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Original Articles

Review

Turkish Journal of Pediatric Disease

Original Article

Evaluation of children with familial hypomagnesemia with hypercalciuria and nephrocalcinosis

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ABSTRACT

Objective: Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) is a rare autosomal-recessive renal tubular disorder. It is characterized by renal wasting of magnesium and calcium, which subsequently leads to bilateral nephrocalcinosis, renal stones, and kidney failure. Early diagnosis of FHHNC is important to prevent morbidity and mortality but due to non-specific symptoms it is difficult to diagnose. In this report, pediatric FHHNC patients are presented to raise awareness about the disease.

Material and Methods: We retrospectively analyzed pediatric FHHNC patients in our hospital between 2010 and 2020.

Results: A total of seven patients, five girls (71.4 %) and two boys (28.5 %) with a median age of four years (min: four months, max:13 years) and a mean follow-up time of 4.4±3.5 years were included. Three patients had been diagnosed incidentally. All patients had nephrocalcinosis, hypercalciuria and high parathormone (PTH) level. One patient had normal serum magnesium level. All patients had high urine fractional excretion of magnesium (FEMg). Five patients had CLDN 16 mutation, and two patients had CLDN19 mutation. None of them had ocular findings. Three patients had kidney failure at the end of the follow-up.

Conclusion: Normal serum magnesium levels do not rule out FHHNC. FEMg value is much more significant in patients with FHHNC. FEMg is recommended in all pediatric patients with nephrocalcinosis even if serum magnesium levels are normal.

Keywords: CLDN16, CLDN19, Hypomagnesemia, Hypercalciuria, Nephrocalcinosis

INTRODUCTION

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) is a rare autosomal-recessive renal tubular disorder. It is characterized by renal wasting of magnesium (Mg) and calcium (Ca) which leads to hypomagnesemia, hypercalciuria, bilateral nephrocalcinosis and kidney failure. This rare disorder is caused by mutation of CLDN16 or CLDN19 genes which encodes claudin-16 and claudin-19 proteins (1,2). Recurrent urinary tract infection, polyuria, polydipsia, enuresis, growth retardation, tetany, and seizures are the most common symptoms of the disease (1). In addition, patients with CLDN19 mutations could be associated with congenital ocular defects (2).

Despite the severe clinical course there is no specific treatment for FHHNC and generally, treatment is supportive such as oral Mg and citrate supplementation, high fluid intake, dietary salt restriction (3). In addition, kidney transplantation is the only curative option for kidney failure. Early diagnosis of FHHNC is important to prevent morbidity and mortality but due to these non-specific symptoms it may be difficult to diagnose. In this report, we present seven pediatric cases of FHHNC to raise awareness about the disease.

MATERIALS and METHODS

Pediatric patients with FHHNC were retrospectively analyzed between 2010-2020 in our hospital. All patients had genetic analysis. Demographic data and medical history were collected from the records of our hospital. Ophthalmologic examinations were also performed in all children.

The fractional excretion of magnesium (FEMg) was calculated using the formula of SeCr×UMg×100/0.7×SeMg×UCr where SeCr = serum creatinine, UMg = urinary magnesium, SeMg = serum magnesium, and UCr = urinary creatinine. FEMg >4% is considered as hypermagnesuria (4). Hypomagnesemia is

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accepted as having serum magnesium lower than 1.46 mg/dL (5). Hypercalciuria is accepted when 24-hour urinary calcium excretion exceeds 4 mg/kg/day, or spot urinary calcium/creatinine ratio > 0.86 mg/mg for children less than seven months of age, and spot urinary calcium/creatinine ratio > 0.2 mg/mg for children older than seven months of age (6,7). Hyperparathyroidism was defined as having serum parathyroid hormone (PTH) level greater than 88 pg/mL according to the references of our laboratory. The 25-OH vitamin D insufficiency is accepted as having levels less than 30 ng/mL (8,9). Hyperuricemia is considered when the serum uric acid level is ≥6 mg/dL in boys and girls younger than 15 years (10). Hypocitraturia is accepted as having urine citrate levels less than 180 mg/g creatinine regardless of gender (11).

Nephrocalcinosis was diagnosed with ultrasonography. The estimated glomerular filtration rate (eGFR) (mL/min/1.73 m^2) was calculated using the original Schwartz equation (12). eGFR levels below 90 mL/min/1.73 m^2 were considered as chronic kidney disease (CKD). Magnesium supplements, usually at a dose of 0.4-0.8 mmol Mg +2 per kilogram of body weight three times a day, and potassium citrate at a daily dose of 0.5-1 mmol/kg were administered. Hydrochlorothiazide was administered at a standard dose of 0.5-1.5 mg/kg/day if the patient has hypercalciuria.

Genetic Analysis -DNA Sequencing and Classification of Variants

In EDTA tubes, peripheral blood samples were collected, and the patients' DNA was isolated using an automated DNA isolation technique (Qiagen Inc. Mississauga, ON, Canada). Sophia DDM software (Sophia Genetics, Saint-Sulp) was used to analyze the data. The variations were evaluated according to the gene, allele frequency, inheritance type, and clinical results of the patient. We removed variants with a MAF greater than 1% on EXAC. The Clinvar and Global Variome LOVD databases were utilized in conjunction with in silico prediction techniques (Mutation taster, SIFT, and Polyphen2). A standardized variant interpretation was undertaken in accordance with the American College of Medical Genetics (ACMG) and Association for Molecular Pathology (AMP) recommendations. This research discusses pathogenic and likely pathogenic variants. The Sanger sequencing was used to validate variants.

Statistical Analyses

Descriptive statistics were presented as numbers and percentages for categorical variables, and as mean values with standard deviations for numerical variables.

RESULTS

A total of seven patients (five female, two male) with FHHNC were included. The median age at diagnosis was four years (minimum: four months, maximum: 13 years), and the mean follow-up time was 4.4±3.57 years.

The most common signs and symptoms during disease course were nephrolithiasis, convulsion, and urinary tract infection (28.6%), vomiting (14.3%), macroscopic hematuria (14.3%) and microscopic hematuria (42.8%).

Case 1.2, being the sibling of Case 1.1, was diagnosed during screening. Similarly, Cases 3.2 and 3.3, as siblings of Case 3.1, were also diagnosed during screening.

All patients exhibited normal percentiles for body weight and height, as well as normal ocular results. The CLDN16 mutation was identified in five cases, while the CLDN19 mutation was found in two. The demographic, genetic and extrarenal findings of the patients are summarized in Table I.

Hypermagnesuria, hypercalciuria, nephrocalcinosis, elevated PTH levels, normal urine oxalate levels, and normal blood gas analyses were present in all patients. Hypomagnesemia was detected in 6 patients except one (Case 3.3). Case 3.3 had normal serum magnesium level at diagnosis. Under magnesium replacement, low serum magnesium levels persisted in three patients. During the follow-up period, three patients remained normocalciuric while undergoing HCT therapy.

One patient with renal failure had hypocalcemia and hyperphosphatemia (Case 2). Three patients had less than 90 mL/min/1.73 m^2 eGFR at the end of the follow-up period (Case 2, Case 3.1, Case 3.2). Selected biochemical laboratory data of patients with FHHNC are summarized in Table II.

At the time of diagnosis, five patients had sterile pyuria, three had low urine citrate levels. Selected urine analysis data of patients with FHHNC are summarized in Table III.

DISCUSSION

In this study, we evaluate seven pediatric patients from four different families diagnosed with FHHNC. In general, FHHNC occurs in childhood or before adolescence. While the incidence of FHHNC is unknown, it is one of the most frequent inherited tubulopathies and an important genetic cause of nephrocalcinosis which leads to chronic kidney disease (2,3). The consanguineous parents had a higher risk for FHHNC, and the clinical course of FHHNC is variable. Bilateral medullary nephrocalcinosis is one of the most important diagnostic clues for FHHNC, and nephrocalcinosis may also be accompanied by urolithiasis (1,13). Generally, initial clinical symptoms are usually mild and non-specific, and patients could present with urinary tract infection, hematuria, polyuria, polydipsia, abdominal pain, vomiting, and occasionally tetany (13).

Even though hypomagnesemia is one of the most common symptoms of FHHNC, 34% of patients had normal serum magnesium levels (13). Hypomagnesemia may diminish over time as CKD progresses, making FHHNC difficult to identify (14). It's important to remember that a normal blood magnesium

Table I: Demographic, genetic and extrarenal findings of the patients

	Case1.1	Case 1.2	Case 2	Case 3.1	Case 3.2	Case 3.3	Case 4
Age at Diagnosis	2 years	3 years	13 years	4 months	6 years	3 years	5 years
Gender	F	F	M	F	F	M	F
Consanguinity	+	+	-	+	+	+	-
Initial signs	Vomiting	-	UTI, Nephrolithiasis, Convulsion	UTI	-	-	Macroscopic Hematuria
Last BW (Percentile)	10-25	> 97	> 97	75	50	50	25-50
Last BH (Percentile)	75-90	> 97	10	75	75-90	75-90	25-50
Follow-up period (Years)	10	6	2	9	1.5	1.5	1
Genetic analysis	CLDN16 c.647G>A p.Arg216His Homozygous	CLDN16 c.647G>A p.Arg216His Homozygous	CLDN19 c.269T>C p.Leu90Pro Homozygous	CLDN16 c.211A>G p.Met71Val Homozygous	CLDN16 c.211A>G p.Met71Val Homozygous	CLDN16 c.211A>G p.Met71Val Homozygous	CLDN19 c.269T>C p.Leu90Pro Homozygous

***F:** Female, **M:** Male, **UTI:** Urinary Tract Infectious, **BW:** Body Weight, **BH:** Body Height*

Table II: Selected biochemical laboratory data of patients with familial hypomagnesemia with hypercalciuria and nephrocalcinosis

	Gender	Creatinine (mg/dL)		eGFR (ml/min/1.73 m^2)		Magnesium (mg/dL)		Calcium (mg/dL)		Phosphorus (mg/dL)		PTH (pg/mL)		25-OH Vitamin D (ng/mL)		Treatment
		First	Last	First	Last	First	Last	First	Last	First	Last	First	Last	First	Last	
Case 1.1	F	0.3	0.69	155	116	1.2	1.7	10	9.1	4	4.9	90	152	17	12.7	Mg, potassium citrate, HCT
Case 1.2	F	0.55	0.62	123	102	1.3	1.9	10	9.7	4.9	4.6	137	71	13.9	13	Mg, potassium citrate, HCT
Case 2	M	1.46	3.57	74	30.3	0.96	1.3	8.5	9.2	6.1	5.5	571	523	10	10.3	Mg, potassium citrate, HCT
Case 3.1	F	0.28	0.81	98	83	0.9	1.5	9.6	9.9	5.3	4.4	271	154	35	48	Mg, potassium citrate, HCT
Case 3.2	F	0.55	0.82	120	86	0.8	1.4	8.7	10.1	4.6	4.3	288	181	19	56	Mg, potassium citrate, HCT
Case 3.3	M	0.45	0.53	124	111	1.5	1.5	9.9	10.3	4.8	4.8	259	201	16	32	Mg, potassium citrate, HCT
Case 4	F	0.46	0.55	127	111	0.9	1.3	9.2	9.5	5.4	5.1	188	66	14	31	Mg, potassium citrate, HCT

***F:** Female, **M:** Male, **eGFR:** estimated Glomerular Filtration Rate, **PTH:** Parathormone, **HCT:** Hydrochlorothiazide*

level doesn't rule out FHHNC, and that high FEMg levels (> 4%) are more significant than low serum magnesium levels (13,14).

Furthermore, Sikora et al. (14) reported also hypocitraturia in 60% of patients with FHHNC. Hypercalciuria, hypocitraturia, and urinary acidification defects also reported as a cause of nephrolithiasis and hypomagnesemia as a cause of high PTH secretion which may maintain normocalcemia (15).

In our study, all patients had hypercalciuria and nephrocalcinosis with a male/female ratio of 2/5. One family had two affected siblings, and one family had three affected siblings. Three patients were asymptomatic and diagnosed because of their sibling's diseases. Three patients (42.8%) had hypocitraturia, two patients (28.6%) had urolithiasis. Hypomagnesemia was detected in six patients. One patient (Case 3.3) had normal serum magnesium level. High FEMg level was found in all children.

It is known that FHHNC frequently leads to renal failure during childhood or adolescence. Progressive renal impairment is correlated with tubulointerstitial nephritis and nephrocalcinosis (16). But the pathogenesis of renal function declines in patients with FHHNC remains unclear (17). The risk of CKD was reported to be high in patients with CLDN19 than in patients with CLDN16 mutations (8). Konrad et al. (17) have also reported a phenotype-genotype correlation regarding renal function decline in patients with CLDN16 mutations and Weber et al. (15) reported a median age for end-stage renal failure as 14.5 years. Extrarenal findings such as ocular abnormalities, hearing impairment and neurological manifestations are observed in patients with CLDN19 mutations (18). In addition, various nonspecific ocular abnormalities have also been reported in patients with CLDN16 mutations (19). Up to now, ocular abnormalities or hearing findings were not detected.

Table III: Selected urine analysis data of patients with familial hypomagnesemia with hypercalciuria and nephrocalcinosis at diagnosis

Patient number	Leucocyturia	Hematuria	24h UCa (mg/kg/day)	FEMg (%)	Ucitrate (mg/gr creatinine)
Case 1.1	-	-	12	4.55	510
Case 1.2	+	+	4.7	5.5	532
Case 2	+	+	5.2	16.5	80
Case 3.1	+	-	5.3	20.5	251
Case 3.2	-	-	11.2	39.7	94
Case 3.3	+	+	11.7	23.2	41
Case 4	+	+	7.4	13.9	289

24h UCa: *24-hour Urinary Calcium,* ***Ucitrate:*** *Urinary Citrate,* ***FEMg:*** *Fractional excretion of Magnesium*

Generally, treatment is supportive. Oral Mg and citrate supplementation, high fluid intake, dietary salt restriction and reduction of urinary Ca excretion with hydrochlorothiazide are some of these treatments (20). Zimmermann et al. (21) demonstrated that hydrochlorothiazide (HCT) is effective in reducing hypercalciuria due to CLDN16 mutation. In our patients, hypercalciuria was treated with HCT and three patients were normocalciuric under HCT therapy during the follow-up period. Six of our patients had low serum magnesium levels at the time of diagnosis. Despite magnesium supplementation, three patients continued to have low serum magnesium levels at their final visits. Sikora et al. (14) reported that only 20% of their patients reached normal serum magnesium levels with magnesium supplementation.

In our patients, renal failure was detected in one patient (with CLDN19 mutation) at the time of diagnosis and in 3 patients at the end of the follow-up period (one with CLDN19, two with CLDN16 mutation). It has been reported that in FHHNC patients, chronic kidney disease frequently occurs beyond the first decade of life, and more than 50% progress to kidney failure within the second or third decade of life. However, some patients, particularly those with CLDN19 mutations, require kidney replacement therapy (dialysis or transplant) during the first decade of life (13).

It is known that supportive treatment does not affect progression of renal failure in these patients and kidney transplantation is the only curative option for kidney failure (14). Therefore, early diagnosis of FHHNC is important to prevent morbidity and mortality. In conclusion, we would like to underline the importance of FHHNC awareness in children with nephrocalsinosis. Because a normal serum magnesium level does not rule out FHHNC, high FEMg (> 4%) values are more significant than low serum magnesium levels for the diagnosis.

Ethics Committee Approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by the Ethics Committee No. 2 of Ankara Bilkent City Hospital.(07.04.2021, reference number: E2-21-325).

Contribution of the Authors

AYDIN Z, ÇAYCI FS: collected and recorded the patients' data, were responsible for literature research, ***ŞAHİN İ, KONRAD M:*** performed the genetic analysis, ***ÇAYCI FS, AYDIN Z, İNÖZÜ M, BAYRAKÇI US:*** followed patients, ***ÇAYCI FS, AYDIN Z:*** took the lead in writing the manuscript. All authors discussed the results and contributed to the final manuscript. Funding This study was not supported.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Investigation of the role of irisin and FABP4 in iron deficiency anemia

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ABSTRACT

Objective: Anemia is defined as a condition in which the hemoglobin level is lower. Irisin (Ir) was a muscle-associated factor. Fatty acid-binding proteins (FABP) are involved in intracellular fatty acid transport. The study aimed to explore whether Ir and FABP4 levels might be linked to symptoms such as coldness, fatigue, and learning difficulties with Iron deficiency.

Material and Methods: Our study evaluated the effects of these three periods of iron deficiency, along with a control group, on serum and urine Ir, as well as FABP4 levels, both before and after iron treatment.

Results: In this study, median serum Ir levels exhibited statistically significant differences between the patient and control groups, with lower levels observed in the patient groups before treatment ($p=0.040$, $p<0.001$ and $p<0.001$). After treatment, a significant increase was noted in median serum Ir levels across all patient groups ($p=0.003$, $p=0.023$ and $p=0.014$).

Conclusion: In our study, we found that the feeling of coldness and decreased cognitive functions seen in iron deficiency may be related to serum Ir level.

Keywords: FABP4, Irisin, Iron deficiency, Iron deficiency anemia

INTRODUCTION

Anemia is clinically defined as a hemoglobin (Hb) level falling below two standard deviations from the mean for age. It is a widespread condition, particularly affecting infants and children globally. Iron deficiency (ID) is the most common cause of anemia. Globally in 2019, 21% of children aged 6–59 months had mild anaemia, 18% had moderate anemia, and 1% had severe anaemia (1). The World Health Organisation (WHO) estimates that 293 million pre-school-age and 305 million school-age children are anemic, and more than 50% are thought to be iron deficient (2). Iron deficiency significantly impacts physical growth, brain development, and early learning, with the most profound effects observed during infancy and preschool years. (3, 4). Iron plays a crucial role in myelin synthesis. Iron is required for myelin production from oligodendrocytes for maturation and function acquisition (5). ID has negative effects on brain development, myelination, and the development of major dopaminergic pathways. Persistent ID has lifelong effects on intelligence and learning functions. If low iron status is not corrected during developmental age, IQ scores may decrease by approximately 5-10 points (6, 7).

Irisin (Ir) was discovered in 2012 to be a muscle-associated factor involved in inducing the browning of white adipose tissue (WAT). Irisin-related pathways are known to be activated by peroxisome proliferator-activated receptor (PPARγ), peroxisome proliferator-activated receptor gamma coactivator 1-alpha coactivator (PGC-1α), and its release is increased by exercise. Irisin is a newly discovered peptide hormone released by proteolysis of FNDC5 protein in circulation (8, 9). Irisin is mainly responsible for the browning of WAT and the release of uncoupling protein-1 (UCP1). UCP1 exerts its effect by increasing total energy expenditure through thermogenesis (10). Irisin levels are thought to be determinant in fat storage and metabolic dysfunction (11).

Fatty acid binding proteins (FABPs) are chaperones involved in intracellular fatty acid transport, regulate lipid responses in cells, and are also linked to metabolic and inflammatory pathways.

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FABPs with a molecular weight of 14-15 kDa bind reversibly with high affinity to hydrophobic ligands such as saturated and unsaturated long-chain fatty acids, eicosanoids, and other fats. To date, nine FABP types have been identified (12, 13). FABP4 release is stimulated during adipocyte differentiation and by PPARγ receptor agonist transcription factors such as insulin, irisin, and fatty acids. Currently, FABP4 has been found to have roles in maintaining glucose homeostasis and energy storage systems. Irisin and FABP4 play a role in metabolic control. Irisin acts in metabolic control by providing thermogenesis with heat energy (14). Fatty acid binding protein-4 plays a role in metabolic events such as fatty acid storage, circulation, and glucose homeostasis, levels are increased in obese individuals (13, 15).

Iron deficiency anemia (IDA) patients tend to experience heightened sensitivity to cold compared to individuals with sufficient iron levels. While there are various theories regarding this phenomenon, the precise underlying cause remains unclear. The currently accepted view is that IDA results in impaired thermoregulation due to insufficiency of the thermoregulatory center, both in mice and humans. At the tissue level, ID is considered to impair the appropriate physiological response to cold because of impaired neurological control of the sympathetic nervous system (16). In addition, ID is thought to affect the ability of the endocrine system to respond to heat production and thermogenic tissues in response to cold (17). Thermogenesis capacity is impaired in ID. Brown adipose tissue (BAT) is a specialized form of adipose tissue characterized by multilocular fat droplets, high mitochondrial density, and abundant sympathetic innervation. After sympathetic stimulation in response to cold, the blood flow to BAT increases (18). Irisin browns WAT, while UCP-1 is released to release heat energy. We thought that the impaired thermogenesis capacity in ID may be due to the concomitant Ir deficiency. Iron deficiency is known to cause a variety of symptoms, but the etiology of these symptoms may not be fully understood. The study's objective is to explore whether Ir and FABP4 levels might be linked to symptoms such as feeling cold, fatigue, learning difficulties, and others in individuals with ID.

MATERIALS and METHODS

The study was conducted by the Department of Pediatric Hematology Oncology and the Department of Biochemistry, Faculty of Medicine, Fırat University. Ethical approval for this study was obtained from the Ethics Committee of Fırat University (02/ 24.03.2015), and informed consent was secured from all participants or their caregivers. This study evaluated ID across three stages, analyzing their effects on serum and urine levels of Ir and FABP4. The diagnosis of the 3 periods of ID was made according to the following laboratory values (19, 20).

1. ***Iron deficiency:*** In ID anemia is not seen, and iron stores are decreased. Serum iron, Hb, serum iron binding capacity (SIBC), and transferrin saturation (TS) are normal, but the ferritin level is <12 ng/mL.
2. ***Latentiron deficiency without anemia (LID):*** There is no anemia, iron stores are depleted and Hb is at the lower limit. Erythrocyte distribution volume and SIBC level increase, serum iron levels decrease, TS is <16% and ferritin level is <12 mL.
3. ***Iron deficiency anemia:*** Hypochrome microcytic anemia has developed. Hb and serum iron decrease, TS is <16% and ferritin level is <12 ng/mL.

In our study, a total of 60 patients from these 3 periods (20 patients diagnosed with ID, 20 patients diagnosed with LID, and 20 patients diagnosed with IDA) were included. In the control group, there were 20 patients with normal iron parameters and no iron deficiency or anemia. Oral iron treatment was started after the diagnosis of ID, LID, and IDA. Patients were administered iron treatment in the form of ferrous iron (Ferro Sanol®) at a dosage of 3-6 mg/kg/day, given 2-3 times daily for 3 months. Blood and urine samples were collected from individuals receiving iron treatment, both immediately before the initiation of the treatment and 3 months later. Additionally, samples were collected from the control group once for comparison. For the diagnosis of IDA, standard diagnostic procedures were followed for all patients presenting for diagnosis and treatment. This included obtaining a complete blood count (CBC), peripheral smear, reticulocyte count, serum iron levels, SIBC, and ferritin levels, as routinely performed in clinical practice. These tests collectively help in assessing various parameters related to red blood cell production, iron levels, and iron storage, aiding in the accurate diagnosis and treatment of iron deficiency anemia. Serum and urine Ir and FABP4 levels were analyzed in the patient group before and after treatment. In the control group, only serum and urine Ir and FABP4 levels were analyzed at baseline. Samples were studied as described in the manufacturer's catalog (Human (irisin) catalog no: 201-12-5328, Human (FABP4) catalog no: 201-12-2037 and manufactured at Awareness Technology, Inc. Palm City, Florida, USA). At the end of the study, the samples were read at 450 nanometres with a ChroMate microplate (ChroMate 4300 Florida, USA) reader.

Patients who were not included in the study; Patients with chronic infection, Patients who developed an allergic reaction with iron therapy or had a history of such a reaction, Patients who used any iron preparation before the study,Patients using vitamins.

Statistical analysis:

All data were analyzed using SPSS version 22.0 (IBM, Chicago, IL, USA). Median and interquartile range (IQR) values were given for non-normally distributed variables. Wilcoxon test was used for the comparison of ranks, Mann-Whitney U test was used for the comparison of two independent groups, and chi-square test was used for comparison of percentages.

Kruskal-Wallis test was used for the comparison of more than two independent groups when the data did not meet the assumptions of normality. A value of p<0.050 was considered statistically significant.

