolism, all cases should be carefully evaluated in detail.

C. glabrata has intrinsic resistance to conventional triazole antifungals such as fluconazole. It can also cross-react to new triazoles. In the study of Odds et al., the resistance rate of C. glabrata strains isolated from blood samples taken from all age groups to fluconazole was determined as 45%.[13] Malani et al. found that 60% of the isolated C. glabrata strains were resistant to fluconazole, 83% to itraconazole, and 44% to voriconazole for all age groups.[14] Similarly, the rate of resistance to fluconazole was found to be 33% by Lamp et al. in their study, which included only patients in tertiary NICUs. No amphotericin-resistant C. glabrata case was identified.[15] In this respect, antifungal susceptibility testing must be performed after the isolation of the pathogen. In our case, contrary to expectations, the isolated pathogen was not resistant to fluconazole. However, in light of the literature, when it was learned that the isolated microorganism was C. Glabrata, amphotericin B was administered in addition to the fluconazole treatment started after the preliminary report, considering the severe clinical condition of the patient. Besides, the fact that the isolated microorganism was sensitive to all antifungal agents led us to believe that this microorganism could have been from the patient's own flora or vertically transmitted rather than being a nosocomial infection. The American Infectious Diseases Society recommends that echinocandins should be used with extreme caution in newborn patients and only in cases of resistance to fluconazole or amphotericin B.[16] Although voriconazole is not widely used in newborns, it can be used in the step-down phase of the treatment in the presence of fluconazole-resistant voriconazole-sensitive pathogens. Since the active form of voriconazole is minimally excreted in the urine, it should not be preferred in cases with urinary candidiasis.[17,18] Although there is uncertainty about the optimal duration of treatment in candidiasis cases, according to the Infectious Diseases Society of America, in cases without end organ involvement, treatment should be completed in 3 weeks after the culture negativity and clinical improvement in the patient.[16] This duration is defined as 10-14 days after culture negativity in the Neonatal Infections Diagnosis and Treatment Guide of the Turkish Society of Neonatology.[19] In our case, candidiasis developed during the administration of fluconazole prophylaxis. In the presence of signs of sepsis, the dose of antifungal treatment was switched from prophylaxis to treatment dosage, and when the yeast signal was detected in the blood culture, the treatment was continued by adding Amphotericin B. In the study of Fridkin et al. involving 1997 newborns, the overall mortality in IC cases was 13%, while the mortality in C. glabrata cases was reported to be 21%.[2] Warris et al. reported that the mortality rate due to C. albicans was 13.6%, while the mortality rate due to C. glabrata was 14.2%.[4]

In the past, C. glabrata was considered one of the relatively non-pathogenic saprophytes of the normal flora, rarely causing serious infections. However, mucosal and systemic C. glabrata infections have escalated significantly with the increase in the survival rates of premature newborns, prolonged hospitalization, and the widespread use of immunosuppressive and broad-spectrum antibiotic treatments, and it has started to appear more frequently in clinical practice as an important nosocomial pathogen, especially with its natural resistance to the azole antifungals.

In conclusion, we aimed to draw attention to the importance of C. Glabrata, which was increased significantly in neonatal intensive care units, by presenting extremely low-birth-weight premature twins with severe clinical course.

Author contribution

Surgical and Medical Practices: EA, BGY, SB, MÖ, AK; Concept: EA, BGY; Design: EA, BGY; Data Collection or Processing: EA, BGY; Analysis or Interpretation: EA, BGY; Literature Search: EA, BGY, SB; Writing: EA, BGY, SB, MÖ, AK. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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