RESULTS

Female gender accounts for 41 patients, representing 51.25%. It is appropriate to give the genders of the patient and control groups separately. There is no statistically significant difference in terms of age and gender between the groups. Demographic characteristics of the patients are shown in Table I. The anthropometric measurements of the patients before and after treatment are given in Table II. Post-treatment comparisons revealed significant increases in Hb, hematocrit, and ferritin levels across all patient groups (Table III). The median serum Ir levels in our study revealed statistically significant differences between the patient groups (ID, LID, IDA) and the control group, with lower levels observed in the patient groups before treatment (p=0.040, p<0.001 and p<0.001, respectively) (Table IV). A statistically significant increase was found in the median serum Ir levels in all patient groups after treatment (p=0.003, p=0.002 and p=0.014). When urine Ir levels were analyzed, an increase in urine Ir levels was found in the ID and IDA groups and a decrease in the LID group after treatment, but these changes were not statistically significant (p=0.057, p=0.314 and p=0.387, respectively) (Table IV).

In our study, there was no statistically significant difference between the groups in serum FABP4 levels of the patients before and after treatment (p=0.423) (Table IV). After treatment, an increase was found in the mean serum FABP4 levels in the ID and LID groups, whereas a decrease was found in the IDA group, but these changes were not statistically significant (p= 0.681, p=0.709, and p= 0.514, respectively) (Table IV). In our study, there was no statistically significant difference between the groups in urinary FABP4 levels before and after treatment (p= 0.083, p=0.247, and p=0.135, respectively).

DISCUSSION

Iron deficiency anemia is an important public health problem in developing countries. The etiology of some of the symptoms seen in ID has not been elucidated. Especially within the scope of our study, we hypothesized that the sensation of coldness in IDA may be linked to decreased Ir levels, based on its known role in thermogenesis through WAT browning (21, 22). Irisin and FABP4 are peptide-structured hormones involved in both energy metabolism and thermoregulation processes (17). As known, iron acts as a cofactor in the enzymes required for energy metabolism, participating in thermoregulation processes. Therefore, we believe that there may be a connection between iron and these two hormones.

In our study, we found that the basal serum Ir levels of ID, LID, and IDA groups were statistically low compared to the control group (p<0.050). Ir, which is known to be synthesized in almost all biological tissues, leads to heat energy production instead of ATP synthesis by increasing UCP-1 proteins (9). An increase in the amount of Ir in biological fluids may be associated with

Table I: Demographic characteristics of the patients

	Control	ID	LID	IDA	p
Age*	8.5 (3.5-13.5)	5.5 (2.5-14.5)	9 (2.5-14)	10.5 (3.75-15.5)	0.090*
Gender†					
Female	11 (55)	9 (45)	9 (45)	12 (60)	0.717†
Male	9 (45)	11 (55)	11 (55)	8 (40)	

:** *median (IQR),* **†:** *n(%),* **‡:** *Kruskal Wallis test,* **ǁ:** *Chi-square test,* ***ID: *Iron depletion,* ***LID:*** *Latent Iron Deficiency,* ***IDA:*** *Iron Deficiency Anemia*

Table II: Demographic characteristics and anthropometric values of the patients before and after treatment

	Control*	ID*	LID*	IDA*
Age				
Before	8.5 (3.5-13.5)	5.5 (2.5-14.5)	9 (2.5-14)	10.5 (3.75-15.5)
Body weight (kg)				
Before	24.5 (13.25-44.5)	18.75 (14-45.75)	32.5 (12.2-56.2)	30 (13.25-52)
After		20.5 (14.6-46)	33 (13.75-56.25)	31.6 (14.72-52.5)
Height (cm)				
Before	124.5 (90.5-152.5)	111 (88-161.5)	139.5 (87.25-159.25)	140 (96.75-158.75)
After		113 (89.5-160.7)	141 (90.25-160.25)	142.5 (98.05-159)
Weight (percentile)				
Before	48 (35-56)	51 (10.25-73.25)	67 (19.25-79)	41 (17.75-57)
After		50 (12.75-77.5)	64.5 (25-80)	44.5 (27.5-60.5)
BMI (kg/m^2)				
Before	16.4 (15.55-18.7)	16.8 (15.27-18.15)	18.65 (14.37-20.37)	16.5 (14.37-20.37)
After		17.1 (15.52-21.12)	18.05 (15.97-18.22)	16.95(15.35-20.17)

:** *median (IQR),* ***ID: *Iron depletion,* ***LID:*** *Latent Iron Deficiency,* ***IDA:*** *Iron Deficiency Anemia*

Table III: Changes in laboratory values of the patients before and after treatment

	Control*	ID*	LID*	IDA*	p†
Hemoglobin (g/dL)					< 0.001‡
Before	13.25 (12.42-13.87)	12.5 (12.2-12.95)	12.6 (12.1-12.97)	9.4 (8.3-11)	0.001‖
After		12.9 (12.52-13.65)	13.25 (12.77-13.92)	12.5 (12-13.1)	< 0.001§
Hematocrit (%)					0.005‡
Before	39.55 (36.62-42.67)	36.9 (35.82-39.3)	37.85 (36.4-39.6)	30.35 (27.85-34.37)	0.002‖
After		38;95 (37-40.6)	40.05 (38.05-42.45)	38.1 (35.22-40)	< 0.001§
MCV (f/L)					0.066‡
Before	81 (78.25-87.5)	81.5 (78.25-85)	79 (77.4-83.4)	62 (59.2-70.3)	0.042‖
After		82.8 (78.5-87.25)	81.2 (79.47-83.75)	77.5 (73.7-82.5)	< 0.001§
RDW					0.053‡
Before	14.6 (13.55-16)	14.25 (13.25-16.65)	14.8 (14.2-16.3)	19 (16.92-21.92)	0.008‖
After		14.25 (12.97-15.2)	14.25 (12.97-15.2)	13.5 (12.62-14.15)	< 0.001§
Ferritin (ng/dL)					< 0.001‡
Before	36.5 (26.3-49.62)	8.5 (6.4-10.6)	9 (7.65-11)b.e	2.75 (1.47-6.6)	< 0.001‖
After		19 (15.22-32.25)	20 (17.85-38.05)	32 (18.92-48)	< 0.001§
Serum Iron (µg/dL)					0.896‡
Before	82 (71.5-119.5)	79 (74.25-105)	30.5 (18-39.5)	21 (16.25-28.5)	< 0.001‖
After		84 (73.25-89.5)	67.5 (57.5-74.75)	67 (56.5-87.5)	< 0.001§
SIBC (µg/dL)					< 0.001‡
Before	341 (314-376.75)	372 (339-389.75)	349 (327.75-404.5)	381.5 (343.75-421)	0.007‖
After		341 (314-376.75)	372 (339-389.75)	349 (327.75-404.5)	< 0.001§
Transferrin Saturation					0.117‡
Before	29 (22-37.5)	21 (19.02-28)	8.5 (5-11)	6.05 (5-7.97)	< 0.001‖
After		24.45 (21-29.7)	21.35 (17.07-28.82)	25.15 (20.4-28.75)	< 0.001§

**: median (IQR), †: Comparison between before and after treatment (Wilcoxon Test), ‡: ID (Iron depletion), ‖: LID (Latent Iron Deficiency), §: IDA (Iron Deficiency Anemia).*

increased heat production in the body. Ir is considered a hormone that regulates energy expenditure and promotes the conversion of WAT to BAT. In this context, elevated levels of Ir in biological fluids may contribute to increased thermogenesis and heat production in the body. There are factors outside the hypothalamus that influence thermogenesis in our body, and Ir is one of these pathways. Ir increases the expression of a protein called UCP1 in white fat cells. UCP1 stimulates thermogenesis by converting energy into heat in the mitochondria of the cell. This process redirects energy towards heat production rather than the normal function of energy storage in WAT. We observed decreased levels of Ir in cases of diminished iron, even in the absence of anemia. Furthermore, there was an elevation in serum Ir levels following iron therapy. Based on this mechanism, we hypothesized that increased cold sensitivity in individuals with iron deficiency (ID) might be associated with reduced irisin levels. In cases of ID, symptoms such as fatigue and weakness often emerge, leading to decreased physical activity and slower movements. This reduction in activity may be due to lower levels of irisin, a myokine predominantly secreted by skeletal muscles. Previous studies have demonstrated a positive correlation between physical activity and irisin levels. In the present study, an increase in irisin levels was observed following iron supplementation, suggesting that the improvement in fatigue and weakness associated with iron deficiency might be linked to this increase in irisin levels. This recovery process appears to support the normalization of physical activity in affected children. The treatment of iron deficiency not only alleviates these debilitating symptoms but also enhances energy levels, thereby supporting a more active and healthier lifestyle. Consequently, we propose that the treatment of iron deficiency, through increased physical activity, may indirectly lead to a rise in irisin levels via this mechanism.

In other studies, the correlations of Ir and FABP4 serum and urine levels with anthropometric measurements were analyzed. In our study, we observed no correlation between the levels of serum and urine Ir and FABP4 and gender, as well as anthropometric measurement data. Similarly, Liuliu et al. (23) and Moreno et al (24) found no relationship between Ir concentrations and gender. However, Al-Dalghri et al. (25) in a cohort study of 153 Saudi Arabian children found that circulating Ir levels in the blood were higher in girls than in boys. Siahanidou et al. (26) found no significant correlation between FABP4 levels and gender, body weight, height, and BMI, but Ibarretxe et al. (27) found high FABP4 levels in females in a study (25).

In our study, we also investigated urine samples to establish a potential link between Ir and ID using a simpler and non-invasive approach. However, we did not find any correlation between the levels of Ir in serum and urine samples. On the other hand, no difference was observed in the changes in urine depending on the treatment, and the possible reason for this was thought to be that there was no correlation between the circulating level of Ir and its excretion from urine.

As it is known, decreases in neurocognitive functions such as attention deficit, learning difficulties, behavioral disorders,

Table IV: Comparison of Ir and FABP4 levels before and after treatment

	Control*	ID*	LID*	IDA*	p†	p‡	p‖	p§	p¶
Serum									
Ir Before Treatment(ng/dL)	43.02 (32.88-60.02)	34.09 (32.19-38.10)	23.64 (20.35-33.65)	24.37 (19.53-29.83)	0.002	0.808	< 0.001	0.003**	0.040**
Ir After Treatment (ng/dL)		36.78 (32.38-41.44)	26.28 (20.56-32.89)	25.05 (22.32-32.19)	0.001	0.766	< 0.001	0.0023†,	< 0.001†,
Urine								0.014‡‡	< 0.001‡‡
Ir Before Treatment (ng/dL)	20.64 (18.93-26.98)	22.5 (20.44-25.16)	24.66 (24.12-26.61)	21.97 (19.9-23.13)	-	-	-	0.057**	-
Ir After Treatment (ng/dL)		25.72 (20.69-29.45)	24.28 (23.11-26.10)	22.91 (19.28-23.57)				0.314†,	
								0.387‡‡	
Serum								0.682**	0.808**
FABP4 Before Treatment (ng/dL)	21.64 (18.06-29.72)	20.02 (10.09-32.98)	12.81 (7.79-31.81)	26.5 (12.27-38.94)	o.433	0.068	0.181	0.709†,	0.607†,
FABP4 After Treatment(ng/dL)		22.35 (7.78-34.82)	12.99 (10.13-33.2)	18.83 (8.19-37.89)	0.579	0.204	0.570	0.514‡‡	0.194‡‡
Urine								0.083**	-
FABP4 Before Treatment (ng/dL)	10.44 (8.93-12.19)	12.79 (7.41-15.41)	11.5 (8.82-15.41)	13.74 (11.8-14.88)13.34 (11.36-13.93)	-	-	-	0.247†,	
FABP4 After Treatment (ng/dL)		14.43 (10.23-15.69)	12.18 (10.7-14.31)					0.135†,	

**: median (IQR), †: Comparison between ID and LID (Mann-Whitney U test), ‡: Comparison between LID and IDA (Mann-Whitney U test), ‖: Comparison between ID and IDA (Mann-Whitney U test), §: Comparison between before and after treatment (Wilcoxon Test), ¶: Comparison between control, **: ID (Iron depletion), †: LID (Latent Iron Deficiency), ‡‡: IDA (Iron Deficiency Anemia)*

decreased perceptual functions, and retardation in motor and mental development tests are observed in ID. Studies in school children have shown that learning and various developmental tests are impaired in ID with or without anemia, but learning difficulty may improve with iron treatment (28). In our study, it was thought that the decline in cognitive functions might be related to Ir, which is known to be released from all biological tissues. FNDC5/irisin has been shown as a new therapeutic factor that can improve cognition, learning, and memory function (29). FNDC5 has been found to reduce some factors that provide neuronal destruction, and it has also been found that FNDC5 administration with adenovirus increases neuroprotective factors (30, 31). Moon et al. (32) found that Ir at pharmacological concentrations increased STAT3 levels in H 19-7 hippocampal neuronal cells and STAT3 levels in mice, and low levels of Ir decreased differentiation in neuronal functions in mouse embryonic stem cells. Low levels of Ir in serum have been shown to reduce the level of FNDC5, an Ir precursor in the human brain. A direct relationship has been shown in hippocampal neurogenesis. Dun et al. (33) showed in another immunohistochemical study that Purkinje cells in rats and mice expressed Ir and also FNDC5 in recent days. It is known that the hippocampus is a critical region in learning and memory formation, and is a very important structure in spatial memory formation. According to our current knowledge, the cellular and molecular mechanisms of learning and memory formation are explained by long-term potentiation (LTP) in the hippocampus (34). Since Ir and hippocampus are especially related to learning, we think that decreased Ir level in ID may be related to the decrease in cognitive functions seen in ID. In addition, the fact that these symptoms are reversible with iron supplementation suggests that they may be directly related to the increased Ir level after iron treatment.

CONCLUSION

In our study, we found that the feeling of coldness and decreased cognitive functions seen in iron deficiency may be related to serum Ir level. Today, IDA is an important public health problem and affects many systems. Additional studies are needed to clarify the pathophysiology of its effects on different systems.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Firat University Ethics Committee (24.03.2015/02).

Contribution of the authors

Selmanoğlu A: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study,

Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***Akarsu S:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***Aydın S:*** Constructing the hypothesis or idea of research and/or article, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Brain magnetic resonance imaging findings and their relationship with prognosis in children with focal epileptic encephalographic discharges

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ABSTRACT

Objective: This study aimed to evaluate the relationship between normal brain magnetic resonance imaging (MRI) findings and prognosis in children with focal epileptic disorder on electroencephalography (EEG) without an epileptic syndrome.

Material and Methods: Data from patients aged 0-18 years, who were followed up with a diagnosis of epilepsy at the pediatric neurology clinics over the last 5 years, were retrospectively reviewed. Patients with focal epileptic disorder on EEG were selected. Those with an epileptic syndrome were excluded from the study. The patients' demographic characteristics, seizure types, etiologies, brain MRI findings, seizure focus, treatment methods, and seizure control were analyzed. Patients were divided into two groups based on their brain MRI findings (normal and abnormal) and compared in terms of treatment resistance, number of medications, and seizure control.

Results: The mean age of the 100 patients included in the study was 8±4.32 years, with an equal gender distribution (50% female, 50% male). Generalized seizures were observed in 72% of patients, while 28% had focal seizures. Seizure freedom was achieved in 60% of cases, and treatment resistance was noted in 23%. Cranial MRI revealed structural abnormalities in 67% of patients, with the majority (84%) showing sequelae-related changes, including hypoxic-ischemic sequelae (16%), encephalomalacia (12%), and structural malformations (10%). Although treatment resistance (28.8% vs. 12.1%) was higher and seizure freedom (56.7% vs. 66.7%) was lower in patients with abnormal MRI findings compared to those with normal MRI, these differences were not statistically significant (p =0.150 and p=0.310 respectively) . However, perinatal (p=0.013) and postnatal complications (p=0.042) were significantly more frequent in patients with abnormal MRI findings.

Conclusion: In children with focal epileptic disorder on EEG, normal brain MRI findings do not predict a better prognosis in terms of seizure control and treatment resistance. Other factors affecting treatment resistance in this population need to be investigated in more detail.

Keywords: Child, Epilepsy, Magnetic Resonance Imaging

INTRODUCTION

Epilepsy is a common neurological disorder that requires a precise understanding of its underlying etiology to guide appropriate management and improve patient outcomes. Identifying the cause of seizures is crucial, as it directly influences treatment decisions and prognosis. Key prognostic factors include etiology, EEG abnormalities, seizure type, the number of seizures before treatment initiation, and the early response to medication (1). Cranial magnetic resonance imaging (MRI) is the preferred imaging modality for assessing epilepsy, given its high sensitivity in detecting structural abnormalities that may contribute to epileptic activity. Common structural etiologies identified on MRI include cortical malformations, gliotic changes, and other focal lesions. However, epilepsy can also result from nonstructural causes, and in some cases, the etiology remains unknown despite comprehensive evaluations (2).

In pediatric epilepsy, interictal focal discharges observed on EEG are strongly associated with focal structural abnormalities on MRI. These findings highlight the complementary role of EEG and MRI in the diagnostic evaluation of epilepsy. However, some patients with focal epileptiform EEG activity have normal MRI findings, raising questions about the underlying mechanisms and their impact on clinical outcomes. Determining whether

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the presence or absence of structural abnormalities influences seizure control, treatment response, or long-term prognosis is essential for optimizing patient management.

Since epilepsy prognosis is closely related to its etiology, the use of MRI is expected to provide valuable insights into the likelihood of achieving seizure freedom and the potential risk of breakthrough seizures, due to its strong ability to determine the underlying cause (3,4).

Symptomatic etiology has traditionally been considered a negative predictor in epilepsy (1). However, little information is known about how patient characteristics and treatment patterns in those with lesional epilepsy compare to those with nonlesional epilepsy. Moreover, recent findings suggest that the distinction between lesional and functional (or non-lesional) epileptogenesis is becoming increasingly less clear (5). This challenges the expectation of significant prognostic differences between the two groups.

This study aimed to assess the prognostic significance of cranial MRI findings in children with focal epileptiform EEG activity. By analyzing differences in seizure control, treatment response, and long-term outcomes between patients with normal and abnormal MRI findings, it was aimed aim to provide clinically relevant insights to improve patient care and management in clinical practice.

MATERIALS and METHODS

The medical records of pediatric patients (0–18 years) diagnosed with epilepsy were retrospectively reviewed from the pediatric neurology outpatient clinic. The study was conducted between 2018 and 2021. A total of 100 patients were included in the study. The study included patients who had undergone both cranial MRI and EEG. Only those diagnosed with nonsyndromic epilepsy and exhibiting focal epileptiform discharges on interictal EEG were included, while patients with generalized epilepsy, syndromic epilepsy, or incomplete data were excluded.

Data extracted from medical records included patient age, gender, perinatal and postnatal complications, history of febrile seizures, prolonged febrile seizures, family history of epilepsy, epilepsy duration, age at seizure onset, seizure types, seizure control, treatment resistance, number of antiseizure medications used, physical examination findings, EEG findings, and cranial MRI results. Based on MRI findings, patients were classified into two groups: those with structural abnormalities and those with normal MRI results (non-structural). Seizure control and treatment resistance were compared between these two groups.

Perinatal problems were defined as conditions that affect development, including premature birth, low birth weight, birth trauma, neonatal infections, respiratory issues, hypoglycemia, hyperbilirubinemia, and congenital anomalies in infants. In mothers, perinatal problems included gestational diabetes, preeclampsia, bleeding, infections, amniotic fluid abnormalities, and early rupture of membranes. Postnatal problems were defined as conditions such as hyperbilirubinemia, encephalitis, meningitis, sepsis, septic shock, neonatal stroke, and asphyxia (including drowning or foreign body-related issues).

EEG recordings were conducted using an 18-channel system, with electrodes placed according to the international 10-20 system. The EEG data were interpreted by two neurologists.

Seizure types were classified as focal or generalized. Treatment resistance was defined as the persistence of seizures despite treatment with at least two antiepileptic drugs (AEDs) at appropriate doses.

Seizure control was defined as the absence of seizures for at least six months.

Treatment resistance in epilepsy is defined as the failure to achieve sustained seizure control despite adequate trials of at least two antiepileptic drugs (AEDs) administered at appropriate doses and for an adequate duration (6).

Statistics analysis:

Statistical analyses were conducted IBM Statistical Package for the Social Sciences, version 23.0 (SPSS Inc., Armonk, NY, IBM Corp., USA). Normality of the data was assessed using the Kolmogorov-Smirnov test. Parametric data were presented as mean and standart deviation values, while categorical variables were expressed as frequency and percentages. The Chi-square test was employed to compare categorical data. Comparisons between groups were made using independent samples t-test and Mann-Whitney U-test. A significance level of $p < 0.050$ was considered statistically significant.

Ethics committee approval was received from the KTU University Clinical Research Ethics Committee dated 27.12.2017-2017/2. The study has been conducted in accordance with the Helsinki Declaration.

RESULTS

General data of patients

A total of 418 patients diagnosed with epilepsy were reviewed. Of these, 318 patients who did not meet the inclusion criteria or had insufficient data were excluded from the study, leaving 100 patients with focal epileptic activity on EEG. The mean age of the patients was 8±4.32 years, with an equal gender distribution of 50% female and 50% male.

Among the patients, 29% had prenatal features, while 27% exhibited postnatal characteristics. Febrile seizures were reported in 21% of the patients, with 4% experiencing prolonged febrile seizures, and 13% having a family history of epilepsy.

Regarding seizure types, 72% had generalized onset seizures, while 28% had focal onset seizures, including 17% with focal

Table I: Comparison of clinical and demographic characteristics between patients with structural and non-structural MRI findings

	Structural n=67 (%)	Non-structural n=33 (%)	p
Age (mean months)	48.14±4.6	55.07±3.8	0.261*
Gender (F/M)8	32/34	18/16	0.834†
Perinatal problem	26 (38.8)	3 (9.1)	0.013†
Postnatal problem	23 (34.3)	4 (12.1)	0.042†
Febrile seizure	11 (16.4)	10 (30.3)	0.142†
Prolonged febrile seizure	3 (4.5)	1 (3)	1.000†
Epilepsy in Family	9 (13.4)	4 (12.1)	1.000†
Age of first seizure ≤5 >5	 52 (77.6) 15 (22.4)	 19 (57.6) 14 (42.4)	0.131†
Focal Seizure	21 (31.3)	7 (21.2)	0.214†
Epilepsy duration m (mean)	53.5	45.06	0.170†
Treatment resistance	19 (28.8)	4 (12.1)	0.150†
Seizure control with one ASM	34 (50.7)	23 (69.7)	0.060†
Seizure freedom	38 (56.7)	22 (66.7)	0.310†

:** *Independent samples t-test.* **†:** *Chi-square test,* ***ASM: *Anti-seizure medicine,* ***F:*** *female,* ***M:*** *male,* ***m:*** *month,* ***MRI:*** *Magnetic Resonance Imaging*

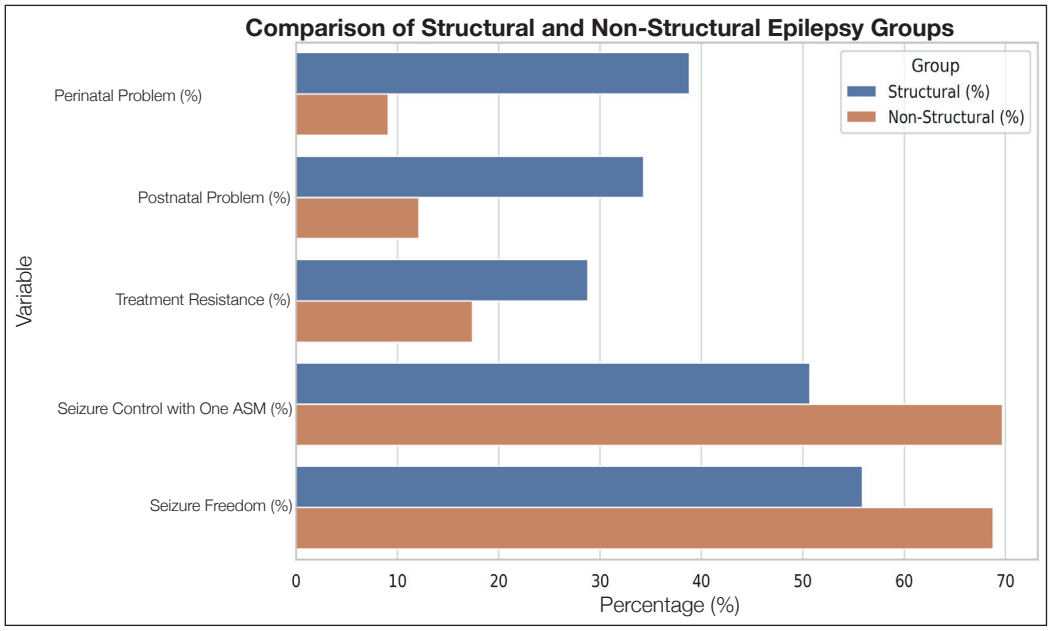

Figure 1: Comparison of structural and nonstructural epilepsy groups.

onset and awareness, 8% with focal onset and impaired awareness, and 3% with focal to bilateral tonic-clonic seizures.

Seizure freedom was achieved in 60% of the patients, while 9% experienced daily seizures, 4% had seizures weekly, 6% monthly, and 21% less frequently than once a month. Treatment resistance was observed in 23% of the patients, and treatment was discontinued in 4%.

Regarding antiseizure medication, 53% of patients were on monotherapy, 23% on dual therapy, 12% on triple therapy, and 8% on more than three medications. Valproic acid was the most commonly prescribed drug in monotherapy (24%), followed by carbamazepine (10%) and levetiracetam (10%).

Frontal lobe seizures were reported in 18% of patients, temporal lobe seizures in 15%, occipital lobe seizures in 5%, and parietal lobe seizures in 3%. However, seizure localization could not be determined in 59% of patients.

Comparison of structural and nonstructural groups

Imaging results revealed normal findings in 33% of patients. Among the remaining 67%, cranial MRI identified sequelae of hypoxia in 16%, encephalomalacia in 12%, structural

malformation in 10%, sequelae of hypoglycemia in 8%, gliosis in 6%, cerebral atrophy in 3%, infarcts in 2%, arachnoid cysts in 2%, cortical dysplasia in 2%, and sequelae of encephalitis in 2%. Additionally, other causes, including mesial temporal sclerosis, hemorrhage, tuberous sclerosis-associated hamartomas, and sequelae of kernicterus, were identified in 4% of cases.

There were no significant differences between the structural and nonstructural groups in terms of mean age, gender distribution, history of febrile seizures, history of prolonged febrile seizures, age at first seizure, presence of focal seizures, duration of epilepsy, or family history of epilepsy. In the nonstructural group, treatment resistance was lower, and seizure control with a single antiseizure medication (ASM) and seizure freedom was higher, but these differences were not statistically significant (Figure 1, Table I). Perinatal and postnatal problems were found to be statistically significantly more common in the group with cranial MRI abnormalities (Table I). Of the 33 patients with normal cranial MRI, 10 underwent high-resolution 3 Tesla cranial MRI due to persistent focal findings on EEG. Cortical dysplasia was detected in one patient, while the others had normal imaging results.

DISCUSSION

The study suggests that MRI findings may not be reliable predictors of prognosis in focal nonsyndromic epilepsy. No significant differences were observed between patients with and without MRI abnormalities in terms of treatment resistance, number of antiepileptic drugs, or seizure control. However, it is important to note that the p-value for seizure control with one antiseizure medication (ASM), which was $p = 0.060$, approached statistical significance and should be interpreted cautiously. Comparing MRI findings was essential to evaluate whether MRI, as the initial diagnostic tool, could offer insights into prognosis and treatment resistance. The results indicate that treatment resistance can persist in focal nonsyndromic epilepsy, even in the absence of MRI abnormalities. This may point to functional impairments that are not detectable by MRI in non-idiopathic focal epilepsies. Further functional studies using advanced imaging techniques, such as 3 Tesla MRI or functional MRI, are needed to investigate this possibility.

Treatment resistance was observed in 23% of all patients, with 28.8% in the group with cranial MRI findings and 17.4% in the group without. Park et al. (7) reported a higher treatment resistance rate of 40%, primarily in patients with structural brain abnormalities, such as hippocampal sclerosis and cortical malformations. This difference may reflect the impact of structural lesions on treatment outcomes, as patients with such conditions often show poorer seizure control. In contrast, our study suggests that patients without significant structural abnormalities may have a more favorable response to treatment, although this difference was not statistically significant. Given the borderline nature of the results, further research with larger sample sizes would be required to clarify whether these trends represent true effects. The treatment response, measured as seizure freedom, was found to be 68.6% in the structural group and 55.9% in the nonstructural group. In lesional epilepsy, the literature reports treatment response rates (seizure freedom) ranging from 24% to 60% (8,9). Several studies have linked treatment response to anomalies during early brain maturation, the nature of the underlying pathology, and the presence of detectable electrophysiological abnormalities in lesional epilepsy (7,8). The variations in response rates between studies may be attributed to differences in study design, borderline p-values in some cases, and the underlying etiology of epilepsy. This emphasizes the need for caution in interpreting findings from studies with small sample sizes or borderline statistical results.

In epilepsy, predictors of treatment resistance and poor prognosis typically include the presence of focal epilepsy and brain lesions (9,10). Based on this, it was expected that patients with focal epilepsies and normal MRI results would show lower treatment resistance and higher rates of seizure freedom. However, the findings of this study contradict this expectation. The existing literature on the prognosis of focal epilepsies is limited and often focuses on specific etiologies or surgical patient cohorts (11-13). For example, a cohort study of 64 patients undergoing surgery for focal epilepsy found that MRI status was a predictor of seizure freedom in a predictive model for drug-resistant focal epilepsy surgery patients (14). In contrast, a study involving 245 epilepsy cases revealed that cranial MRI identified an etiology in 62.8% of cases, but no difference in treatment response was observed between MRI-positive and MRI-negative groups (15). Furthermore, a study on MRI-negative patients undergoing epilepsy surgery found that one to two-thirds of resected specimens showed specific pathological lesions associated with epileptogenicity (16). These findings align with our study's observation that there was no significant difference in treatment resistance or seizure control between MRI-negative and MRI-positive groups.

Epilepsy is one of the most common neurological disorders, with focal seizures being the most prevalent type in childhood (17). Among focal seizures, focal impaired awareness seizures are the most frequent, accounting for 36% of all seizures (18). However, in our study, the rate of focal awareness seizures was lower, at 8%. This discrepancy may be attributed to the exclusion of patients with specific epileptic syndromes and combined focal and generalized epilepsy, as well as the selection of patients based on EEG findings rather than seizure type.

In our study, 70% of patients with focal nonsyndromic epilepsy exhibited generalized seizures. It is important to note that generalized motor symptoms can present in children with focal epilepsy (19). The higher rate of generalized seizures in our study may be due to inadequate seizure descriptions and limited observation of seizure onset. Moreover, focal interictal abnormalities can sometimes mimic focal epilepsy in patients with generalized epilepsy (18). Studies have shown that focal interictal abnormalities are present in 14% to 56% of patients

with generalized epilepsies, such as juvenile myoclonic epilepsy (19). However, we excluded patients with diagnoses of specific epileptic syndromes or those who showed generalized discharges on EEG.

Carbamazepine is generally the first-line treatment for focal epilepsy; however, in our study, valproic acid was the most commonly prescribed antiseizure medication. This may be due to the high prevalence of generalized seizures in our cohort, with some patients reporting focal seizures as generalized. Additionally, the safer side effect profiles of oxcarbazepine and levetiracetam compared to carbamazepine likely contributed to their increased use. These factors suggest a preference for broader-spectrum medications, but a better analysis of seizure type and patient characteristics is necessary for optimal treatment selection.

Temporal lobe seizures are generally reported to account for the majority (70%) of focal seizures, followed by frontal lobe seizures (20%) and seizures from other lobes (10%) (20). However, in our study, the most common seizures were frontal lobe seizures. This discrepancy in seizure distribution may stem from the selection of patients based on EEG and cranial MRI findings rather than seizure type. Additionally, the retrospective nature of our study, along with limited contributions from anamnesis data to seizure semiology, may have influenced the rates of diagnosis. In infants and children, EEG findings may not always identify the epileptogenic region due to factors such as brain immaturity, challenges in obtaining accurate medical history, and age-related differences in seizure presentation (21).

Among 10 patients with normal 1.5 Tesla cranial MRI but persistent focal abnormalities on EEG, follow-up 3 Tesla MRI revealed cortical dysplasia in one. Several studies highlight the superiority of 3 Tesla MRI (22). For instance, Sawaish et al. (23) identified a hippocampal lesion with 3 Tesla MRI that was undetected on 1 Tesla MRI. Similarly, Bachman et al. (24) demonstrated better lesion detectability with 3 Tesla compared to 1.5 Tesla in multiple sclerosis patients. However, a systematic review comparing 1.5 Tesla and 3 Tesla MRI suggests that while 3 Tesla MRI offers subjective improvements in lesion detection, finer anatomical details, and enhanced resolution, there is no conclusive evidence of increased diagnostic accuracy (25). Some studies have found that, despite the higher resolution and detailed imaging offered by 3T MRI compared to 1.5T MRI, there is no significant difference in diagnostic accuracy (26). Nevertheless, 3 Tesla MRI may offer practical advantages in certain cases. This suggests that while 3 Tesla MRI can provide enhanced imaging, its clinical benefit should be evaluated on a case-by-case basis.

Recent data suggest that functional imaging studies provide more informative insights than traditional MRI techniques in the evaluation of MRI-negative epilepsy. The role of functional imaging in detecting epileptogenic zones in patients with negative MRI results has become increasingly prominent. A comprehensive review discusses the integration of structural and functional imaging techniques, such as functional MRI (fMRI), single-photon emission computed tomography (SPECT), and positron emission tomography (PET), in the preoperative assessment of patients with drug-resistant focal epilepsy. The study emphasizes that in MRI-negative cases, these functional imaging modalities can identify hypometabolic or hyperperfused regions, aiding in the precise localization of the epileptogenic zone and improving surgical planning and outcomes (27). Multimodal neuroimaging has been shown to enhance the detection rate of structural and functional abnormalities, facilitating personalized treatment plans and improving diagnostic accuracy in the identification of the epileptogenic zone (28). These findings underscore the critical role of functional imaging in the comprehensive evaluation of patients with MRI-negative epilepsy, providing valuable insights that guide treatment decisions and ultimately improve patient outcomes.

CONCLUSION

Our study suggests that cranial MRI may not reliably predict prognosis in focal nonsyndromic epilepsy. Further large-scale studies are needed to determine whether patients with normal MRI findings have a better prognosis and to explore differences between those with and without MRI abnormalities. Future research should also include functional imaging to shed light on underlying mechanisms and improve prognostic predictions for this group, particularly those with refractory epilepsy.

Limitations

This study has several limitations that need to be acknowledged. First, the relatively small sample size may have limited the ability to detect significant differences in treatment resistance and seizure control between the structural and nonstructural groups, potentially affecting the robustness of the results. Additionally, the retrospective design of the study introduces certain biases, particularly due to reliance on patient history (anamnesis) for seizure type classification, rather than using video EEG, which may have compromised the accuracy of seizure type categorization. Another limitation is the imaging approach; while standard cranial MRI was used, the limited application of advanced techniques such as high-resolution 3 Tesla MRI and functional imaging may have resulted in missed diagnoses of subtle or early structural brain abnormalities, especially in patients with MRI-negative epilepsy. These imaging constraints could have impacted the comprehensive assessment of brain abnormalities and their correlation with seizure activity. To address these limitations, future studies with larger sample sizes, prospective designs, and the inclusion of advanced imaging modalities are essential to further explore and validate these findings.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. Ethics committee approval was received

from the KTU University Clinical Research Ethics Committee dated 27.12.2017-2017/2.

Contribution of the authors

Diler Durgut B: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, data management and reporting,Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***Kamaşak T:*** Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***Kul S:*** Supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up. ***Acar Arslan E:*** Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***Şahin S:*** Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***Dilber B:*** Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***Cansu A:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, data management and reporting, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Predictors of persistent polyarticular involvement in patients with systemic juvenile idiopathic arthritis

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ABSTRACT

Objective: The aim of this study was to determine the predictors at the time of diagnosis that could predict the course of persistent polyarticular disease in systemic juvenile idiopathic arthritis (sJIA) patients at follow-up.

Material and Methods: This retrospective observational study was conducted in patients diagnosed with sJIA in Ankara Bilkent City Hospitalbetween January 2002 and August 2024. The relationship between demographic, clinical, laboratory findings and complications in sJIA patients with and without persistent polyarticular involvement was analyzed.

Results: Of the 56 patients diagnosed with sJIA, 27 (48.21%) patients had monocyclic, 8 (14.28%) polycyclic, and 21 (37.50%) persistent disease course. Persistent arthritis was observed in 16 (28.57%) patients, with polyarticular pattern in 11 (19.64%). Polyarticular involvement at the time of diagnosis and involvement of the knee, hip, wrist and small joints of the hand were associated with persistent polyarticular arthritis ($p<0.001$, $p<0.001$, $p=0.001$, $p<0.001$, $p=0.003$). In addition, the use of steroids, conventional disease-modifying antirheumatic drugs (cDMARD) and biological disease-modifying antirheumatic drugs (bDMARD) combination and methotrexate, etanercept and tocilizumab were more common in persistent polyarticular arthritis ($p=0.018$, $p=0.027$, $p=0.006$, $p=0.018$).

Conclusion: Approximately 40% of sJIA patients develop a persistent disease course. Patients with early polyarticular involvement should be followed closely and carefully for persistent polyarticular course.

Keywords: Arthritis, Disease progression, Juvenile, Polyarthritis, Risk factors, Systemic juvenile idiopathic arthritis

INTRODUCTION

Systemic juvenile idiopathic arthritis (sJIA) is a unique type of juvenile idiopathic arthritis (JIA) characterized by systemic features including fever, arthritis, rash, diffuse lymphadenopathy, hepatomegaly, splenomegaly and/or serositis (1). Unlike other JIA subtypes, arthritis may not be present at the time of diagnosis and may develop over weeks, months or even years (2).

Patients with sJIA have findings indicating systemic inflammation at the time of diagnosis and flare-ups resembling autoinflammatory diseases may develop in the follow-up. Approximately 40% of patients have a monocyclic course while 10% develop a polycyclic course. On the other hand, a persistent course is observed in about 50% of patients. Monocyclic disease typically presents with a short period of active symptoms and usually results in favorable outcomes. Prior to biologic therapies, patients with a chronic disease course often experienced severe, erosive polyarticular arthritis. This often required long-term glucocorticoid use for symptom management and led to side effects associated with long-term glucocorticoid exposure. It is still unclear which patients will develop a polycyclic or persistent pattern (3,4). Nigrovic et al. (5) reported that early use of biologic therapies after diagnosis may provide a window of opportunity and prevent the development of polyarticular involvement.

It is very tempting to identify sJIA patients who are likely to develop polyarticular involvement in follow-up at the time of diagnosis so that biologic agents can be started early in the required patients. Because, a persistent disease with synovitis in patients with polyarticular involvement poses a significant clinical challenge and increases morbidity. The aim of this study was to determine the predictors at the time of diagnosis that could predict the course of persistent polyarticular disease in sJIA patients at follow-up.

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MATERIALS and METHODS

This retrospective observational study included patients who met the International League of Rheumatology Societies (ILAR) classification criteria for sJIA and were followed up in the pediatric rheumatology clinic of Ankara Bilkent City Hospital for at least 6 months between January 2002 and August 2024 (1). Diseases that could mimic sJIA such as infections, malignancies and autoinflammatory diseases were excluded. Patients with sJIA who had missing data and a follow-up period less than 6 months were also excluded from the study (Figure 1).

Patients' data were collected from Ankara Bilkent City Hospital electronic health records. Age at diagnosis, gender, clinical findings, duration of symptoms, time from presentation to diagnosis, presence and distribution of joint involvement, laboratory findings including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin, white blood cell count (WBC), neutrophil counts, biochemistry parameters, fibrinogen, triglyceride were recorded. Treatments [nonsteroidal anti-inflammatory drugs, steroids, conventional disease-modifying antirheumatic drugs (cDMARDs) and biological disease-modifying antirheumatic drugs (bDMARDs), intravenous immunoglobulin (IVIG), plasmapheresis], duration of treatments, and complications [macrophage activation syndrome (MAS), interstitial lung disease (ILD), uveitis and persistent arthritis] were also noted. Disease activity score was calculated with systemic Juvenile Arthritis Disease Activity Score (sJADAS71) (6).

A diagnosis of sJIA was established in children under 16 years old who met the ILAR criteria: fever for more than 2 weeks (including at least 3 consecutive days), arthritis, and two or more of the following: rash, hepatomegaly, splenomegaly, lymphadenopathy, or serositis. (1). The diagnosis of MAS was made according to the 2016 MAS criteria. (7).

Using the Wallace criteria, clinical remission was defined as a 3-month period of inactive disease without the use of medications (8). The clinical course of the disease is categorized into three different groups: monocyclic, polycyclic, and persistent. In the monocyclic course, sJIA presents with a single episode of systemic symptoms and arthritis that resolves within 24 months. The polycyclic course is characterized by multiple flare-ups of active disease, interspersed with periods of remission. Persistent sJIA is defined as a lack of response to IL-1 and IL-6 inhibitors or the need for ongoing treatment with long-term glucocorticoids (longer than 6 months) with persistence of systemic and/or arthritic features (4,9,10). Persistent sJIA arthritis is defined as arthritis that persists despite treatment with IL-1 or IL-6 inhibitors, requiring maintenance glucocorticoid therapy and without significant systemic symptoms (11).

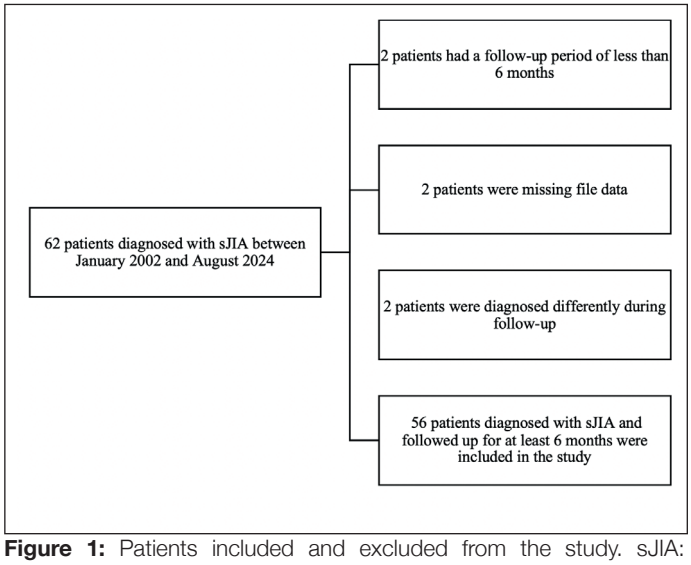

Figure 1: Patients included and excluded from the study. sJIA: systemic juvenile idiopathic arthritis

Statistical Analysis

Statistical analyses were performed using IBM Statistical Package for the Social Sciences, version 26.0 (SPSS Inc., Armonk, NY, IBM Corp., USA). Descriptive statistics were reported as, medians and interquartile ranges (IQR,Q1-Q3) for non-normally distributed and ordinal variables, and frequencies and percentagesfor categorical variables. For statistical comparisons, Mann–Whitney U test for non-normally distributed and ordinal variables, and chi-square or Fisher's exact tests for categorical variables. A p-value of less than 0.050 was considered statistically significant.

RESULTS

A total of 56 patients with sJIA were included in the study.

Demographic Characteristics, Clinical and Laboratory Findings of sJIA Patients

Of the 56 patients, 26 (46.42%) were female. The median (IQR) age at diagnosis was 89.50 (32.25-124) months. The median (IQR) duration of follow-up was 47 (17.50-63.75) months.

All patients had fever at diagnosis. The median (IQR) time from onset of fever to diagnosis was 20 (15-45) days. At the first flare-up, 45 (80.35%) patients had arthritis, of which 27 (48.21%) had oligoarticular involvement and 18 (32.14%) had polyarticular involvement.

Demographic characteristics, clinical features and laboratory findings at the onset of the disease are shown in Table I.

Course of sJIA Patients

Eleven patients (19.64%) developed MAS, 1 (1.78%) patient developed ILD, and 2 (3.57%) patients experienced uveitis as complications of the disease.

The disease course was monocyclic in 27 (48.21%) patients, polycyclic in 8 (14.28%) patients, and persistent in 21 (37.50%) patients. Persistent arthritis was observed in 16 (28.57%) patients, with oligoarticular pattern in 5 (8.92%) and polyarticular pattern in 11 (19.64%). During follow-up, persistent polyarticular

Table I: Demographic, clinical, and laboratory findings of systemic juvenile idiopathic arthritis patients

Variables	Values
Demographic Findings	
Gender*	56
Male	30 (53.57)
Female	26 (46.42)
Age, Months†	159 (88-201.75)
Time Between the Symptom Onset and Diagnosis, Days†	20 (15-45)
Age at Diagnosis, Months†	89.50 (32.25-124)
Follow-up Period, Months†	47 (17.50-63.75)
Baseline Clinical Findings*	
Fever	56
Arthritis	45 (80.35)
Oligoarthritis	27 (48.21)
Polyarthritis	18 (32.14)
Joint Involvement*	
Knee	28 (50)
Ankle	21 (37.50)
Hip	6 (10.71)
Small Joints of the Foot	1 (1.78)
Wrist	14 (25)
Elbow	3 (3.35)
Small Joints of the Hand	14 (25)
Rash*	43 (76.78)
Hepatomegaly*	24 (42.85)
Splenomegaly*	23 (41.07)
Lymphadenopathy*	27 (48.21)
Serositis*	10 (17.85)
Pleural	6 (10.71)
Pericardial	5 (8.92)
Peritoneal	2 (3.57)
Systemic JADAS71†	30.76 (26.17-34.52)
Baseline Laboratory Findings†	
WBCs, $\times 10^6$	14.725 (9575-19.437)
Neutrophil, $\times 10^6$	10.200 (5395-13.842)
Lymphocyte, $\times 10$	2400 (1500-3297)
Haemoglobin, g/dL	10.35 (9.10-11.52)
Platelet, $\times 10^6$	391.000 (294.750-604.500)
ESR, mm/h	70.50 (45-90.25)
CRP, mg/L	100.5 (27.60-142.25)
Ferritin, µg/L	463.5 (210.20-4133.50)
Ferritin/ESR	13.90 (2.85-57.68)
Aspartate aminotransferase, U/L	31.50 (22-56)
Alanine aminotransferase, U/L	17 (10.25-45.25)
Lactate dehydrogenase, U/L	408 (276.50-538.70)
Triglyceride, mg/dL	109 (80.25-197)
Fibrinogen, g/L	4.58 (3.22-6.61)

:** *n (%),* **†:** *median (IQR),* ***IQR: *interquartile range,* ***WBCs:*** *white blood cells,* ***JADAS71:*** *Juvenile Arthritis Disease Activity Score 71,* ***ESR:*** *erythrocyte sedimentation rate*

involvement developed in 11 (19.64%) patients. The knee joint was affected in all patients with persistent polyarticular arthritis. Eight (72.72%) patients had wrist involvement, 7 (63.63%) had ankle involvement, and 7 (63.63%) had involvement of the small joints of the hand, 5 (45.45%) had hip involvement and 4 (36.36%) had elbow involvement. Comparison of demographics, clinical and laboratory findings and complications of sJIA patients with and without persistent polyarticular arthritis are given in Table II.

Treatments of sJIA Patients

All patients received steroids at the time of diagnosis. Pulse methylprednisolone (PMP) therapy was administered to 24 (42.85%) patients. The dosing regimen was as follows: 2 doses in 4 (7.14%) patients, 3 doses in 15 (26.78%) patients, 5 doses in 3 (5.35%) patients, and 6 doses in 2 (3.57%) patients. The median (IQR) duration of steroid treatment was 215.88 (122.25-267.25) days. Fifteen (26.78%) of all patients received steroid treatment only. Details of cDMARD, bDMARD and other treatments given according to disease course are given in Table III.

Comparison of Patients with and without Persistent Polyarticular Arthritis in sJIA

Of the patients with persistent polyarticular arthritis, 10 (17.85%) had polyarticular involvement and 1 (1.78%) patient had oligoarticular involvement at diagnosis. Polyarticular onset was a significant predictor of persistent polyarticular arthritis ($p<0.001$). Persistent polyarticular arthritis was more frequently associated with involvement of the knee, hip, wrist, and small joints of the hand ($p<0.001$, $p=0.001$, $p<0.001$, $p=0.003$, respectively).

Rash at the time of diagnosis was statistically more common in patients without persistent polyarticular arthritis than in those with persistent polyarticular arthritis ($p=0.002$).

The median follow-up duration was longer in patients with persistent polyarticular arthritis, but this difference was not statistically significant ($p=0.063$).

Median white blood cell (WBC) and neutrophil counts at diagnosis were higher in patients without persistent polyarticular arthritis ($p=0.028$, $p=0.031$, respectively). Patients with higher ferritin levels at diagnosis had statistically less persistent polyarticular arthritis ($p=0.036$). Patients without persistent polyarticular arthritis had higher median lactate dehydrogenase levels at diagnosis ($p=0.016$). There was no significant statistical difference in other laboratory parameters between the two groups.

When comparing patients with and without persistent polyarticular arthritis, there was no significant difference in the frequency of MAS, ILD, or uveitis.

Concomitant use of steroid, cDMARD and bDMARD therapies was more common in patients with persistent polyarticular arthritis ($p=0.018$). Methotrexate, etanercept and tocilizumab treatments were more frequently used in patients with persistent polyarticular arthritis ($p=0.027$, $p=0.006$, $p=0.018$, respectively). There was no significant difference in the use of steroid, anakinra, canakinumab, tofacitinib, cyclosporine, etoposide, IVIG, plasmapheresis treatments between patients with and without persistent polyarticular arthritis ($p=1.000$, $p=0.708$, $p=0.196$, $p=1.000$, $p=1.000$, $p=0.180$, $p=1.000$, respectively). Similarly, sJADAS71 scores did not differ significantly between the two groups ($p=0.091$).

Table II: Comparison of demographics, clinical and laboratory findings and complications of systemic juvenile idiopathic arthritis patients with and without persistent polyarticular arthritis

	Persistent Polyarticular Arthritis (n=11,19.64%)	Other Patients (n=45, 80.35%)	p
Demographic Findings			
Age, Months*	179 (137-225)	143 (83.50-201.50)	0.173‡
Gender†			
Male	5 (8.92)	25 (44.64)	0.547§
Female	6 (10.71)	20 (35.71)	
Time Between the Symptom Onset and Diagnosis, Days*	45 (16-60)	20 (15-30)	0.143‡
Age at Diagnosis, Months*	100 (21-121)	75 (32.50-133.50)	0.951‡
Follow-Up Period, Months*	54 (39-96)	42 (13-58)	0.063‡
Baseline Clinical Findings†			
Fever	11 (19.64)	45 (80.35)	-
Arthritis			
Oligoarthritis	1 (1.78)	26 (46.42)	0.004§
Polyarthritis	10 (17.85)	8 (14.28)	<0.001§
Joint Involvement			
Knee	11 (19.64)	17 (30.35)	<0.001§
Ankle	7 (12.50)	14 (25)	0.080§
Hip	5 (8.92)	1 (1.78)	0.001§
Small Joints of the Foot	-	1 (1.78)	1.000§
Wrist	8 (14.28)	6 (10.71)	<0.001§
Elbow	4 (7.14)	9 (16.07)	0.259§
Small Joints of the Hand	7 (12.50)	7 (12.50)	0.003§
Rash	4 (7.14)	39 (69.64)	0.002§
Hepatomegaly	4 (7.14)	20 (35.71)	0.741§
Splenomegaly	3 (5.35)	20 (35.71)	0.496§
Lymphadenopathy	4 (7.14)	23 (41.07)	0.380§
Serositis	-	10 (17.85)	0.183§
Pleural	-	6 (10.71)	0.334§
Pericardial	-	5 (8.92)	0.571§
Peritoneal	-	2 (3.57)	1.000§
Systemic JADAS71*	34 (28.20-45)	30.60 (25.35-34.10)	0.091‡
Baseline Laboratory Findings*			
WBCs, $\times 10^6$	9800 (7200-14.690)	14.800 (10.330-21050)	0.028‡
Neutrophil, $\times 10^6$	6310 (3140-10.100)	10.700 (5955-17.465)	0.031‡
Lymphocyte, $\times 10$	2500 (1500-2940)	2300 (1500-3370)	0.992‡
Haemoglobin, g/dL	10.50 (9.40-11.60)	10.20 (9.05-11.50)	0.489‡
Platelet, $\times 10^6$	461.000 (365000-540.000)	389.000 (281.500-627.500)	0.571‡
ESR, mm/h	82 (22-91)	68 (48-89.50)	0.951‡
CRP, mg/L	108 (27.60-146)	93.40 (27.30-141)	0.765‡
Ferritin, µg/L	230 (219-444)	948 (234-4562.50)	0.036‡
Ferritin/ESR	4.53 (2.18-43.47)	19.56 (3.41-66.47)	0.130‡
Aspartate aminotransferase, U/L	24 (14-45)	32 (22.50-59.50)	0.327‡
Alanine aminotransferase, U/L	14 (10-60)	17 (11-44.50)	0.476‡
Lactate dehydrogenase, U/L	252 (219-495)	421 (320.50-564.50)	0.016‡
Triglyceride, mg/dL	109 (80.20-197)	113 (81.50-221.50)	0.261‡
Fibrinogen, g/L	3.90 (3.20-6.78)	4.70 (3.24-6.61)	0.726‡
Complications†			
Macrophage Activation Syndrome	2 (3.57)	9 (16.07)	1.000§
Interstitial Lung disease	-	1 (1.78)	1.000§
Uveitis	1 (1.78)	1 (1.78)	0.357§

:** *median (IQR),* **†:** *n(%),* **‡:Mann-Whitney U Test,* **§:** *Fisher's Exact Test*

DISCUSSION

Systemic juvenile idiopathic arthritis is a chronic disease that causes significant morbidity in children and in some cases can remain active for years. Although three different disease courses have been described, the predictors that determine the disease course are still unclear. This study aimed to investigate the determinants of persistent polyarticular arthritis in a cohort of sJIA patients with a persistent disease course. In the present study, patients with polyarticular involvement at the time of

Table III: Treatments used in systemic juvenile idiopathic arthritis patients with and without persistent polyarticular arthritis

Treatment	All patients (n=56)	Persistent Polyarticular Arthritis (n=11, 19.64%)	Other Patients (n=45, 80.35%)	p
Only Steroid	15 (26.78)	1 (1.78)	14 (25)	0.255‡
Steroid+bDMARDs	17 (30.35)	3 (5.35)	14 (25)	1.000‡
Steroid+cDMARDs	14 (25)	2 (3.57)	12 (21.42)	0.711‡
Steroid+bDMARDs+cDMARDs	10 (17.85)	5 (8.92)	5 (8.92)	0.018‡
bDMARD Switch	10 (17.85)	3 (5.35)	7 (12.50)	0.393‡
Pulse Methylprednisolone*	24 (42.85)	2 (3.57)	22 (39.28)	0.093‡
Methylprednisolone 2 mg/kg/d*	56 (100)	11 (100)	45 (100)	-
Total Steroid Duration, Day†	215.88 (122.25-267.25)	220.64 (90-304)	214.71 (123-200)	0.813§
Anakinra*	12 (21.42)	2 (3.57)	10 (17.85)	1.000‡
Canakinumab*	15 (26.78)	2 (3.57)	13 (23.21)	0.708‡
Tocilizumab*	10 (17.85)	5 (8.92)	5 (8.92)	0.018‡
Etanercept*	3 (5.35)	3 (5.35)	-	0.006‡
Tofacitinib*	1 (1.78)	1 (1.78)	-	0.196‡
Methotrexate*	18 (32.14)	7 (12.50)	11 (19.64)	0.027‡
Cyclosporine*	6 (10.71)	1 (1.78)	5 (8.92)	1.000‡
Etoposide*	1 (1.78)	-	1 (1.78)	1.000‡
IVIG*	9 (16.07)	-	9 (16.07)	0.180‡
Plasmapheresis*	3 (5.35)	-	3 (5.35)	1.000‡

:** *n (%),* **†:** *median (IQR),* **‡ :** *Fisher's Exact Test,* **§:Mann-Whitney U Test,* ***bDMARDs:** Biological Disease-Modifying Antirheumatic Drugs,* ***cDMARDs:** Conventional Disease-Modifying Antirheumatic Drugs,* ***IVIG:** Intravenous Immunoglobulin*

diagnosis may also have a persistent polyarticular course in follow-up. On the other hand, rash, elevated WBC and ferritin at baseline were observed more frequently in patients without polyarticular involvement at follow-up.

Long-term follow-up of our sJIA cohort showed three different disease courses: 48.21% of patients had a monocyclic course, 37.50% a persistent course, and 14.28% a polycyclic course. Half of those with a persistent course had persistent polyarticular arthritis. In contrast to Singh-Grewal et al. (3), who reported a higher prevalence of persistent disease, our study found a higher proportion of patients with a monocyclic disease course. Increased awareness of sJIA, rapid initiation of appropriate treatment, and the advantage of being in the biological era to provide intensive treatment in necessary patients may play a role in the change in the distribution of the disease course.

Half of our sJIA patients with persistent course had persistent polyarticular arthritis. Of the patients with persistent polyarticular arthritis, 91% had polyarticular involvement at diagnosis. Polyarticular onset was a significant predictor of persistent polyarticular arthritis. Walliman and colleagues found that nearly all patients with a persistent disease course had arthritis at the time of diagnosis, with half presenting with polyarticular involvement (12). Persistent polyarticular arthritis was associated with a higher involvement of the knee, hip, wrist, and small joints of the hand. Modesto et al. (13) showed that polyarticular involvement was associated with worse outcomes.

Disease activity is a term representing the signs and symptoms associated with inflammation (14,15). Prolonged synovial inflammation can lead to joint destruction and consequent growth abnormalities and functional disability. Therefore, assessment of ongoing inflammation or disease activity in sJIA is crucial to prevent long-term complications and manage the disease (16,17). The presence of elevated systemic inflammatory markers, including ESR, CRP, WBC and ferritin levels, helps to diagnose sJIA and their use as a prognostic factor has also been investigated (18). In our study, no significant relationship was found between sJADAS scores used to assess disease activity and persistent polyarticular involvement. On the other hand, there was no significant correlation between baseline ESR and CRP levels and the persistence of polyarticular arthritis in our cohort. However, we found a positive correlation between elevated WBC and neutrophil counts, and higher ferritin levels, and the absence of persistent polyarticular disease. While autoinflammatory mechanisms play a role in the pathogenesis of the disease in the early stages, autoimmune mechanisms come to the fore in the later stages when persistent arthritis develops. Elevated inflammatory markers in the early phase of our study seem to indicate autoinflammation, whereas low baseline WBC and neutrophil counts in patients with persistent arthritis seem to indicate an autoimmune component in the pathogenesis.

Nigrovic et al. (5) reported that early initiation of biologic agents may provide a therapeutic window of opportunity to prevent disease progression. Our study demonstrated that half of

patients exhibited a monocyclic disease course, which was not associated with the use of biologic agents. However, persistent disease activity was observed in 21.42% patients who initiated therapy with a biologic agent at disease onset. These results suggest that the course of the disease may not be related solely to the time of starting the biologic agent. Statistical analysis revealed no significant association between the use of steroids, anakinra, canakinumab, tofacitinib, cyclosporine, etoposide, IVIG, or plasmapheresis and the specific disease subgroup. In contrast, patients receiving methotrexate, etanercept, or tocilizumab demonstrated a more persistent course of polyarticular arthritis. The treatment approach for these children often reflects that of polyarticular JIA rather than sJIA. This difference may be explained by the clinician's choice of treatment based on polyarticular involvement, as the present study showed that the main determinant of persistent polyarticular course was initial polyarticular involvement. Janow et al. also reported that cDMARDs and IL-6 inhibitors such as tocilizumab were more commonly used in patients with persistent arthritis. Anti-TNF drugs are commonly used to treat sJIA patients with persistent arthritis (19). According to the BIKER registry, patients with sJIA who no longer have systemic symptoms can achieve favorable results with anti-TNF agents (20). The use of a combination of steroids, cDMARDs, and bDMARDs was more common among patients with persistent polyarticular arthritis. These pediatric patients typically exhibit a higher number of affected joints, a decreased quality of life, and increased functional abnormalities. As a result, healthcare providers may need to make complex therapeutic choices in the persistent polyarticular course (12).

The main limitations of our study are its retrospective nature, single-center design, and relatively small sample size. On the other hand, the determination of predictors of persistent polyarticular course of sJIA that may result in destructive joint damage is a strength of our study.

In conclusion, sJIA is a challenging disease with both its early systemic findings and its persistent polyarticular course during follow-up. Patients with polyarticular involvement at the time of diagnosis may have a persistent polyarticular course during follow-up. Therefore, patients with early polyarticular involvement should be followed closely and carefully for persistent polyarticular course. Multicenter studies are needed to reveal other predictors of persistent polyarticular course in this rare disease.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by the Ankara Bilkent City Hospital Ethics Committee (Date: 04 September 2024; No: TABED 2-24-436).

Contribution of the authors

Conceptualization: ***Uğur Es Y, Çelikel Acar B***; Methodology: ***Uğur Es Y, Çelikel Acar B, Çelikel E, Ekici Tekin Z, Ertem Ş***; Formal analysis and investigation: ***Polat Mc, Işıklar Ekici M, Öztürk D, Yoğun Sn, Erdem Torun Ş***; Writing - original draft preparation: ***Uğur Es Y, Çelikel Acar, B Elif Çelikel, Ekici Tekin Z***; Writing - review and editing: ***Uğur Es Y, Çelikel Acar B***; The final manuscript was approved by all the authors. Funding acquisition: None ; Resources: None; Supervision: ***Çelikel Acar B***.

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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 the bleeding symptoms in first-degree female relatives of patients with hemophilia A

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ABSTRACT

Objective: Carriers of hemophilia may have an increased bleeding tendency even if they have normal factor VIII levels. The aim of this study was to investigate the bleeding tendency with using a Bleeding Assessment Tool (BAT) in first-degree relatives of hemophilia A patients and to compare with women without family history of hemophilia or other bleeding disorders.

Material and Methods: First-degree relatives of hemophilia A patients (study group) were investigated prospectively evaluated and compared them with women without a family history of hemophilia or other bleeding disorders (controls group), including factor VIII levels, coagulation parameters and bleeding scores.

Results: The study included 30 women in the study group and 30 women in the control group. The mean FVIII levels in the study group and control group were 75.95±34.88 IU/m L and 112.83±25.44 IU/mL, respectively. In the study group, one woman had a moderate factor VIII deficiency (factor VIII level was 5 IU/mL). In addition, 4 women were found to have Factor VIII level between 5-39 IU/mL (24, 31, 36, and 39 IU/mL) which was compatible with mild factor VIII deficiency. Menorrhagia was the most common type of bleeding in the study group (83.3%), followed by cutaneous (60%) and oral cavity bleedings (56.6%). Menorrhagia, oral cavity bleeding and epistaxis were significantly more frequent in the study group compared to the control group ($p<0.001$, $p<0.001$, and $p<0.001$, respectively). No correlation was found between factor VIII level and bleeding score.

Conclusion: Our study showed that first-degree female relatives of hemophiliacs experienced at least one bleeding episode during their lifetime, regardless of factor VIII levels. Therefore, careful collection of bleeding histories in female relatives of hemophiliacs may help determine the necessary treatment methods to reduce mucosal and gynecologic bleeding.

Keywords: Bleeding tendency, Epistaxis, Hemophilia, Menorrhagia

INTRODUCTION

Hemophilia A, a deficiency of coagulation factor VIII (FVIII), is an inherited bleeding disorder that affects one in 5.000 male births (1). Females with a defective X chromosome are referred to as hemophilia carriers. The cellular mosaicism in the expression of the parental normal X chromosome allows the synthesis of normal FVIII in half of the FVIII -producing cells , while the other half express the defective FVIII gene and are therefore unable to produce the FVIII. However, FVIII levels vary from one carrier to carrier due to Lyonization, in which the expression of one of the two X chromosomes is randomly suppressed (1-3).

Carriers of hemophilia A usually have a sufficient (>40%) FVIII levels to control bleeding, but they may have an increased bleeding tendency even with normal FVIII levels (3). Age at diagnosis is usually delayed in hemophilia carriers compared to boys with hemophilia (4). Delayed diagnosis of a carrier with a potential bleeding risk may limit access to medical care (5). Recent studies have shown that carriers of hemophilia experience bleeding symptoms such as menorrhagia, postpartum hemorrhage, excessive postsurgical bleeding, epistaxis, easy bruising, and oral cavity bleeding (3,6). In this study, we aimed to investigate the bleeding tendency, bleeding scores, coagulation parameters, and FVIII levels in the first-degree female relatives of our patients with hemophilia A and compare our findings with those obtained in the women without family history of hemophilia or other bleeding disorders.

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MATERIALS and METHODS

This prospective study was conducted at Ankara Child Health and Diseases Hematology and Oncology Hospital, certified as the European Hemophilia Comprehensive Care Center, between June 2019 and January 2021. This study was approved by the local ethics committee (2019-211/ 27.06.2019). It was conducted in accordance with the latest version of the Declaration of Helsinki and good clinical practices. Informed consent was obtained from all participants.

First degree relatives (mothers and sisters) of hemophilia A patients who were being followed up in our hospital were included in the study group. We excluded women in the control group if they have a family history of hemophilia or other bleeding diathesis and also if they had a disease that could cause coagulation disorder or were taking medication. Women who admitted to our hospital for another reason and volunteered to participate in the study were recruited as the control group. Those who have vonWillebrand Factor deficiency or dysfunction, or other bleeding disorders, taking antiplatelet or anticoagulant medications or oral contraceptives, who have pregnancy, liver disease, malignancy, primary amenorrhea were excluded from the study.

Bleeding risk assessment

Bleeding risk assessment of the participants was determined by using the ISTH-BAT (International Society on Thrombosis and Hemostasis-Bleeding Assessment Tool) questionnaire (7). A physician (E.E.G) administered the questionnaire to the participants. Oral, muscular, cutaneous, gastrointestinal, surgical or trauma, tooth extraction, postpartum, and central nervous system bleeding, epistaxis, menorrhagia and hemarthrosis were evaluated. Each parameter was based on clinical criteria or treatments and rated from 1 to 4 depending on intensity and severity of the bleeding.

A bleeding score ranging from 0 to 56 points was determined by completing this 14-domain questionnaire. Bleeding risk assessment scores, factor VIII levels, and coagulation parameters were compared between the study and control groups.

Laboratory evaluation

Venous blood samples for measurement of activated partial thromboplastin time (aPTT) and FVIII, FIX, and vWF levels were drawn into tubes containing a standardized amount of sodium citrate (BD Vacutainer, 9NC 0,109M). The samples were centrifuged and processed in the coagulation laboratory of our hospital. Plasma aPTT and coagulation factor levels were measured by the Siemens Atellica COAG 360 (Erlangen, Germany) using standard kits according to the manufacturer's instructions. Plasma factor VIII levels were measured by means of a PTT-based one-stage assay method. Von Willebrand factor (vWf) levels and activity were assessed by enzyme-linked immunosorbent assay to exclude von Willebrand's disease. Factor VIII, FIX and activated partial thromboblastin time (aPTT) results of all participants were recorded for statistical analysis. Genetic analysis for hemophilia-causing mutations was not performed on individuals in the study and control groups.

Statistical Analysis

Data analysis was performed using SPSS Statistics for Windows, version 15.0 (SPSS Inc., Chicago, Ill., USA). The conformity of the variables to the normal distribution was examined by visual (histogram and probability plots) and analytical methods (Kolmogorov-Smirnov tests). Analysis of data was primarily descriptive for continuous variables using standard deviations, minimum-maximum, mean, and median values. The Mann-Whitney U test was used for independent groups, and Chi-squared test was used to compare categorical variables. When $p<0.050$, the results were considered as statistically significant

RESULTS

Sixty-six women who were fisrt- degree relatives of 45 patients with hemophilia A followed up at our center were eligible for the study. Twenty-two participants did not agree to participate in the study and 14 participants did not meet the inclusion criteria.

Therefore, the study group comprised of 30 women. Thirty heatlhy volunteer women were recruited as the control group. Two of the five subjects in the study group were mothers of two hemophiliac children, and the other three were mothers of one hemophiliac child with a hemophiliac family member. The mean age of the subjects of study and control groups were 28.97± 8.60, and 29.10±8.06 (p=0.031), respectively.

There was no significant difference in mean aPTT values between the study and control groups (p=0.100). Two participants in the study group were found to have prolonged aPTT values. Individuals with prolonged aPTT values were found to have factor VIII levels of 5 IU/mL and 24 IU/mL, respectively. They were classified as having mild hemophilia. The mean FVIII level was statistically significantly lower in the study group (75.95± 34.88 IU/mL) compared to those in the control group (112.83 ±25.44 IU/mL;p<0.001). One women in the study group had a moderate factor VIII deficiency (factor VIII level was 5 IU/mL). In addition, 4 women were found to have Factor VIII levels between 5-39 IU/mL (24, 31, 36, and 39 IU/mL) which was compatible with mild factor VIII deficiency.

Comparison of the bleeding symptoms between the study and control groups is shown in Table I. Menorrhagia was the most common type of bleeding in the study group (83.3%) followed by cutaneous (60%), and oral cavity bleeding (56.6%).

Menorrhagia, oral cavity bleeding and epistaxis were significantly more frequent in the study group compared to the control group (p<0.001, p<0.001, and p<0.001, respectively). Although, cutaneous bleeding was the most common symptom

Table I: Distribution of bleeding in the Study and Control Group.

	Study Group	Control Group	p†
Menorrhagia*	25 (83.3)	11 (36.6)	< 0.001
Skin-subcutaneous bleeding*	18 (60)	19 (63.3)	0.800
Oral cavity associated bleeding*	17 (56.6)	3 (10)	< 0.001
Epistaxis*	14 (46.6)	3 (10)	<0.001
Postpartum bleeding*	2 (6.6)	1 (3.3)	0.550
Gastrointestinal tract bleeding*	1 (3.3)	1(3.3)	1
Surgical operation-related bleeding*	1 (3.3)	-	-
Total skin and mucosal bleeding*	78	38	<0.001
Bleeding after minor injury*	6 (20)	5 (16.6)	0.740
Tooth extraction related bleeding*	5 (16.6)	4 (13.3)	0.720
Bleeding of CNS*	-	1 (3.3)	-
Hemarthrosis*	-	1 (3.3)	-
Intramuscular bleeding	89	50	<0.001

***:** *n(%),* **†:** *Chi-squared test*

Table II: Bleeding scores of the study groups and control groups.

	Study Group*	Control Group*	p†	Obligatory Carrier*	Possible Carrier*	p†
Epistaxis	1 (1-4) *	1 (1-5)	<0.001	1 (1-4)	1 (1-4)	0.960
Oral cavity associated bleeding	2 (1-3) *	1 (1-3)	<0.001	2 (1-3)	2 (1-3)	0.590
Surgical operation-related bleeding	0 ((-1)-4)	0 (0-0)	0.310	0 ((-1)-4)	0 ((-1)-0)	0.830
Muscle hematoma	1 (1-1)	1 (1-5)	0.320	1 (1-1)	1 (1-1)	1
Skin-subcutaneous hemorrhage	2 (1-3)	2 (1-3)	0.110	2 (2-3)	2 (1-3)	0.110
Gastrointestinal tract bleeding	1 (1-2)	1 (1-3)	0.980	1 (1-1)	1 (1-2)	0.910
Menarche	2 (1-4) *	1 (1-5)	0.020	2 (2-4)	2 (1-4)	0.750
Hemarthrosis	1 (1-1)	1 (1-5)	0.320	1 (1-1)	1 (1-1)	1
Bleeding after minor injury	1 (1-3)	1 (1-3)	0.710	1 (1-3)	1 (1-3)	0.380
Tooth extraction related bleeding	1 ((-1)-3)	1 ((-1)-3)	0.980	1 ((-1)-2)	1 ((-1-)-3)	0.590
Postpartum bleeding	0 ((-1)-3)	0 (0-2) *	<0.001	(-1) ((-1)-3)	0 ((-1-)-3)	0.590
CNS bleeding	1 (1-1)	1 (1-5)	0.320	1 (1-1)	1 (1-1)	1
Total	13 (9-21)	13 (8-19)	0.550	14 (12-21)	13 (9-18)	0.070

:** *median (min-max),* **†:** *Mann-Whitney U test,* ***CNS: *Central nervous system*

in the control group (63.3%), it was not significantly different from the study group (60%). In the study group, 17 women (56.6%) experienced menorrhagia requiring medical assessment, three of whom (10%) were taking antifibrinolytics or oral contraceptivess. In five (16.6%) of the women from the study group menorrhagia caused anemia requiring curettage or iron treatment. None of the women in the study group required blood transfusion, desmopressin, factor replacement therapy, or hysterectomy due to menorrhagia. In the control group, four women (13.3%) experienced menorrhagia requiring medical assessment, and six (20%) had menorrhagia causing anemia requiring curettage or iron treatment. One (3.3%) woman in the control group had a history of blood transfusion due to menorrhagia.

Bleeding risk assessment showed that all of the women in the study and the control groups experienced at least one bleeding episode. Epistaxis and oral cavity bleeding scores were significantly higher in the study group compared to those in the control group (p<0.001, respectively). In the study group, 11 women (36.6%) experienced at least one oral cavity bleeding episode in their lifetime, and six of them required medical assessment. In the control group, two women experienced at least one oral cavity bleeding episode in their lifetime, and one required medical assessment. None of the participants in either group required surgical intervention, antifibrinolytics, blood transfusion, or factor replacement therapy for oral cavity bleeding. In the study group, 10 women (33.3%) had epistaxis more than five times

Table III: Comparison of study and control groups between FVIII level and bleeding susceptibility

Types of bleeding	Study Group				Control Group	
	Factor VIII level (IU/mL)			Total number of bleeding (n=30)	Factor VIII level (IU/mL)	Total number of bleeding (n=30)
	≤5 IU/mL (n=1)	5-40 IU/mL (n=4)	>40 IU/mL (n=25)		>40 IU/mL	
Menorrhagia	1	2	22	25	11	11
Skin and subcutaneous hemorrhages	1	3	14	18	19	19
Oral cavity bleeding	-	1	16	17	3	3
Epistaxis	1	3	10	14	3	3
Minor injury-related bleeding	-	-	6	6	5	5
Tooth extraction related bleeding	-	-	5	5	4	4
Postpartum hemorrhages	-	-	2	2	1	1
Gastrointestinal system bleeding	-	-	1	1	1	1
Surgery-related bleeding	-	-	1	1	-	0
Intramuscular hemorrhages	-	-	-	0	1	1
Hemarthrosis	-	-	-	0	1	1
Central nervous system related hemorrhages	-	-	-	0	1	1
Total	3	9	77	89	50	50

or lasting more than 10 minutes during their lifetime. Among them one had epistaxis requiring medical assessment, and three required medical intervention such as nasal tampon, cauterization, or antifibrinolytic drug administration. None of the women in the study group received blood transfusion, factor replacement therapy, or desmopressin for epistaxis. In the control group, one woman reported epistaxis more than five times or lasting more than 10 minutes; one woman required medical intervention for bleeding, and another one required blood transfusion. Menorrhagia scores were significantly higher in the study group than in the control group ($p = 0.020$). Two women in the study group had postpartum bleeding requiring blood transfusion; whereas only one woman in the study group required iron replacement therapy due to postpartum bleeding ($p<0.001$). Comparison of the median bleeding scores between the study and control groups is shown in Table II. There was no difference between FVIII levels and bleeding risk in hemophilia carriers and controls (Table III).

DISCUSSION

A woman with an affected X chromosome is called a hemophilia carrier (8). First-degree female relatives of hemophiliacs may be obligate or probable carriers of hemophilia, depending on whether they received the hemophilia gene from their father or mother, respectively (9). The World Federation of Hemophilia recommends genetic testing to identify carriers to define biology of the disease, to diagnose difficult cases, to estimate the risk of developing inhibitors, and to provide prenatal diagnosis (8). However, the facilities required for genetic evaluation may not always be adequate. Under these conditions, particularly in first-degree female relatives of hemophiliacs significant bleeding abnormalities may occur but be overlooked. The aim of this study was to determine the bleeding phenotypes of first-degree female relatives of our patients diagnosed with hemophilia A, their relationship with factor VIII levels, and to compare them with individuals without bleeding disorders.

In the study group, one woman had a moderate factor VIII deficiency, four women were found to have FVIII levels between 5-39 IU/mL (24, 31, 36, and 39 IU/mL) which was compatible with mild factor VIII deficiency. These individuals could be defined as having mild and moderate hemophilia according to the new classification. To eliminate confusion in the definition of hemophilia A carrier state, five clinical situations were defined in which personal bleeding history and baseline plasma FVIII levels were assessed. According to factor levels, women/girls with mild, moderate or severe

hemophilia (FVIII/IX >0.05 and <0.40 IU/ml, 0.01–0.05 IU/ml and <0.01 IU/ml, respectively) and hemophilia carriers with and without bleeding phenotype (FVIII level ≥0.40 IU/ml) were grouped (9). These results indicate that women who are relatives of hemophilia patients are at risk for bleeding and should be carefully monitored (10). Several studies using standardized bleeding assessment tools have reported that hemophilia carriers have increased bleeding scores compared to the general female population (11, 12).

The most commonly reported symptoms include menorrhagia, oral cavity bleeding, bleeding after tooth extraction, cutaneous bleeding, epistaxis and postsurgical bleeding and postpartum bleeding (11,13). Menorrhagia was the most common type of bleeding in the study group (83.3%) followed by cutaneous (60%) and oral cavity bleedings (56.6%). Menorrhagia, oral cavity bleeding and epistaxis were significantly more common in the study group than in the control group. In the review conducted by D'Oiron et al. (14), similar to our study, they reported that there was no significant relationship between FVIII levels and bleeding scores in hemophilia carriers.

A recent study from Türkiye in which sisters of 46 patients with hemophilia A or B were evaluated,reported that prolonged bleeding after minor injuries and tooth extraction was significantly higher in the sisters than in controls. Sisters also had longer menstrual periods compared to controls (15). Besides, the rate of postpartum bleeding was reported to be in the range of 13-22% in various studies (13,16,17). However, the rate of postpartum bleeding in our study was low, because of the relatively young age of the participants.

A retrospective study to determine the rate of joint disease in 539 potential hemophilia carriers revealed that the age of first hemarthrosis in women with FVIII level<50 IU/mL was earlier than in their healthy counterparts. They also noted that by the age of 60 years, 37% of the carriers had a joint disease, and they had a 2.3-fold higher risk for joint-related diagnoses compared with the general population (18). In our study, none of the women in the study group had hemarthrosis; however, one woman in the control group had hemarthrosis after trauma and required surgical intervention.

Coagulation reflects the balance between procoagulant and anticoagulant factors. Recent studies have investigated whether the FVIII mutation influences the bleeding phenotype in carriers. A correlation was shown between the severity of bleeding tendency in carriers and the type of FVIII gene mutation (19). However, another study found no correlation in bleeding scores or factor levels between carriers with null and non-null mutations (13).

One of the major limitations of our study was the lack of genetic analysis. Although it could not be determined whether the individuals in the study group were definitely hemophilia carriers, our findings are valuable in that they experienced more bleeding compared to the control group and show that hemophiliacs, especially their first-degree relatives, need to be monitored more closely. Another limitation of our study is that psychosocial aspects were not evaluated. In a previous study, the presence of psychological symptoms in individuals with hemophilia carriers has been noted (20).

In conclusion, our study showed that first-degree female relatives of hemophiliacs experienced at least one bleeding episode during their lifetime, regardless of factor VIII levels. Therefore, careful collection of bleeding histories in female relatives of hemophiliacs may help determine the necessary treatment methods to reduce mucosal and gynecologic bleeding.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Pediatrics Hematology Oncology Training and Research Hospital (27.06.2019, reference number: 2019-211).

Contribution of the authors

Genç EE: Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Takingresponsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. **Güzelküçük Z:** Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. **Koşan Çulha V:** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results. **Işık M**: Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. **Gürlek Gökçebay D:** Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. **Özbek NY:** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/ study, Reviewing the article before submission scientifically besides spelling and grammar.

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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 drug allergy awareness and rational drug use among parents of hospitalized pediatric patients

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ABSTRACT

Objective: Adverse drug reactions, including drug allergies, can be life-threatening and are often unpredictable. Identifying whether reactions are drug-related is critical, and obtaining a detailed history from parents is essential, especially in pediatric cases. This study aimed to assess parents' awareness of drug allergies and the rational use of medicines.

Material and Methods: A questionnaire was developed to evaluate the awareness of drug allergies among parents of pediatric patients at Ankara Bilkent City Hospital. Additionally, a scale measuring parental attitudes toward rational drug use was used. These instruments were administered to a total of 191 participants.

Results: The study included 191 parent-patient pairs, with an average age of 35±7.5 years for the parents and 6.1±5.6 years for the patients. Chronic illnesses were reported in 52.4% of patients, and 46.6% were on regular medication. A history of drug allergy was noted in 9.9% of patients with antibiotics identified as the most common trigger (68.4%). Parents showed high recognition of skin (89.5%) and gastrointestinal (56%) symptoms but were less aware of respiratory (39.3%) and cardiovascular (16.2%) symptoms. Parents with higher education levels demonstrated a greater awareness that skin symptoms could be accompanied by other system symptoms (respiratory and cardiovascular systems; p=0.004, p=0.001). The average score on the parental attitudes scale was 178.6±14.7, with correct and conscious use and effective and safe use subscale scores of 133±13.6 and 45±7.9, respectively. Higher parental education was associated with better awareness of rational drug use (OR=1.89; 95% CI=1.05-3.42; p=0.030).

Conclusion: Educating parents about drug allergy symptoms and involving them in the management of drug allergies is essential for improving pediatric care outcomes.

Keywords: Children, Drug allergy, Drug utilization, Health attitudes, Medication errors, Nonprescription drugs, Surveys and questionnaires

INTRODUCTION

Drug allergies are adverse drug reactions that occur through immunological mechanisms. Representing 5-10% of all adverse drug reactions, drug allergies are significant due to their unpredictable nature and potential to lead to life-threatening reactions (1-3). Parental report is crucial in distinguishing whether reactions in pediatric patients are drug-related. The enhancement of awareness among families with regard to drug allergies is likely to facilitate more accurate diagnostic approaches (4).

The World Health Organization (WHO) defined the concept of rational drug use in 1985 as "a set of rules requiring that patients receive medications appropriate to their clinical needs, in doses that meet their individual requirements, for an adequate period of time, and at the lowest cost to themselves and their community" (5). Rational use of medicines involves first establishing the diagnosis of the disease, selecting the appropriate medication for treatment, prescribing it to the family, providing detailed information regarding drug use, and monitoring outcomes. The provision of rational drug use in children depends on their parents' attitudes towards this issue.

This study aims to evaluate the awareness levels of parents of hospitalized patients regarding drug allergies and rational use of medicines.

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MATERIALS and METHODS

The study was conducted at the Pediatric Allergy and Immunology Clinic of Ankara Bilkent City Hospital.

The study included 191 parent-patient pairs who were hospitalized in the pediatric wards of Ankara Bilkent City Hospital from October 1 to 31, 2024, and who volunteered to participate. Written consent was obtained from patients over nine years old and their parents, as well as from parents of patients under nine years old.

Demographic characteristics of the patients, length of hospitalization, chronic illnesses, and presence of regular medication usage were recorded. A history of drug allergies was queried, and the responsible drugs and clinical features of reactions were noted. Case scenarios were developed by researchers to assess parents' awareness levels regarding drug allergies and side effects. Additionally, a parental attitude toward rational drug use was applied to all participants. This scale, validated in Turkish by Sarıalioğlu et al. (6), consists of 40 items on a Likert-type scale. Each statement is rated on scale from 1 to 5, with positive questions scored as "strongly disagree", "disagree", "neutral", "agree" and "strongly agree" (1-5). The scale includes two sub-dimensions: correct and conscious use, and effective and safe use, with a maximum score of 145 for correct and conscious use, and 55 for effective and safe use, totaling a maximum of 200 points. Higher scores indicate a more positive attitude towards rational drug use among parents.

Statistical analysis was performed using IBM Statistical Package for the Social Sciences, version 25.0 (SPSS Inc., Armonk, NY, IBM Corp., USA). Categorical variables were expressed as percentages (%) and counts (n), while numerical variables were expressed as mean, standard deviation, minimum, and maximum values. Normality of continuous variables was tested using the Kolmogorov-Smirnov test. The t-test was used for analysis of normally distributed continuous variables between two groups, and the Mann-Whitney U test was used for comparing non-normally distributed continuous variables. Regression analysis was conducted to measure the relationship between two or more quantitative variables. Pearson's chi-square test and Fisher's Exact Test were used for the analysis of categorical variables, with $p<0.050$ accepted as the significance threshold.

RESULTS

A total of 191 parent-patient pairs were included in the study. The average age of the parents was 35±7.5 years, while the average age of the patients was 6.1±5.6 years. The average length of hospital stay for patients was 17±46 days (median, 5 days; range, 1-360 days). Chronic illness was present in 52.4% of patients ((Examples of prevalant chronic conditions observed

Table I: Demographic characteristics of participants and clinical features related to drug allergy history

Characteristics of parents	
Parent age (years)*	35±7.5
Number of children†	2 (1-3) (1-7)
Educational status‡	
Secondary education or lower	73 (38.2)
High school or higher	118 (61.7)
Residence‡	
Village	16 (8.4)
District	85 (44.5)
City	90 (47.1)
Patient age (years)*	6.1±5.6
Gender (male)†	97 (50.8)
Presence of chronic illness‡	100 (52.4)
Chronic illnesses	
Congenital metabolic diseases	11
Epilepsy	8
Chronic kidney disease	8
Asthma	7
Cerebral palsy	7
Hydronephrosis	6
Type 1 Diabetes Mellitus	4
Down syndrome	4
Hypothyroidism	3
Multiple Sclerosis	3
Ataxia	2
Common variable immune deficiency	2
Severe combined immunodeficiency	2
Increased intracranial pressure syndrome	2
Osteogenesis imperfecta	2
Autoimmune hepatitis	2
Bronchopulmonary dysplasia	2
Systemic lupus erythematosus	2
Other chronic diseases	23
Presence of concomitant atopic disease‡	12 (6.2)
Presence of regular treatment‡	89 (46.6)
Presence of history of multiple hospital admissions‡	134 (70.2)
Presence of history of drug-related side effects‡	12 (6.3)
Presence of history of drug-related allergic reactions‡	19 (9.9)
Antibiotics	13 (68.4)
NSAIDs	2 (10.5)
Other§	4 (21.1)
Organ systems affected by drug-related allergic reactions‡	
Skin	15 (78.9)
Respiratory	8 (42.1)
Gastrointestinal	2 (10.5)
Cardiovascular	5 (26.3)

**: mean (SD), †: median (IQR) (min-max), ‡: n(%), §: (Antiepileptics, antiemetics, chemotherapeutic agents)*

include congenital metabolic disorders [n=11], epilepsy [n=8], chronic kidney disease [n=8], asthma [n=7], and cerebral palsy [n=7]). Additionally, 46.6% of the patients (n:89) reported regular medication use, while 53.4% (n:102) did not require regular medication.

When queried about drug side effects and allergies, 12 (6.3%) parents reported that their children had experienced at least one side effect from previously used medications. These reports were based on the parental observations, rather than doctor-diagnosed drug-related reactions. The frequency of drug-related side effects was significantly higher in children recieving regular medication for chronic illness compared to those without regular treatment (p<0.001). A history of drug allergies was reported by 19 (9.9%) parents, with antibiotics being the most implicated drug group (n=13, %68.4). The most frequently affected systems in patients with reported drug allergies were the skin and respiratory system. Additionally, based on information provided by families, five patients were considered to have experienced drug-induced anaphylaxis. It was observed that the parents of these patients avoided the suspected drug. Socio-demographic data and clinical characteristics related to participants' drug allergy history are summarized in Table I.

Responses to questions designed to evaluate parents' awareness of drug allergies indicated that skin (89.5%) and gastrointestinal system (56%) symptoms were most often linked to drug allergies. In contrast, symptoms associated with the respiratory system (39.3%) and cardiovascular system (16.2%) showed lower association rates. A total of 12% (n=23) of participants reported that allergic reactions to medications could present symptoms in all four systems. Parents with a high school education or above showed higher awareness regarding the possibility of skin, respiratory, and cardiovascular symptoms, compared to parents with lower education levels (p<0.001, p=0.004 and p<0.001 respectively). Ten parents in the study reported having prior knowledge of drug adverse reactions. Since the number of participants who received education on adverse drug reactions was insufficient, no statistical comparison was performed.

Responses to the questions designed by researchers regarding drug allergies and side effects showed that 90.6% (n=173) of participants accurately defined side effects, while 79.6% (n=152) correctly identified drug allergies. Parents whose children received regular treatment for chronic illness were more likely to recognize drug side effects compared to parents of children who did not receive regular treatment (p<0.001). Data is summarized in Table II.

Among the parents surveyed about their use of nonprescription medications, 112 participants (58.6%) reported using at least one. The most commonly used nonprescription drug group was analgesics, accounting for 46.4% of cases. Additionally, 24.1% of participants reported that they frequently used vitamin supplements without a prescription.

Table II: Responses of parents to questions regarding drug allergy and drug side effects

Questions (True frequencies)	
Allergic reactions may occur in the future even for medications that were previously taken without issues	148 (77.5)
Drug allergies are independent of the dosage used	161 (84.3)
Drug allergies are unpredictable	163 (85.3)
Drug side effects are predictable	63 (33)
Herbal products can also cause allergies	162 (84.8)
What is the most common group of drugs that cause allergies in children in Türkiye?	
Antibiotics	154 (80.6)
NSAIDs	21 (11)
Vitamin syrups	8 (4.2)
Cough syrups	8 (4.2)

***:** *n(%)*

Data from the parental attitude scale regarding rational drug use revealed a total score average of 178.6±14.7. The sub-dimension score for correct and conscious use averaged 133±13.6, while the effective and safe use sub-dimension averaged 45±7.9. Analysis of factors influencing the total score on the rational drug use scale identified parental education level as a significant positive factor (OR = 1.89; 95% CI = 1.05-3.42; p=0.030). Notably, parents with only one child scored significantly higher in the correct and conscious use sub-dimension compared to those with multiple children (p = 0.005). No statistically significant difference was observed in the effective and safe use sub-dimension.

DISCUSSION

This study aimed to assess the awareness of parents of hospitalized children regarding drug allergies, drug side effects, and rational use of medications. Notably, 9.9% of parents reported that their child had previously experienced at least one drug-related allergic reaction. Literature indicates that the prevalence of reported drug allergy histories among families during childhood varies between 2.9% and 16.8%, with only 4% confirmed as true drug allergies. In the United States, approximately 32 million people report penicillin allergy; however, after appropriate allergic evaluation, more than 95% can tolerate the responsible drug. This highlights the importance of diagnostic evaluation in accurately identifying or rule out incorrect drug allergy labels (7,8).

In studies involving adults, the prevalence of drug allergies in hospitalized patients has been reported between 0.4% and 1.14% (9-12). A study conducted in our clinic examining drug allergies in hospitalized children reported a confirmed drug allergy prevalence of 1.1% (13). In our study, patients reporting a history of drug allergies were referred to the pediatric allergy clinic for diagnostic testing.

Clinical manifestations of drug allergies often present as isolated skin reactions but can also escalate into life-threatening reactions involving the respiratory and cardiovascular systems (14). Our findings indicated a high level of parental awareness regarding cutaneous symptoms; however, the recognition of respiratory and cardiovascular symptoms as potential signs of drug allergies was notably lower. Given that drug allergies often present with skin findings, it is encouraging that parents exhibit high awareness in this area. However, the low recognition of early-type drug reactions absent skin manifestations highlights a critical need for enhanced education for families.

In a 2016 study in the UK, 19.3% of 411 adult participants reported nonprescription medication use, primarily analgesics (15). In Türkiye, a study in 2016 found that 30% of 15.697 adults used nonprescription medications (16). Our study revealed a notably high nonprescription medication use rate of 58.6%. This may be attributed to the prevalence of children with chronic illnesses requiring frequent hospitalizations and regular medication. In Türkiye, analgesics, vitamin-containing products, and herbal supplements can be obtained without a prescription, leading parents of chronically ill children to seek additional benefits from these products. It is imperative to increase awareness regarding the potential adverse effects and allergic reactions associated with these medications.

Rational use of medicines has been a subject of global discourse for many years. According to WHO data, approximately 50% of all medications are inappropriately prescribed and sold, and around 50% of patients do not use their medications correctly (17,18). In the literature, a study evaluating medications prescribed for childhood pneumonia report that 99.4% of patients received at least one antibiotic, with 87.4% receiving multiple prescriptions (19). Additionally, studies from developing countries emphasize that medications are often prescribed at inappropriate doses for a patient's age and weight (20).

In a study from Türkiye utilizing the parental attitude scale for rational drug use, a total score of 143.8±16.5 was reported, with a significant increase in the correct and conscious use sub-dimension scores as parental education level rose (21). In contrast, our study found the average total score on the rational drug use scale to be 157.1±16.2, with the correct and conscious use sub-dimension averaging 120.6±11.5, and the effective and safe use sub-dimension averaging 36.5±7.6. According to the literature, the high scale scores observed in our study can be explained by the fact that the study was conducted in a tertiary hospital, where parents are more frequently informed about medication use by healthcare professionals. Additionally, more than half of the parents had a high school education or higher.

In conclusion, hospitalized patients are at increased risk of adverse drug reactions due to the concurrent use of multiple medications and the presence of coexisting conditions, such as infections. This risk is particularly pronounced in children with chronic illnesses who require frequent hospitalizations and regular medication. Educating parents about the symptoms of adverse drug reactions, along with facilitating detailed allergic evaluations for those with a history of drug allergies, is crucial. Involving parents as key partners in a systematic approach to rational drug use— which includes accurate diagnosis, selecting the right treatment, ensuring proper dosing and duration, and ongoing monitoring—will greatly improve outcomes in pediatric care.

Ethics Committee Approval

This study was conducted in accordance with the Helsinki Declaration Principles. Ethics approval was granted by Ankara Bilkent City Hospital Clinical Trials (decision number 2-24-529).

Contribution of the Authors

Kuzu Kuşaklı A: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***Aytekin Güvenir F:*** Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study. ***Kalaycı F:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in necessary literature review for the study. ***Selmanoğlu A:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results. ***Şengül Emeksiz Z:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Reviewing the article before submission scientifically besides spelling and grammar. ***Dibek Mısırlıoğlu E:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Reviewing the article before submission scientifically besides spelling and grammar.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Ureteroscopy for ureteral stones in children: what has changed with the increase in experience?

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ABSTRACT

Objective: With advancements in endourological equipment and the routine use of the Holmium:YAG laser, endoscopic treatment has become the first-line approach for managing ureteral stones in children. Although ureteroscopy is widely performed, the literature reports varying outcomes regarding its efficacy in pediatric cases. This study aimed to evaluate the impact of increasing endourological experience on stone-free rates and procedure-related complications in children undergoing ureteroscopy with Holmium: YAG laser for ureteral stones

Material and Methods: A comparative analysis was conducted on 32 cases treated with URS for ureteral stones between 2009-2011, the initial three years of our endourological interventions in children, and 78 cases treated with URS for ureteral stones between 2020-2022, the final three years of our 15-year endourological experience, utilising hospital records as the primary data source. Demographic data, stone-free rates, and recorded complications were evaluated in both groups.

Results: In our initial cohort of 32 cases, the stone-free rate at first attempt was 57%, with a complication rate of 15.6% and a conversion rate to open surgery of 18.75%. In contrast, during the last three years, 73 patients (93.5%) achieved stone-free status with a single URS session. Only one case (1.3%) required conversion to open surgery. Complications were observed in 10.2% of cases. Notably, the use of passive dilation with preoperative JJ stent placement became more prevalent during the latter period.

Conclusion: Increasing surgical experience is associated with higher stone-free rates following a single intervention. There were no significant differences in the overall or major complication rates between the two periods. Postoperative fever remains a common complication, underscoring the importance of careful management of JJ stent placement. The most notable parameter that showed a significant improvement with increased experience was the reduced rate of conversion to open surgery.

Keywords: Children, Complication, Ureteroscopy, Ureterolithiasis

INTRODUCTION

Due to changing dietary habits and increasingly sedentary lifestyles, urolithiasis is being encountered more frequently in the pediatric population (1–3). Ureteral stones in children are now commonly managed with endourological interventions, facilitated by the development of smaller-caliber ureteroscopes (4–10). Despite advances in endoscopic technology and the narrower ureteral diameter in children compared to adults, concerns remain regarding key outcomes such as the stone-free rate (SFR) and the complication profile of ureteroscopy (URS) (4,5,9).

We previously published findings based on our initial 32 cases, where we began using routine endourological methods for treating ureteral stones in pediatric patients between 2009 and 2011. During this period, we achieved a stone-free rate of 57% in one session, a complication rate of 15.6%, and a conversion rate of 18.75% to open surgery (4). However, the literature presents varying results concerning stone-free rates and complications following ureteroscopy treatment for ureteral stones in children (4-10).

As our experience with endourological procedures in children has gradually increased over the years, we aimed to evaluate how this enhanced expertise has impacted the outcomes of endoscopic treatment for pediatric ureteral stones. To achieve this, we analyzed cases of ureteroscopy (URS) performed for ureteral stones over the past three years. Our primary objective was to assess the stone-free rate, procedure-related complications, and the conversion rate to open surgery. We sought to compare these results with those from a period when

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our experience was more limited, by presenting data from patients treated with ureteroscopy and Holmium: YAG laser over the past three years, following 15 years of endourological practice.

MATERIALS and METHODS

The cases between 2009-2011, when we initiated routine ureteroscopy for treating ureteral stones in children at our clinic, and the pediatric cases treated with ureteroscopy for ureteral stones between 2020-2022, during which our endourological experience increased, were retrospectively evaluated from hospital records.

Patient age, sex, stone size, stone number, stone location, dilation method, use of a postoperative stent, intraoperative complications, stone-free status, postoperative complications, and conversion to open procedure were recorded. Preoperative ultrasonographic examination was routinely performed in all patients to determine stone size and location. Where ureteral stones could not be detected by ultrasonography, the location and size of the stones were evaluated by computed tomography. We routinely prefer observation as the initial management strategy for pediatric patients with newly diagnosed ureteral stones. Ureteroscopy procedures were performed under direct videoscopic guidance. The semirigid URS (4.5F, R. Wolf, Knittingen, Germany; 7.5F, Karl Storz, Tuttingen, Germany) was advanced into the ureter over a guidewire. Antibiotic prophylaxis, which was started in the perioperative period, was continued as long as the JJ catheter was present.

A manual irrigation pump system was used for ureteral hydrodilation during URS. If hydrodilation was insufficient, a double-J catheter was placed for passive dilation. Active coaxial dilation is not routinely performed in our clinic. An ureteral access sheath and flexible ureterorenocope were not used.

To prevent hypothermia and hyponatremia, isotonic fluid heated to 32 degrees Celsius was used during the procedure. Stones were fragmented using the Holmium: YAG laser (Litho Quanta System, Solbiate Olona Italy) and grasped using a stone basket if applicable. At the end of lithotripsy, stone-free status was confirmed visually and re-evaluated by ultrasonography within a month. Postoperative ureteral stent placement was decided based on visible mucosal or ureteral trauma.

Intraoperative complications recorded included mucosal injury, ureteral perforation, contrast material extravasation, ureterovesical junction injury, and avulsion. Postoperative complications comprised fever (>38^{0}C), ureteral stricture or obstruction, and vesicoureteral reflux. Stone specimens were sent for analysis, and medical therapy and dietary planning were provided postoperatively based on the stone composition. Ultrasonography was performed at first and third months post-procedure to assess for stone recurrence and hydronephrosis. In cases where hydronephrosis was detected in the follow-up USG examination, VUR and ureteral stenosis were tried to be ruled out by performing VCUG and, when deemed necessary, retrograde ureterography.

Statistical analysis was performed using Student's t-tests and Chi-Square tests in SPSS 17.0 Statistical Package Program for Windows, with p <0.050 0considered statistically significant.

RESULTS

In the first period (2009–2011), a total of 32 pediatric patients underwent ureteroscopy (URS) for ureteral stones. In the second period (2020–2022), URS was performed in 78 children for the same indication. The demographic data of both groups are presented in Table I. The follow-up period ranged from 10 to 32 months, with a mean of 21 months. The number of cases significantly increased during the second period, indicating a growing trend in the use of URS for pediatric ureteral stones. While there was no difference in gender distribution between the groups, the mean age of patients in the first period was significantly lower than in the second period (p = 0.001). Renal colic remained the most common presenting symptom in both groups.

The operative data of the patients are summarized in Table II. The rate of multiple stones was significantly higher in the first period, whereas only a few cases with multiple stones were observed in the second period. Although the average stone size was greater in the first period compared to the second, the difference was not statistically significant (p = 0.785). The conversion rate to open surgery was 18.75% in the first period. In the second period, open surgery was required in only one patient due to a severe postural deformity that precluded endoscopic intervention.

While in the first period, in four, URS could not be conducted because of ureterovesical obstruction and edema, and ureterotomy was performed to remove the ureteral stone. Two patients underwent an open procedure because of impacted stones, and ureteroneocystostomy was performed in both. In

Table I: Demographic data of patients

	2009-2011*	2020-2022*
Sex		
Male	16 (50)	40 (51)
Female	16 (50)	38 (49)
Age (years)	5.91±4.98 (0.57-7)	9.64±4.91 (0.74-17)
Patients aged <5 years*	18 (56.2)	29 (37.2)
Symptoms*		
Flank pain	23 (71.8)	5 (65.1)
Urinary tract infection	6 (18.7)	12 (15.4)
Hematuria	2 (6.3)	13 (16.7)
Obstruction	1 (3.2)	2 (2.6)

**: n(%), †: mean±SD (Range)*

Table II: Operative data of patients

	2009-2011	2020-2022
Laterality*		
Right	12 (37.5)	45 (57.7)
Left	11 (34.37)	30 (38.5)
Bilateral	9 (28.13)	3 (3.8)
Stone location*		
Distal	23 (56.1)	51 (65.3)
Mid	4 (9.8)	14 (17.9)
Proximal	8 (19.5)	11 (14.1)
Distal and mid	6 (14.6)	2 (2.7)
Stone number*		
Single	14 (41.5)	73 (93,6)
Multiple	24 (58.5)	5 (6.4)
Stone burden (mm)	8.76±3.08 (4-18)	6.58±2.94 (3.5-20)
Orifice dilation*		
Passive dilation	8 (19.5)	53 (67.9)
No dilation	33 (80.5)	25 (32.1)
Postoperative JJ stent (ureter)*	27 (70.7)	41 (50.6)
Conversion to open surgery*	6 (18.75)	1 (1.28)
Stone free rate in first sesion	57%	93.5%
Over all	92.7%	100%

**: n(%),†: mean±SD (Range)*

Table III: Postoperative complications

	2009-2011	2019-2022
Ureter perforation or extravasation	3	1
Ureterovesical stricture	-	2
Fever	1	5
UV Junction injury (UNC)	1	-
Total	5 (15.6%)	8 (10.2%)

the first period, a Holmium: YAG laser was used to fragment the stones in 9 patients (34.6%), pneumatic lithotripsy in 2 (7.7%), a basket catheter to extract ureteral stones in 4 patients (15.4%), and a combination of Holmium: YAG laser plus pneumatic lithotripsy in 11 patients (42.3%) (2). In the second period, only Holmium: YAG laser was used for fragmentation.

A stone-free rate of 57% was achieved with a single intervention in patients during the first period, whereas this rate increased to 93.5% in the second period (p = 0.001). The overall stone-free rate reached 92.7% in the first period, while all patients in the second period ultimately achieved stone-free status.

Passive dilation by applying a JJ stent before the procedure was performed in 19.5 % of the cases in the first-period patients, increasing to 67.9% in the second-period patients. After the procedure, the JJ stent placement rate was 70.7% in the first group and 50.6% in the second group.

While complications were detected in 15.6% of the first-period patients, a major complication requiring serious surgical intervention was encountered in one patient. No major complications were encountered in the second period, with the total complication rate at 10.2% (Table III). There was no significant difference in complication rates or major complications (p =0.082 and p =0.393, respectively).

DISCUSSION

Ureteroscopy for pediatric ureteric stones stands a safe and effective first-line treatment, particularly when conservative therapy proves ineffective (11,12). Since 2009, our clinic has routinely performed ureteroscopy with Holmium: YAG laser lithotripsy for pediatric patients with ureteral stones. In this study, we evaluated the treatment of ureteral stones using this approach, comparing two periods: one with limited experience (2009-2011) and another with increased proficiency (2020-2022).

The significant increase in cases during the second period (2020–2022) reflects a rising trend in the utilization of URS for pediatric ureteral stones. The higher mean age of patients observed in this period may be attributed to the redirection of cases to our clinic due to COVID-19–related restrictions in other healthcare facilities.

The second period showed a decrease in the incidence of multiple stones and a reduction in the mean stone size, which may reflect improvements in early detection and intervention, thereby preventing stone progression.

Notably, the stone-free rate after a single session significantly improved, rising from 57% in the first period to 93.5% in the second period, highlighting enhanced proficiency in stone fragmentation. The increased use of pre-intervention JJ stent placement during the second period likely contributed to the higher stone-free rate in a single attempt. Furthermore, passive dilation with preoperative JJ stent placement became more prevalent in the second period, potentially influencing the improved outcomes. Additionally, preoperative JJ stent insertion reduced the need for postoperative stent placement.

The substantial decrease in conversion to open surgery from 18.75% in the first period to 1.28% in the second period demonstrates advancement in surgical techniques and decision-making.

Although ureteroscopy is a minimally invasive, it may lead to intra and/or postoperative complications. Those complications included stone migration, ureteral perforation, mucosal laceration, hematuria, pain, and urinary tract infection. Notably, our study did not encounter stone migration, likely due to careful procedural techniques, including low fluid pressure, laser power, and catheter placement. The overall complication rate decreased from 15.6% to 10.2% between the two periods, with no major complications in the latter. There was no statistically significant difference in the complication rate or major complications between the two periods. According to our data, increasing experience had no effect on the complication

rate. Although it is not possible to avoid some complications due to the nature of the procedure, meticulous work from the beginning under the supervision of a single senior surgeon has ensured that our complication rates are within acceptable limits, according to the literature.

Postoperative fever emerged as the most common complication in the second period, despite clean urine tests and cultures preoperatively. This underscores the need for judicious JJ stent use to minimize postoperative UTI rates (14). Postoperative UTI rates increased with prolonged indwelling time. This was attributed to JJ stent placement and colonization, highlighting the need for careful consideration of stent use (15).

Campbell et al. (16) advocate for primary URS whenever possible due to the excellent SFR and potential for single anesthetic treatment (17). However, some authors suggest preoperative JJ stent replacement when ureterorenoscopy is planned (18). While JJ stent is preferred in adults to reduce postoperative complications, in our pediatric series, JJ stents were primarily used for passive ureteral dilation, enhancing safety (19,20).

Limitations of our study include its retrospective nature and the involvement of various fellows in procedures, which could introduce variability. Additionally, pneumatic lithotripsy was utilized for stone fragmentation in patients in the early period. Future studies with a prospective design and a standardized approach may offer further insight.

Nonetheless, our study underscores the importance of continuous learning and experience in improving outcomes. Ongoing education and mentoring programs are crucial for advancing urologists' skills.

CONCLUSION

Ureteroscopy with laser lithotripsy stands as an excellent first-line treatment for pediatric ureteral stones, especially following failed conservative therapy. We advocate for preoperative JJ stent placement to enhance stone-free rates in a single session and reduce conversion to open surgery, although experience did not significantly affect complication rates. Double-J stent application may increase postoperative fever incidence. We also observed that preoperative JJ stent insertion reduced the need for postoperative stent placement.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. This study was approved by the Bilkent City Hospital Ethics Committee (Approval no. E-2-23-5304; Clinical Research ID NCT06147817).

Contribution of the authors

Demirtaş G: Taking responsibility in the writing of the whole or important parts of the study. ***Tagcı S:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. Taking responsibility in logical interpretation and conclusion of the results. ***Ekberli G:*** Taking responsibility in necessary literature review for the study. ***Karabulut B:*** Planning methodology to reach the Conclusions. Reviewing the article before submission scientifically besides spelling and grammar. ***Tiryaki HT:*** Constructing the hypothesis or idea of research and/or article. Organizing, supervising the course of progress and taking the responsibility of the research/study.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Clinical characteristics, antibiotic susceptibilities, treatment characteristics and outcomes in pediatric patients with *Sfingomonas paucimobilis* bacteremia

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ABSTRACT

Objective: This study aimed to examine the clinical and laboratory features, antibiotic susceptibilities, treatment characteristics, and outcomes of pediatric patients with *Sphingomonas paucimobilis* bacteremia.

Material and Methods: This single-center, retrospective study included patients aged between 1 month and 18 years who were treated for *Sphingomonas paucimobilis* bacteremia between September 2019 and December 2022.

Results: The study population included 12 pediatric patients with *S. paucimobilis* bacteremia. The median age of the patients was 28.5 months (range 7-215 months) and 50% were male. All patients had hospital-acquired infections (HAIs). The presence of comorbidities such as hematological-oncological malignancies, neurological disorders, burns and immunological disorders, the presence of a central venous catheter and a history of hospitalization within the last 12 months were prominent risk factors. Bacterial isolates were susceptible at different rates to antibiotics used as follows: piperacillin-tazobactam (83.3%), ceftazidime (91.7%), cefepime (91.7%) and meropenem (100%). The patients were treated with meropenem, cefepime, ceftazidime and piperacillin-tazobactam and the median duration of systemic antibiotic treatment was 10 days (range 10-14 days). Central venous catheters (CVCs) were removed in 3 patients who developed catheter-related bloodstream infections (CRBSIs). Persistent bacteremia, recurrence and 30-day mortality were not observed in any patient.

Conclusion: *Sphingomonas paucimobilis* remains an important opportunistic pathogen of hospital-acquired bacteremia, especially in children with risk factors. Successful treatment seems possible with systemic antibiotic therapy and removal of CVC in the presence of CRBSI.

Keywords: Antibiotic susceptibility, Bacteremia, Children, *Sphingomonas paucimobilis*, Treatment

INTRODUCTION

Sphingomonas paucimobilis (*S. paucimobilis*) is a non-fermentative, yellow-pigmented, aerobic opportunistic gram-negative bacillus (1). *S.paucimobilis* can be found in nature, on the skin, among oropharyngeal flora, and on surfaces and medical equipment in hospital environments (2-4). Community or hospital-acquired *S.paucimobilis* infections may occur (3). It is a common cause of hospital-acquired infections because it colonizes in hospitalized patients. The source of nosocomial infections may be previous colonization of the patient or biofilm formation in various contaminated medical equipment and water distribution systems (5,6). Although it rarely causes serious life-threatening infections, it may be the responsible infectious agent in bacteremia, sepsis, septic shock, endocarditis, peritonitis, meningitis, ventriculitis, adenitis, gastroenteritis, visceral abscesses, respiratory and urinary tract infections, septic arthtitis, osteomyelitis, spondylodiscitis and among them, bacteremia ranks first (3,4,7). Risk factors for *S.paucimobilis* bacteremia include predominantly malignancy, immunosuppression, comorbidities such as diabetes mellitus, end-stage renal disease, and use of central venous catheters (8-10). *S.paucimobilis* is generally resistant to penicillins and first-generation cephalosporins due to the formation of beta-

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lactamases (11). There is no definite guideline for antimicrobial treatment of *S.paucimobilis* infections. There are sporadic case reports (12-14), case series (1,8,9) and outbreak notification studies (15-17) related to *S.paucimobilis* infections in the pediatric age group. This study evaluated clinical and laboratory characteristics, antibiotic susceptibilities, treatment characteristics and outcomes of pediatric patients with *S.paucimobilis* bacteremic.

MATERIALS and METHODS

Study design and participants

This retrospective, single-center study included 12 pediatric patients with *S.paucimobilis* bacteremia at Ankara Bilkent Children's Hospital between September 2019 and December 2022.

Data collection

Data on demographic, clinical, laboratory and treatment characteristics and clinical outcomes were obtained from the hospital's electronic medical records. The study included patients aged 1 month to 18 years with complete data but without polymicrobial bloodstream infection, patients with *S.paucimobilis* bacteremia, and patients who received appropriate antibiotic therapy after the onset of bacteremia. Patients aged <1 month to >18 years with polymicrobial bloodstream infections or missing data and patients referred from another hospital were excluded from the study.

Definitions

S.paucimobilis bacteremia was defined as a single blood culture positivity for *Sphingomonas paucimobilis* in a patient with clinical findings consistent with bacteremia. Bacteremia was considered community-acquired (CA) if detected within the first 48 hours of hospitalization and hospital-acquired (HA) if detected after the first 48 hours of hospitalization (18). Duration of hospitalization was defined as the number of days from the day of the patient's first hospitalization until discharge. Duration of hospital stay associated with bacteremia was defined as the time from the initial detection of *Sphingomonas paucimobilis* bacteremia during hospitalization to completion of antibiotic therapy and treatment of complications. The duration of antibiotic therapy received was measured as the time from the first positive blood culture to the administration of the last dose of effective antibiotic therapy. Duration of bacteremia was defined as the number of days between the first positive and first negative blood culture for *S. paucimobilis*. In a patient with a central venous catheter (CVC), a catheter-related bloodstream infection (CRBSI) was considered if the time to growth signal positivity in the catheter hub sample was detected at least 2 hours before the differential positivity time (DTP) in the peripheral vein sample (19).

Microbiological methods

Assisted Laser Desorption Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS) system and VITEK® MS v3.2.0 (bioMerieux, Marcy-l'Etoile, France) database were used for identification of the causative pathogen and antibiotic susceptibility testing. Since there were no standard clinical cut-off values for *S.paucimobilis*, the pharmacokinetic and pharmacodynamic breakpoint values of the Clinical and Laboratory Standards Institute (CLSI) for other non-Enterobactereles species specified on the Vitek 2 (Biomerieux Inc., France) were used (20). Considering the differences that occurred over the years due to changes in the panel content and antibiotics used, piperacillin-tazobactam, ceftazidime, meropenem, amikacin, gentamicin, ciprofloxacin and trimethoprim-sulfamethoxazole antibiotics were evaluated.

Statistical analysis

Statistical analysis were performed using SPSS software, version 26.0 (IBM Inc., Chicago, IL). The Kolmogorov-Smirnov test was used to determine whether the data were normally distributed. Results were reported as median (min-max). A p-value of <0.050 was considered statistically significant.

RESULTS

S. paucimobilis was identified in the bacterial culture media of 12 patients. The median age of the study population was 28.5 months (range 7-215 months) and 50% were male. Risk factors included hematologic-oncologic malignancy in 8, a neurologic disorder in 2, a burn in 1, an immunologic disorder in 1, a history of central venous catheter insertion in 7, and hospitalization within the previous 12 months in all patients. The median duration of hospitalization before bacteremia was 20 days (range 10-124 days). All patients had hospital-acquired infections (HAIs). Demographic and clinical characteristics of patients with *S.paucimobilis* bacteremia and laboratory findings are shown in Tables I and II, respectively.

Antimicrobial susceptibilities

The antimicrobial susceptibilities of the reported isolates are shown in Figure 1. Multidrug resistance was not observed.

Systemic treatments

Patients received antibiotherapies with meropenem (n=4), cefepime (n=2), ceftazidime (n=2) and piperacillin-tazobactam (n=4). The median duration of systemic antibiotic treatment was 10 days (range 10-14 days). Three patients with CRBSI had their infected CVC removed.

Outcomes

The median duration of infection-related hospital stay was 10 days (range 10-14 days), and the duration of bacteremia was 3 days (range 2-3 days). None of the patients experienced

Table I: Demographic and epidemiologic laboratory characteristics of patients with Sphingomonas paucimobilis bacteremia

Patient no	Age (months)	Gender	Underlying diseases	Hospital stay before the onset of bacteremia (days)	Presence of CVC	Sources of infection	Hospital stay within the previous 12 months
1	26	M	Surgical morbidity (burn)	34	No	Primary bacteremia	Yes
2	12	F	Hematologic-oncologic malignancy (rhabdomyosarcoma)	16	implantable port	CRBSI	Yes
3	72	F	Hematologic-oncologic malignity (neuroblastoma)	19	Non-tunnelled central venous catheter	Primary bacteremia	Yes
4	66	M	Hematologic-oncologic malignancy (neuroblastoma)	6	implantable port	CRBSI	Yes
5	215	M	Hematologic-oncologic malignancy (Ewing sarcoma)	8	No	Primary bacteremia	Yes
6	70	F	Hematologic-oncologic malignancy (acute lymphoblastic leukemia)	94	implantablel port	Primary bacteremia	Yes
7	161	M	Hematologic-oncologic malignancy (Hodgkin lymphoma)	21	No	Primary bacteremia	Yes
8	30	M	Hematologic-oncologic malignancy (acute lymphoblastic leukemia)	42	implantable port	Primary bacteremia	Yes
9	84	F	Hematologic-oncologic malignancy (acute lymphoblastic leukemia)	16	Tunneled central venous catheter	CRBSI	Yes
10	27	M	Immunologic disorder (common variable immunodeficiency)	51	No	Primary bacteremia	Yes
11	16	F	Neurologic disorder (hypotonic infant, epilepsy)	25	No	Primary bacteremia	Yes
12	7	F	Neurologic disorder (hydrocephalus, epilepsy)	5	Non-tunneled central venous catheter	Primary bacteremia	Yes

M: *Male,* ***F:*** *Female,* ***CRBSI:*** *Catheter-related Bloodstream Infection*

Table II: Laboratory characteristics of the patients with Sphingomonas paucimobilis bacteremia

	WBC at the onset of bacteremia × 10^9/L	ANC during bacteremia × 10^9/L	CRP levels during bacteremia (mg/dL)
1	13760	5610	26
2	2160	920	10
3	40	20	98
4	4810	1960	28
5	290	30	120
6	3620	3010	90
7	20	0	84
8	970	230	100
9	2700	2120	91
10	9910	7620	52
11	25250	14420	30
12	6520	2140	46

WBC: *White Blood Cell,* ***ANC:*** *Absolute Neutrophil Count,* ***CRP:*** *C-reactive Protein*

Table III: Antibiotics are given to patients with Sphingomonas paucimobilis bacteremia and treatment outcomes

Case no	Antibiotics used	Duration of antibiotic therapy (days)	Removal of CVC	Hospital stay after the onset of bacteremia (days)	Total duration of hospital stay	Duration of bacteremia (days)
1	Piperacillin-tazobactam	10	No	20	136	3
2	Cefepime	10	Yes	24	40	3
3	Meropenem	14	No	20	39	2
4	Piperacillin-tazobactam	10	Yes	11	17	3
5	Meropenem	14	No	16	24	2
6	Piperacillin-tazobactam	10	No	17	111	3
7	Meropenem	14	No	55	76	2
8	Meropenem	14	No	124	166	2
9	Cefepime	10	Yes	10	26	3
10	Piperacillin-tazobactam	10	No	32	83	3
11	Ceftazidime	10	No	95	120	3
12	Ceftazidime	10	No	10	15	2

CVC: *Central venous Catheter*

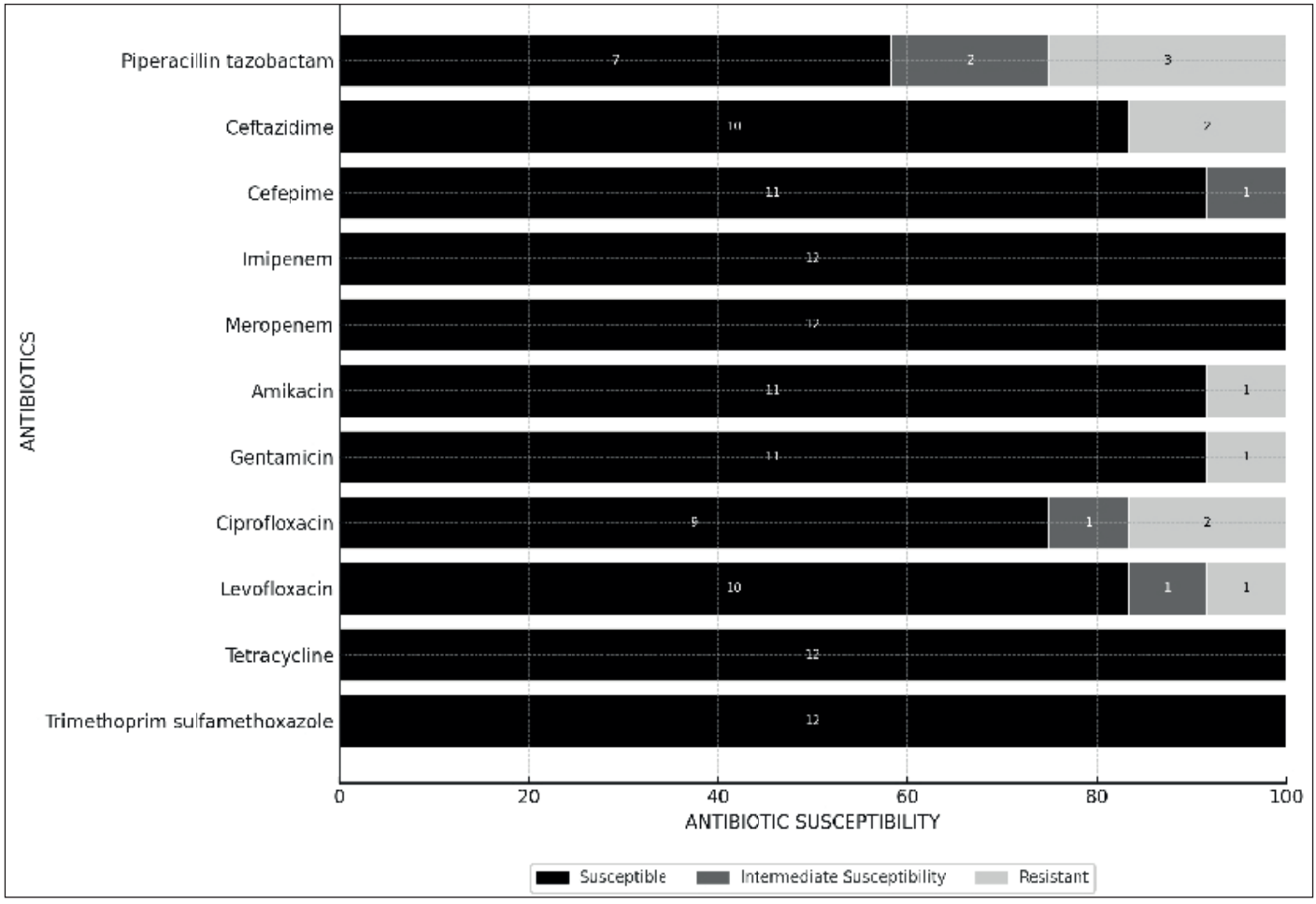

Figure 1: Antimicrobial susceptibilities of blood isolates obtained from patients with Sphingomonas paucimobilis bacteremia

persistent bacteremia, recurrence, *S. paucimobilis* bacteremia or death. Table III presents the treatment characteristics and results of patients with *S.paucimobilis* bacteremia are presented in Table III.

DISCUSSION

Although case reports, case series and outbreak reports of *S.paucimobilis* infection in pediatric patients have been published, the clinical features, treatment options and clinical outcomes of *S.paucimobilis* infections are still poorly known. Therefore, we retrospectively evaluated the clinical features, treatment options and outcomes in our pediatric cases of *S.paucimobilis* bacteremia.

S.paucimobilis can infect all age groups, from neonates to adults. In the literature, sporadic case reports, case series and outbreak reports in the neonatal age group have also been published (9,12,15,16). *S.paucimobilis*-associated infections, such as bacteremia as well as mastoiditis and peritonitis in previously healthy children with comorbidities, have been reported as sporadic case reports, as have pediatric case series and pediatric outbreak studies (1,8,9,13,15,16). During an *S.paucimobilis* bacteremia outbreak in a pediatric hematology-oncology ward, the median age of the patients was 5 years (1 year-17 years). In another case series, pediatric patients were between 6-12 years of age (1,16). In pediatric series, the male ratio varies between 57.1% and 58.3% (8,9). The median age of our study population was younger than the median age in the pediatric case series reported in the literature, and the gender ratios were similar to the values reported in other studies. Since our study did not include the neonatal age group, there were no patients in this population.

In patients infected with *S.paucimobilis*, primary bacteremia rates vary between 35.7% and 66% and catheter-related bloodstream infection (CRBSI) rates vary between 12.7% and 33% (1,8,9,14,16). In a pediatric case series, 20 of 24 patients had primary bacteremia and 2 had CRBSI (9). Most of the *S.paucimobilis* infections reported in the literature are hospital-acquired infections (4,8). However, in contrast to recent publications, most of the infections in this study were community-acquired infections. In a pediatric case series, community-acquired *S.paucimobilis* infections were detected in 54.2% of previously healthy children (9). In an adult case series, the rate of community-acquired cases reportedly varied between 52.7% and 77% (3,21,22). Patients with community-acquired disease were younger on average, had fewer comorbidities and were less likely to have polymicrobial infections. In particular, comorbid diagnoses of cancer and renal disease were not frequently seen in cases with hospital-acquired infections (21). In our study, the incidence rates of primary bacteremia and catheter-related bloodstream infections (CRBSI) were similar to those reported in the literature. Although community-acquired (CA) *S.paucimobilis* bacteremia cases have also been reported in the literature, all of our cases were hospital-acquired (HA) infections and we had no community-acquired (CA) cases. Risk factors for *S.paucimobilis* bacteremia have been reported as hematologic-oncologic malignancies (ALL, solid tumors, lymphomas), immunosuppression, immunodeficiency, surgical diseases, burns, prematurity, diabetes mellitus, alcoholism, end-stage renal disease, permanent intravenous device use, Down syndrome, intensive care unit hospitalization, and use of contaminated water (1-3,8,15,16). The time from hospital admission to the development of *S.paucimobilis* bacteremia varies between 4-47 days and the median time was reported to be 12 days (9). In the pediatric case series, the median length of hospital stay was 7 days, ranging between 4 and 22 days (8,9). In various case series, bacteremia was the most common hospital-acquired infection, while skin soft tissue and lower respiratory tract infections were the most common community-acquired infections (3,9,21,22). In our study, all patients had a history of hospitalization within the last 12 months, suggesting that *S.paucimobilis* colonization may also be an important risk factor for *S.paucimobilis* bacteremia. However, the effect of hospitalization on *S.paucimobilis* colonization is beyond the scope of our study. Although the risk factors in our study are similar to those reported in the literature, the presence of patients with immunological and neurological disorders suggests that these may also be risk factors for *S.paucimobilis* bacteremia.

S.paucimobilis is generally sensitive to carbapenems, aminoglycosides, fluoroquinolones, trimethoprim-sulfamethoxazole and piperacillin/tazobactam (2). Due to chromosomally encoded beta-lactamase production, this microorganism resists penicillin and the first generation of cephalosporins (9). In a pediatric case series (37.5%), isolates resisted at least one antibiotic (9). The highest resistance rate was detected against 3rd generation cephalosporins (20.9%). In this case, series rates of resistance against ampicillin (12.5%), amikacin (8.3%), piperacillin (8.3%) and cefuroxime (8.3%) were as indicated. All isolates were susceptible to imipenem, ciprofloxacin and trimethoprim/sulfamethoxazole (9). In a pediatric study, all isolates were susceptible to cefoperazone-sulbactam, as revealed using the disc diffusion method (16). Very different antibiotic susceptibility rates to various antibiotics used for the treatment of *S.paucimobilis* have been reported in the literature as follows: meropenem (67-100%), imipenem (81.3-100%), ciprofloxacin (81.3-100%), levofloxacin (92.9-100%), piperacillin-tazobactam (42-100%), cefepime (89.2-100%), ceftazidime (68.8-100%), cefoperazone-sulbactam (100%), trimethoprim-sulfomethoxazole (75-100%), tigecycline (100%), amikacin (59-100%), gentamicin (59-90.6%) (3-6,8,21). *S.paucimobilis* has a natural resistance to colistin (1,15). Multidrug-resistant (MDR) strains of *S.paucimobilis* have also been indicated (2). In our study, antibiotic susceptibility rates for meropenem, ceftazidime, cefepime and piperacillin-tazobactam were high and no multidrug-resistant (MDR) isolates were detected.

There is no standardized and recommended treatment for S. paucimobilis infections, especially *S.paucimobilis* bacteremia (2). Therefore, antibiotic treatment is individualized according to the susceptibility pattern of bacterial isolate (2). In studies reported in the literature, the central venous catheter was replaced, removed or not in the presence of catheter-related bloodstream infections caused by *S.paucimobilis* (5,14,16). The reason why removal of the central venous catheter is not necessary may be explained by the low virulence of S. paucimobilis (23). *S.paucimobilis* shows low virulence due to its different glycosphingolipid structure in the cell wall and the absence of lipopolysaccharide components (2). The duration of treatment in *S.paucimobilis* bacteremia usually varies between 7-14 days, depending on the clinical response (9,24). In some cases, 21 days of intravenous treatment was administered (25). In complicated patients, patients who received treatment for up to 6 weeks have been reported (26,27). Antibiotherapies for *S.paucimobilis* bacteremia were reportedly performed with ciprofloxacin and cefepime in adults, cefoperazone-sulbactam in pediatric, with meropenem, levofloxacin, piperacillin-tazobactam, ceftazidime, ceftriaxone, cefuroxime, ampicillin-sulbactam, aminoglycosides in combination with other beta-lactam antibiotics in adult and pediatric patients (5,8-10,14-16,23-28). In our study, meropenem, ceftazidime, cefepime and piperacillin-tazobactam were used, as in pediatric studies, which have been observed to have high antibiotic susceptibility rates. Although the use of cefoperazone-sulbactam, ceftriaxone, cefuroxime, and ampicillin-sulbactam in pediatric patients has been reported in the literature, they were not used in the treatment of patients because they were not studied in our antibiotic susceptibility tests.

While no mortality has been reported in some case series of pediatric *S.paucimobilis* bacteremia (9), mortality rates ranging between 3.9% and 7.7% have also been indicated in some other case series (16). In these studies, two pediatric patients with acute lymphocytic leukemia (ALL) died in the intensive care unit due to sepsis (16) and one premature patient died in the neonatal intensive care unit due to septic shock (29). There is also a report of pediatric sporadic mortality (13). Sporadic mortality cases have been reported in adults (1,2). In addition, adult infection-related mortality ranges from 0% to 5.5% (3,8,21). The development of septic shock has also been reported (8). In one study, recurrence was not observed after resolution of *S.paucimobilis* bacteremia (5).

The study's limitations include its single-center retrospective design, the scarce number of cases included in our study population, and the lack of colonization status. However, the study's strengths include considering immunological and neurological disorders and other risk factors as potential risk factors for *S.paucimobilis* bacteremia in the pediatric age group. All patients had hospital-acquired infections (HAIs) and a history of hospitalization within the previous 12 months. The antibacterial susceptibility tests were performed, and successful treatment regimens that could be used to treat HAIs were mentioned.

In conclusion, it should remembered that *S.paucimobilis* bacteremia may lead to hospital-acquired (HA) bacteremia in immunocompromised pediatric patients with comorbidities, in the presence of central venous catheters and pediatric patients with a history of previous hospitalization. Although *S.paucimobilis* bacteremia has low virulence, it should be kept in mind that it can lead to serious conditions such as septic shock. To treat *S.paucimobilis* bacteremia, removing the infected central venous catheter and applying systemic antibiotic therapy are important. In pediatric patients, piperacillin-tazobactam, ceftazidime, cefepime and meropenem are antimicrobial agents that can successfully treat *S.paucimobilis* bacteremia.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by the Ankara City Hospital Clinical Research Ethics Committee (Date: 01.03.2023, Decision number: E2-23-3575).

Contribution of the authors

Güneş Ö: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***Özkaya Parlakay A:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, , Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***Güney AY***: Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experimentsTaking responsibility in necessary literature review for the study. ***Coşkun ZN:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***Üçkardeş F:*** Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in the writing of the whole or important parts of the study. Yahşi A: Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in necessary literature review for the study. ***Özen S:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***Erat T:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in necessary literature review for the study. ***Gülhan B:*** Organizing, supervising the course of progress and taking the responsibility

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Original Article

Hidden risks, timely solutions: pediatric penoscrotal trauma and clinical outcomes

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ABSTRACT

Objective: Pediatric penoscrotal trauma, though relatively uncommon, can lead to significant clinical consequences. These injuries, predominantly caused by blunt mechanisms, can also result from penetrating trauma, potentially leading to severe complications. Ultrasonography serves as a critical diagnostic tool, with timely surgical intervention being crucial, particularly in testicular rupture. This study aimed to evaluate the injury mechanisms, diagnostic processes, and treatment outcomes in pediatric patients sustaining penoscrotal trauma.

Material and Methods: This retrospective observational study included 31 male patients under 18 years old treated for isolated penoscrotal trauma from October 2020 to July 2024. Data collected included demographics, trauma type, injury mechanisms, ultrasonographic findings, and treatment methods. Patients were categorized into blunt and penetrating trauma groups, with age distribution and ultrasonographic follow-up comparisons conducted. SPSS version 25.0 was used for statistical analysis, and $p<0.050$ was considered statistically significant.

Results: The mean patient age was 8.94±3.52 years. Scrotal trauma accounted for 64.5% of cases, penile trauma 32.3%, and combined penoscrotal trauma 3.2%. Penetrating trauma (58.1%) was more prevalent than blunt trauma (41.9%), with bicycle accidents being the most frequent cause (38.7%). Most penetrating injuries required surgical intervention (15 patients), while blunt injuries were typically managed conservatively (10 patients). No significant difference in testicular volume was observed during follow-up ultrasonography among blunt trauma patients ($p=0.068$).

Conclusion: Management strategies for pediatric penoscrotal trauma differ based on trauma type. Early diagnosis and appropriate intervention appear essential for preserving testicular function and morphology.

Keywords: Chilhood trauma, doppler, genitourinary injury, ultrasonography

INTRODUCTION

Penoscrotal trauma is a rare but potentially severe condition among children. Although uncommon, scrotal injuries bear significant clinical importance, accounting for less than 1% of all trauma cases (1,2). However, conditions like testicular rupture may jeopardize future fertility and require prompt and appropriate intervention (2–4).

The most common causes of penoscrotal trauma in children include blunt mechanisms such as falls, sports-related injuries, and bicycle accidents, although penetrating injuries also constitute a significant portion (4–6). Intratesticular hematomas from blunt trauma can progress to testicular rupture, often requiring surgical intervention (7,8).

Physical examination is vital in diagnosing scrotal trauma but can be hindered by acute-phase pain, swelling and edema (1). Ultrasonography, however, remains an invaluable diagnostic tool, identifying key indicators of testicular rupture such as heterogeneous echotexture and disrupted testicular contours (4,9,10). Doppler ultrasound additionally provides crucial information on testicular perfusion (11,12).

Numerous studies emphasize the importance of early surgical intervention in the management of penoscrotal trauma (4,13).

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Conservative management of testicular rupture is generally discouraged due to the risk of severe complications, including infection and testicular atrophy (7,8).

This study aimed to evaluate the injury mechanisms, diagnostic processes, and treatment outcomes in pediatric patients sustaining penoscrotal trauma.

MATERIALS and METHODS

Patients under 18 treated for isolated penoscrotal trauma between October 2020 and July 2024 were included. Exclusion criteria encompassed patients with incomplete medical records, significant concomitant injuries, or unavailable follow-up data.

Collected data included patient age, injury location (penile, scrotal, or penoscrotal), trauma type (blunt or penetrating), injury mechanism (fall, collision, bicycle accident, direct blow, traffic accident, animal bite), treatment method (surgical or conservative), ultrasonography (US) findings, follow-up duration, and if available, control US results.

Patients were categorized into blunt and penetrating trauma groups, and the age distribution was compared statistically. Testicular volume changes post-blunt trauma was also assessed using US follow-up.

Data were analyzed using IBM Statistical Package for the Social Sciences, version 25.0 (SPSS Inc., Armonk, NY, IBM Corp., USA). Continuous variables were reported as mean±SD; categorical variables were expressed as frequencies and percentages. The relationships between trauma type, mechanism, treatment modality, and ultrasonographic findings were assessed using the chi-square test. A comparison of the age of participants was conducted using an independent sample t-test according to trauma type, and an analysis of variance (ANOVA) test according to trauma mechanism. A p-value of less than 0.050 was considered statistically significant.

RESULTS

Thirty-one male patients were included, with an average age of 8.94 ± 3.52 years. Injury distribution comprised scrotal trauma (64.5%), penile trauma (32.3%), and combined penoscrotal trauma (3.2%). Penetrating trauma (58.1%) surpassed blunt trauma (41.9%), with bicycle accidents being the primary cause (38.7%). No significant associations were found between trauma type or mechanism and patient age (p=0.933 and p=0.342) (Table I).

Ten blunt trauma cases were conservatively managed; three required surgical intervention. Conversely, most penetrating trauma patients underwent surgery, with only three receiving conservative care. Among blunt trauma cases, US revealed normal or unnecessary imaging in five patients, while in penetrating trauma, eight had normal imaging, and six required no US.

Table I: Comparison of patient age according to trauma type and trauma mechanism

	Age*	p†
Trauma type		
Blunt trauma	9±4.5 (3-16)	0.933
Penetrating trauma	8.9±2.7 (4-14)	
Trauma mechanism		
Motor-vehicle accident	7.5±6.3 (3-12)	0.342
Bicycle accident	9.3±2.7 (6-14)	
Direct blow (Knee, Punch)	11.2±4.8 (6-16)	
Fall/collision	7.5±3.1 (3-13)	
Animal bite	11 (11)	

**: mean±SD (min-max), †: ANOVA test used*

Table II: Comparison of testicular volume after trauma and at follow-up in patients with blunt scrotal trauma

	Testis volume (ml)		follow up (month)*	p†
	After trauma	Control		
Age‡				
6	1.73	1.75		
14	10.23	10.18		
14	9.68	9.62		
6	2.12	2.23	5.44±0.8	0.068
16	16.34	16.38		
12	4.82	4.9		
14	11.45	11.61		
10	2.88	2.93		
7	2.67	2.8		

**: (month) (mean ±SD), †: paired sample t test used, ‡: year*

Testicular volume measurements conducted in nine blunt trauma patients showed no significant difference from initial to follow-up ultrasounds (p=0.068), suggesting minimal long-term impact on testicular volume (Table II). This finding suggests that blunt scrotal trauma does not result in significant long-term impact on testicular volume. Furthermore, in the 3 patients who underwent surgical intervention, the absence of significant changes in testicular volume supports the notion that timely surgical management plays a critical role in preserving testicular function and morphological integrity.

DISCUSSION

This study thoroughly evaluated demographic and clinical characteristics of pediatric penoscrotal trauma cases. Contrary to literature indicating predominantly blunt trauma (75-80%), our cohort showed a higher incidence of penetrating trauma (58.1%), possibly due to regional factors influencing injury mechanisms (14,15).

Penetrating trauma typically requires surgical intervention, aligning with our findings (16,17). Consistent with these findings, our study also demonstrated that most patients with

penetrating injuries required surgical management. Furthermore, similar to previous reports, our results showed that the majority of patients with blunt trauma could be successfully managed through conservative treatment approaches (18,19).

Consistent with global studies, bicycle accidents were the predominant trauma mechanism, emphasizing the need for protective gear use (14,20). This highlights the need to raise awareness regarding the importance of protective equipment use during bicycle riding.

Finally, the absence of significant changes in testicular volume during follow-up suggests that early and appropriate intervention positively influences long-term outcomes. Similar findings have been reported in the literature, indicating that testicular volume and function are preserved in pediatric patients who receive timely and appropriate management (2,21).

Limitations include retrospective design, limited sample size, and short follow-up, restricting long-term functional and fertility assessments. Future prospective studies with larger cohorts are recommended to enhance result reliability.

CONCLUSION

The study suggests trauma type significantly influences treatment strategies for pediatric penoscrotal injuries. US emerges as a valuable diagnostic tool, and early, appropriate intervention appears critical for preserving testicular morphology and function.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. This study has been approved by the Ankara Bilkent City Hospital Ethics Committee (TABED: 2-24-476/18.09.2024).

Contribution of the authors

Bostancı SA: Constructing the hypothesis or idea of research and/or article, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***Erten EE:*** Constructing the hypothesis or idea of research and/or article, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***Ertürk A:*** Planning methodology to reach the conclusions, Reviewing the article before submission scientifically besides spelling and grammar. ***Öztorun Cİ:*** Planning methodology to reach the conclusions, Reviewing the article before submission scientifically besides spelling and grammar. ***Çayhan VS:*** Taking responsibility in logical interpretation and conclusion of the results. Akbaş İ: Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***Abay AN:*** Taking responsibility in logical interpretation and conclusion of the results. ***Demir S:*** Constructing the hypothesis or idea of research and/or article, Taking responsibility in the writing of the whole or important parts of the study. ***Azılı MN:*** Organizing, supervising the course of progress and taking the responsibility of the research/study. ***Şenel E:*** Organizing, supervising the course of progress and taking the responsibility of the research/study.

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Original Article

Two-year neurodevelopmental outcomes after therapeutic hypothermia in neonatal hypoxic-ischemic encephalopathy: a retrospective cohort study

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ABSTRACT

Objective: Therapeutic hypothermia is the standard neuroprotective treatment for neonates with hypoxic-ischemic encephalopathy (HIE). However, neurodevelopmental outcomes may still vary depending on the severity of encephalopathy. This study aimed to evaluate two-year neurodevelopmental outcomes in infants with HIE treated with therapeutic hypothermia and compare outcomes between Stage 2 and Stage 3 cases classified according to the Sarnat & Sarnat staging system.

Material and Methods: We conducted a retrospective cross-sectional study including 138 infants born at ≥35 weeks of gestation who were diagnosed with HIE and received therapeutic hypothermia in a Level III NICU between January 2016 and December 2017. Neurodevelopment was assessed at 24 months using the Bayley Scales of Infant and Toddler Development-II (BSID-II), focusing on Mental Development Index (MDI) and Psychomotor Development Index (PDI) scores.

Results: Infants in the Stage 3 group required significantly more respiratory support, had a higher frequency of aEEG abnormalities, and more often received anticonvulsant therapy ($p=0.020$, $p<0.001$ and $p<0.001$, respectively). The Stage 3 group had significantly lower mean MDI and PDI scores (84±10 and 71±11, respectively) than the Stage 2 group (89±17 and 94±18; $p=0.049$ and $p=0.001$). Neurodevelopmental impairment was more prevalent in Stage 3 patients (36.5% vs. 17.3%, $p=0.012$).

Conclusion: Despite uniform application of therapeutic hypothermia, neurodevelopmental outcomes at 24 months differ significantly by HIE severity. These findings highlight the importance of timely intervention, individualized follow-up, and the need for additional strategies in managing severe HIE cases.

Keywords: Hypothermia, hypoxic-ischemic encephalopathy, newborn

INTRODUCTION

Neonatal encephalopathy is a clinical condition characterized by altered consciousness or seizures in the early postnatal period, accompanied by respiratory depression and hypotonia, in infants born at or above 35 weeks of gestation (1,2). The combination of early hypoperfusion followed by abrupt reperfusion can lead to significant damage in brain tissue (3). Neonatal encephalopathy can develop due to various causes such as intrauterine growth restriction (IUGR), maternal thyroid diseases, thrombophilia, fetal inflammation, infection, and hypoxic-ischemic encephalopathy (HIE) (4,5). Although the incidence varies depending on the cause, studies have reported an incidence of 1-3 per 1000 live births (6). According to data from the Turkish Neonatal Society Hypoxic Ischemic Encephalopathy Study Group, the incidence was found as 2.6 per 1000 live births (4).

Despite advances in perinatal and neonatal care, reductions in neonatal mortality rates and significant improvements in long-term prognosis, HIE remains a major cause of neonatal death, acute neurological injury in the early period and severe long-term neurodevelopmental impairments (7,8). HIE has been associated with neurodevelopmental disorders, neuromotor retardation, epilepsy, behavioral and speech difficulties, visual

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and hearing loss, academic failure, learning disabilities, growth retardation, and autism, many of which have not yet been fully elucidated in terms of their etiology (9,10).

In addition to these diagnostic criteria, various scoring systems have been developed in recent years for the follow-up of HIE (11-14). The Sarnat & Sarnat classification, which has been widely used since 1976, is a scoring system that helps predict neurological prognosis in HIE (14).

The most effective neuroprotective approach in the treatment of HIE is the application of therapeutic hypothermia within the first 6 hours of life, as soon as possible (15). Therapeutic hypothermia has been shown to reduce the risk of mortality, moderate-to-severe neurodevelopmental disorders in childhood, cerebral palsy (CP), cognitive impairment, and psychomotor retardation (10).

The aim of this study was to examine neonatal HIE patients who completed their neurodevelopmental assessment at the postnatal 24th month in our clinic. Additionally, the study aimed to compare the clinical features of Stage 2 and Stage 3 patients, as classified by the Sarnat & Sarnat system, who received therapeutic hypothermia.

MATERIALS and METHODS

This study included toddlers who were followed in a level III neonatal intensive care unit (NICU) between January 2016 and December 2017, born at a gestational age of ≥35 weeks, diagnosed with HIE, and treated with therapeutic hypothermia, and who presented to the outpatient clinic for their second-year follow-up. Data related to the neonatal period were retrieved from patient records and files. Infants with major congenital or chromosomal anomalies were excluded from the study.

Procedures performed in the delivery room followed current neonatal resuscitation guidelines. A history of cardiopulmonary resuscitation (CPR) was recorded. Umbilical cord blood gas samples were analyzed using standardized and calibrated devices, and pH, BE, and HCO3 values were documented.

The diagnosis of hypoxic-ischemic encephalopathy was made according to the diagnostic criteria outlined in the Turkish Neonatology Association (TND) Neonatal Encephalopathy Diagnosis and Treatment Guidelines (4):

The presence of the following findings/acute events:

APGAR score <5 at the 5th and 10th minutes

Fetal umbilical cord blood gas pH<7.00 or BE<-12 mmol/L

Brain injury consistent with HIE detected on magnetic resonance imaging (MRI) or magnetic resonance spectroscopy (MRS)

Presence of multiple organ failure or dysfunction

The presence of an acute peripartum-intrapartum event:

Conditions such as uterine rupture, placental abruption, cord prolapse, maternal hypotension, amniotic fluid embolism, maternal hypoxemia, maternal cardiovascular collapse, vasa previa, or fetomaternal hemorrhage during delivery.

Typical imaging findings such as deep gray matter lesions or cortical injury (watershed areas)

Exclusion of the following conditions: abnormal fetal growth, maternal infections, fetomaternal hemorrhage, neonatal sepsis, or chronic placental lesions

Patients were classified into two groups based on the Sarnat & Sarnat classification as Stage 2 and Stage 3 encephalopathy (14).

During the study period, the Arctic Sun® (Medivance, Inc., Louisville, CO) hypothermia device was used for whole-body cooling. Therapeutic hypothermia treatment was applied according to protocols lasting 72 hours, followed by slow rewarming, in line with current guidelines (15).

Data on the number of days the patients remained intubated were obtained from physician observations and nurse records. The duration and need for oxygen support were documented. aEEG was performed on all neonates receiving therapeutic hypothermia, and aEEG traces were categorized as normal or abnormal based on voltage and pattern classification. Neonates receiving anticonvulsant therapy were also recorded.

The Bayley Scales of Infant and Toddler Development (BSID), developed by Nancy Bayley in 1969, is designed to assess the neurodevelopment of children aged 1-42 months. While BSID-II evaluates cognitive, motor, and behavioral domains, BSID-III consists of subscales that assess cognitive, language, motor, social-emotional development, and adaptive behaviors (16, 17). This scale not only provides detailed information about the developing skills of the child from birth but also offers a comprehensive evaluation of children by integrating parental questionnaires (16).

At the second-year follow-up, neurodevelopmental assessments were conducted using the BSID-II by a Developmental Pediatrician and Child Development Specialists. Mental Development Index (MDI) and Psychomotor Development Index (PDI) scores were evaluated (17). Standardized scores were calculated with a mean score of 100 and a standard deviation (SD) of 15. Scores below -2 SD were considered abnormal. Scores between -2 SD and -3 SD (50-69 points) were categorized as moderate delay, while scores below -3 SD (<50 points) were categorized as severe delay. Neurodevelopmental impairment (NDI) was defined as a score below 70 on at least one of the indices (17).

Statistical Analysis

The demographic characteristics, encephalopathy staging, and BSID-II scores of the infants were recorded. Statistical analyses

were performed using the IBM Statistical Package for the Social Sciences, version 22.0 (SPSS Inc., Armonk, NY, IBM Corp., USA). The demographic characteristics of the infants were expressed as frequency and percentage. The normality of the variables was assessed using visual and analytical methods. Descriptive analyses were presented as mean and standart deviation for normally distributed variables. Independent group comparisons for normally distributed variables were performed using the independent samples t-test. Categorical variables were compared using the Fisher's exact test. A $p<0.050$ was considered statistically significant for all tests.

RESULTS

A total of 138 toddlers who had previously received therapeutic hypothermia treatment and presented for their second-year follow-up were included in the study. According to the Sarnat & Sarnat classification, 75 patients were categorized as Stage 2 encephalopathy and 63 patients as Stage 3 encephalopathy. The demographic and clinical characteristics of the patients are summarized in Table I. The mean birth weight of the patients was 3410±447 g in the Stage 2 group and 3321±592 g in the Stage 3 group. Gestational age was 39.1±1.3 weeks for the Stage 2 group and 38.7±1.5 weeks for the Stage 3 group. There were no statistically significant differences between the two groups in terms of birth weight or gestational age ($p= 0.317$ and $p=0.081$, respectively). Additionally, no significant differences were found between the groups regarding gender ($p=0.397$).

In the Stage 3 group, one out of three infants underwent cardiopulmonary resuscitation (CPR), while one out of seven infants in the Stage 2 group required CPR ($p=0.002$). According to umbilical cord blood gas results, no differences were observed between the two groups in terms of pH and HCO3 levels, but BE was found to be higher in the Stage 3 group ($p=0.001$).

Infants in the Stage 3 encephalopathy group required more respiratory support, including oxygen and mechanical ventilation, compared to the Stage 2 group ($p=0.020$ and $p=0.001$, respectively). Abnormalities in aEEG were more frequently observed in the Stage 3 group, and a higher proportion of these infants required anticonvulsant therapy ($p<0.001$ and $p<0.001$, respectively).

The mean Mental Development Index (MDI) score for infants with Stage 2 encephalopathy was 89±17, while the mean Psychomotor Development Index (PDI) score was 94±18 (Table II). For infants with Stage 3 encephalopathy, the mean MDI score was 84±10, and the mean PDI score was 71±11 ($p=0.049$ and $p=0.001$, respectively). Neurodevelopmental impairment (NDI) was identified in one out of three infants in the Stage 3 group, compared to one out of six infants in the Stage 2 group ($p=0.012$).

Table I: Demographic and clinical characteristics of the patients.

	Stage 2	Stage 3	p
Number of patients	75	63	-
Gestational week*	39.1±1.3	38.7±1.5	0.081
Birth weight, gram*	3410±447	3321±592	0.317
C/S†	37 (49)	31 (49)	1.000
Male gender†	36 (48)	35 (55)	0.397
CPR†	10 (13)	23 (36)	0.002
pH*	6.88±0.07	6.86±0.06	0.075
HCO3*	8.85±1.7	8.86±1.5	0.989
BE*	-17.8±1.3	-19.4±1.5	0.001
Days of mechanical ventilation*	2.5±2.3	7.8±9	0.001
Total respiratory support days (O_2 days) **	4.9±2.3	8.8±10	0.020
Disorder in aEEG †	25 (33.3)	40 (63.4)	<0.001
Anticonvulsant history†	30 (40.0)	51 (80.9)	<0.001

:** *mean±SD (independent samples t-test),* **†:** *n(%) (Fisher's exact test),* ***C/S: *Cesarean section,* ***CPR:*** *Cardiopulmonary Resuscitation,* ***HCO3:*** *bicarbonate,* ***BE:*** *Base Excess,* ***aEEG:*** *amplitude-integrated electroencephalography*

Table II: Neurodevelopmental outcomes of the patients.

	Stage 2	Stage 3	p
MDI*	89±17	84±10	0.049
PDI*	94±18	71±11	0.001
NDI †	13 (17.3)	23 (36.5)	0.012

:** *mean±SD (independent samples t-test),* **†:** *n(%) (Fisher's exact test),* ***MDI: *Mental Development Index,* ***PDI:*** *Psychomotor Development Index,* ***NDI:*** *Neurodevelopmental Impairment*

DISCUSSION

In our study, we observed that the neurodevelopmental scores of patients classified as Stage 3 according to the Sarnat & Sarnat classification and treated with hypothermia were lower than those in Stage 2. These patients required more respiratory support in intensive care units, had more abnormalities detected in aEEG results, and received anticonvulsant therapy more frequently. Given that the first two years of life are critical for establishing the foundations of life and completing a significant portion of brain development, it is essential that these patients are followed by specialized teams. As a center that has been implementing therapeutic hypothermia for HIE for many years, we aimed to share these data, which involve a substantial number of patients. Reviewing the situation in our country and evaluating the outcomes of patients classified as Stage 2 and 3 and treated with therapeutic hypothermia not only provides valuable insights for clinicians but also allows for the evaluation of the long-term effectiveness of applied treatments. Moreover, despite the identical therapeutic hypothermia protocol being

used for these two groups, we demonstrated that there can be differences in their neonatal intensive care follow-up and outcomes in the first two years of life.

Hypoxic-ischemic encephalopathy (HIE) is a significant clinical syndrome that can affect long-term neurodevelopmental outcomes (18). Various studies have reported that early initiation of therapeutic hypothermia treatment after the diagnosis of HIE reduces mortality and improves neurodevelopmental outcomes (18, 19). These findings underscore the critical importance of developing effective strategies to prevent HIE and ensuring the timely initiation of therapeutic hypothermia to improve patient outcomes.

Similar to our findings, a retrospective study conducted in Türkiye by Çelik et al. (20) also emphasized that, despite receiving therapeutic hypothermia, nearly half of the surviving infants with HIE showed neurodevelopmental impairments at follow-up. In their cohort of 47 patients, the median MDI and PDI scores were significantly lower in infants with severe HIE compared to those with moderate HIE, and only 44.6% of the cohort had normal BSID-II scores (20).

In a study conducted in England evaluating the two-year neurological outcomes of 107 children followed with a diagnosis of neonatal HIE, significant deterioration in the BSID-III scores was observed in the group with minor neurological signs compared to the group with normal neurological examinations (21). Although the BSID-III scale was used in that study, the results are consistent with our findings.

In another study evaluating the neurodevelopmental outcomes of 29 HIE cases, 11 patients were found to have brain injury on neonatal MR imaging. At the second-year follow-up, 6 patients had normal outcomes, while 5 had neurodevelopmental issues (22). Although our study does not include neuroimaging data, we found that the neurodevelopmental outcomes of patients with Stage 3 encephalopathy were worse than those of the other group.

Our study utilized the BSID-II. A study comparing the BSID-II and BSID-III found that, in infants diagnosed with neonatal encephalopathy at 18 months, BSID-III scores were higher than BSID-II scores. According to this study, BSID-III scores reduced the proportion of infants classified as severely impaired (23). Similar findings have been reported in other studies (24,25). These findings raise the question of whether BSID-II underestimates scores or BSID-III overestimates neurodevelopmental scores. Both possibilities remain plausible, and further studies will provide more clarity on this matter.

In neonatal hypoxic-ischemic encephalopathy, the therapeutic hypothermia protocol applied in Stage 2 and Stage 3 cases is identical. However, the findings during neonatal intensive care and neurodevelopmental outcomes differ between these groups, necessitating different approaches during follow-up. Further studies are needed to propose strategies for managing these patients effectively.

Although the BSID-II is no longer the most current version, it was the standard neurodevelopmental assessment tool used in our institution during the study period. Several comparative studies have indicated that BSID-III often yields higher scores than BSID-II, potentially underestimating developmental delays. As such, the use of BSID-II in this study may present a more conservative estimate of neurodevelopmental impairment. Despite these differences, our results remain relevant and provide a valuable historical benchmark for comparing outcomes across different time periods and assessment tools. Future studies employing BSID-III or BSID-IV may benefit from these findings by evaluating trends in developmental trajectories following therapeutic hypothermia.

Limitations

One significant limitation of our study is the use of the BSID-II system for neurodevelopmental evaluation. However, during the study period, BSID-II was still in use, and all high-risk infants were regularly followed up by an experienced developmental pediatrics unit, where detailed testing and examinations were performed.

The lack of data on cerebral palsy history, hearing, and vision status represents another limitation of our study. Additionally, routine imaging was not performed in the early period, and we were unable to access imaging results, which is a notable drawback. Although nearly all patients underwent cranial ultrasonography, it was not useful for either diagnosis or follow-up in HIE cases, so no additional data analysis was performed. Since cranial MRI was not available in the hospital where the patients were included in the study, and some patients were transferred to other hospitals for cranial MRI, imaging data were incomplete and not analyzed.

A more comprehensive cohort plan could have identified which patients were lost to follow-up, failed to attend follow-ups, or discontinued follow-up care. However, we were able to include only the infants who attended the two-year follow-up, which likely represents those with the best clinical course. Therefore, our results should be interpreted in light of this limitation. Including long-term outcomes of Stage I patients and those who did not receive hypothermia would have strengthened the study. Future studies incorporating these groups, especially those investigating borderline cases or patients with uncertain indications for hypothermia, are needed.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Bilkent City Hospital (12.03.2020, reference number: E1-19-165).

Contribution of the authors

Küçükoğlu Keser M: Planning methodology to reach the conclusions, Organizing, supervising the course of progress and tak-

ing the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***Kadıoğlu Şimşek G:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***Beşer E:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in necessary literature review for the study, Reviewing the article before submission scientifically besides spelling and grammar. ***Okman E:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in necessary literature review for the study, Reviewing the article before submission scientifically besides spelling and grammar. ***Kanmaz Kutman HG:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar.

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Review

Climate change and pediatric rheumatic diseases: a growing concern

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ABSTRACT

Pediatric rheumatic diseases (PRDs) comprise a diverse group of inflammatory disorders affecting the musculoskeletal system and connective tissues, with multifactorial etiologies involving genetic and environmental factors. Climate change driven by rising greenhouse gas emissions and global warming, has profound implications for PRDs through increased air pollution, extreme weather events, and ultraviolet radiation exposure. Children with chronic rheumatic disorders, particularly those with systemic involvement, are especially vulnerable to these environmental stressors. This review explores the association between climate change and PRDs, with a focus on juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), juvenile dermatomyositis (JDM), immunoglobulin A vasculitis, Kawasaki disease, and familial Mediterranean fever (FMF).

Understanding the interplay between climate change and PRDs is crucial for developing adaptive strategies for disease management and public health interventions. Future research should focus on mitigating environmental risks and identifying protective measures to improve the outcomes of pediatric patients with rheumatic diseases.

Keywords: Air pollution, Climate change, Rheumatic diseases

INTRODUCTION

Pediatric rheumatic diseases (PRDs) encompass diverse inflammatory conditions that primarily affect many organs, particularly the musculoskeletal system and connective tissue (1). These diseases have a complex etiology, typically arising in genetically predisposed individuals under the influence of various environmental factors (1,2). Advances in our understanding of inflammation, immune dysregulation, and environmental triggers are transforming the approach to diagnosing and managing pediatric rheumatic diseases (3). However, studying the epidemiology and environmental risk factors of PRDs presents challenges due to their low incidence and heterogeneous nature (4). Research has explored a wide range of potential risk factors, including genetic predisposition, hormonal influences, perinatal conditions, the hygiene hypothesis, infections, vaccinations, antibiotic use, dietary factors, gut microbiota, trauma, physical activity, psychological stress, adverse childhood events, seasonal variations, air pollution, ultraviolet radiation exposure, tobacco smoke, and other environmental pollutants (3-8).

Climate change is a major environmental challenge affecting living conditions, public health, and the future of our planet. The increasing levels of greenhouse gases [CO_2, N_2O, CH_2, ozone, etc.] are driving global warming and consequently, climate change, leading to a rise in environmental pollutants, particularly air pollution (9). Extreme weather events, worsening air quality due to forest fires, the spread of vector-borne diseases, and disruptions in healthcare access are some of the direct and indirect consequences of climate change. Children with rheumatic disorders, especially those with systemic comorbidities, are particularly vulnerable to these environmental changes and their associated health risks (10).

Recently, the impact of climate change on PRDs has received increasing attention. The most common PRDs are juvenile idiopathic arthritis, systemic lupus erythematosus, juvenile dermatomyositis, Immunoglobulin A vasculitis, and Kawasaki disease. Familial Mediterranean fever is prevalent in the Mediterranean and Middle Eastern regions, including our country. Although these conditions share some overlapping features, they differ in etiology, clinical presentation, prognosis, and treatment strategies. In this article, we review the relationship

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Table I: Characteristics of studies on the relationship between Pediatric rheumatic diseases and climate-related parameters and air pollution

Disease	Ref.	Country	Method	CAFP	Weather/ Climate	
					Parameters	Conclusion-Suggestions
JIA	8	Israel	Case/control (558/104058)*	-	Seasonality of birth	Gender-specific birth month rhythmicity in enthesitis-related arthritis suggests in utero or perinatal autoimmune triggering by seasonal environmental factors.
JIA	18	Australia	Case/control (202/202)*	Vitamin D status	Sunlight exposure	Lower exposure to sunlight and thus UVR may increase the risk of JIA.
JIA	5	Taiwan	Case/control (2363/23630)*	Gestational age Birth weight Socioeconomic status Maternal age M/G Dis. Maternal SARDs	CO, NO_2, PM2.5, SO_2	$PM_{2.5}$ exposure from 11–40 gestational weeks to 1–14 weeks after birth can increase the risk for PRDs in a non- linear dose-response fashion.
JIA	13	Brazil	Case/control (66/125)*	GP factors Inhalable environmental elements† (pregnancy and after birth)	PM_{10}, SO_2, NO_2, O_3, CO	Cigarette smoke exposure (intrauterine and after birth) and exposure to O_3 in the second year of life were identified as potential risk factors for JIA
JIA SLE DM	16	Brazil	Time-series (2922)*	Short-term trend Seasonality Holidays Temperature Humidity	PM_{10}, SO_2, CO, NO_2 O_3	The SO_2 interquartile range (7.79 µg/ m3) was associated with an increase of 1.98% in the number of hospital admissions of PRDs due to outcome studied after 14 days of exposure.
JIA	19	Taiwan	Cross sectional Comparative (52)*	-	Temperature, Humidity Barometric pressure etc.	A dramatic weather change such as a sudden cold wave might significantly influence the experience of joint pain.
JIA	20	Canada	Multicenter Descriptive (221)*	-	Season of disease onset	No seasonal pattern was found in sJIA onset.
JIA	17	USA	Case crossover Multicenter (253)*	-	$PM_{2.5}$	Statistically insignificant PM2.5- sJIA. The $PM_{2.5}$-sJIA association is most suggestive in preschool aged children.
JIA	21	Israel	Multicenter Retrospective Descriptive (59)*	-	Seasonal peak onset of sJIA	There is no seasonal pattern.
SLE DM IgAV-HSP	5	Taiwan	Case/control (2363/23630)*	Gestational age, Birth weight Socio-economic status Maternal age, M/G Dis. Maternal SARDs	CO, NO_2, $PM_{2.5}$, SO_2	$PM_{2.5}$ exposure from 11–40 gestational weeks to 1–14 weeks after birth can increase the risk for PRDs in a non-linear dose- response fashion.
SLE	26	USA	Regression (1628)*	Age Gender Income Racial distribution Rural vs. urban residence	$PM_{2.5}$ Ozone Temperature Residual wind, Relative humidity Barometric pressure	There is a strong association between changes in atmospheric and environmental variables ten days prior to patient visit and organ specific lupus activity at the visit.
SLE	32	Canada	Clinical cohort (237)	Ozone Outdoor ambient temperatures	$PM_{2.5}$	$PM_{2.5}$ levels were associated with elevated anti-dsDNA and cellular casts, and thus SLE activity.
SLE	30	Brazil	Longitudinal Observational (9)* 108 medical appointments	Inflammatory indicators Body mass index Infections Medication	$PM_{2.5}$, NO_2 Ambient temperature Humidity	Exposure to inhalable fine particles ($PM_{2.5}$) increases airway inflammation and then pulmonary and systemic inflammation in SLE patients.

Disease	Ref.	Country	Method	CAFP	Weather/ Climate	
					Parameters	Conclusion-Suggestions
SLE	33	China	Population-based Cohort (2231)*	NOx (Drinking water)	NOx (Air)	NOx in air and drinking water may be one of the important predispositions of SLE, especially for patients with renal involvement.
SLE	29	Canada	Open cohort (6 104 859)*	Age Gender Deprivation index, Urban–rural residence Smoking	$PM_{2.5}$ and ozone	$PM_{2.5}$ exposures were associated with higher risks of SARDs onset including SLE.
DM	37	Scotland Sweden Poland Netherlands Germany Japan US Canada Korea Chile Spain India Mexico Guatemala	Multticenter (919)* (468 DM, 451 polymyositis)	-	Surface UVR Sunlight Temperature Precipitation Elevation Atmospheric pressure Vapor pressure Relative humidity Wind speed Absolute latitude	Surface UVR intensity most strongly contributed to the relative proportion of DM and was strongly related to the proportion of anti-Mi-2 autoantibodies (weighted r = 0.939, p<4x10(-7) and weighted r=0.69, p= 0.020, respectively). UV radiation exposure may modulate the clinical and immunologic expression of an autoimmune disease in different populations around the world.
DM	42	China	Time-series	-	Temperature Relative humidity Wind speed $PM_{2.5}$,NO_2, SO_2, O_3, CO	Exposure to low temperature, extreme relative humidity, and temperature changes were associated with an increased risk of DM outpatient visits.
DM	40	USA Canada	Retrospective Observational (210)* (164 juvenile and 46 adult)	Photoprotective measures Smoking Infections Medications Vaccines, Stressful life events Physical activity	Sunlight exposure	Sun exposure (p=0.030; OR =2.0, 95% CI: 1.1, 3.7) associated with disease flare. Patients who flared more frequently spent time outdoors (but <30 min/day) compared with those who did not flare (p=0.040; OR = 2.5, 95% CI: 1.1, 6.1).
DM	36	Brazil	Case/control (20/50)*	Environmental inhalation exposure during pregnancy‡	PM_{10}, SO_2, NO_2, O_3, and CO	The highest tertile of tropospheric CO (3.2–5.4 parts per million) in the third trimester of gestation were significantly associated with juvenile DM. Inhaled pollutants and tobacco smoking during fetal development may contribute to juvenile DM.
IgAV-HSP	43	Korea	Ttime series (16940)*	Respiratory viruses§ Enteric viruses‖	Seasonality of disease onset	Pediatric HSP incidence shows age-related seasonal variation linked to infectious exposure.
KD	55	Canada	Multifactorial etiologic model (5616)*	Population composition Aeroallergen exposure Atmospheric concentration of spores and algae, Incidence of healthcare encounters for bacterial pneumonia or viral intestinal infections	$PM_{2.5}$, NO_2, O_3, SO_2 and CO	In this study, an association between higher atmospheric concentration of SO_2 and NO_2 and increased risk of KD was noted.
KD	57	Japan	Retrospective observational (185)*	Epidemic conditions of 14 infectious diseases	Ambient air Temperature Atmospheric pressure Relative air humidity Precipitation, Sunshine duration Wind velocity NO, NO_2, SO_2	The incidence of Kawasaki disease had positive associations with preceding hot temperature and increased concentrations of nitric oxide and sulfur dioxide and a negative association with epidemic herpangina.
KD	58	South Korea	Time-stratified Case-crossover (51486)	Temperature Relative humidity	PM_{10}, $PM_{2.5}$, NO2, SO_2, CO, O_3	The short-term elevations in $PM_{2.5}$ and SO_2 may trigger the onset of KD among children under 5 years of age.

Disease	Ref.	Country	Method	CAFP	Weather/ Climate	
					Parameters	Conclusion-Suggestions
KD	60	Japan	Nationwide population-based longitudinal (30367)	-	Particulate matter	Early life exposure to particulate air pollution, especially prenatally, is linked to higher KD hospitalization risk (OR: 1.59 for prenatal, 1.41 for postnatal exposure).
KD	56	Italy	Correlation analysis (516)*	-	Wind direction / intensity Surface temperature Precipitation Particulate matter	Certain wind conditions are more favorable for disease onset, which are possibly associated with one or more airborne agents.
FMF	66	Türkiye	Descriptive (275)*	Emotional stress Tiredness Long-duration standing /travel Starvation High intake of food, Trauma Infection	Cold exposure	One of the most common triggering factors for the attacks with serositis were cold exposure.
FMF	67	Türkiye	Descriptive study n= 882	Psychological stress Tea and coffee Mense Menopause Post-menopause Long-duration travel Relocation Starvation Sleeplessness Fatigue	Seasonal changes Cold exposure Wind exposure Humidity	Exposure to cold, humidity, seasonal changes, long-term travel, relocation and hunger may be triggers for FMF attacks, depending on the underlying mutation type.
FMF	68	Armenia	Descriptive (413)*	Emotional stress Physical exhaustion Diet (“fat” food)	Cold/ hypothermia	Regardless of the type of MEFV mutations, cold/hypothermia is one of the most common triggers for FMF symptoms in children.

:** *n,* **†:** *Occupational exposure to inhalable particles and/or volatile vapor, exposure to cigarette smoke, and the presence of industrial activities or gas stations near the home, work, daycare, or school,* **‡:** *occupational exposure to demolition, chalk, construction and/or quarry dust, paints, varnish, gasoline vapor, and/or battery fluids; stationary sources of inhaled pollution near the mother’s home; and maternal tobacco exposure,* **§:** *adenovirus, parainfluenza virus, respiratory syncytial virus, influenza virus, coronavirus, rhinovirus, bocavirus, and metapneumovirus,* **‖:** *Rotavirus, norovirus, enteric adenovirus, and astrovirus,* ***JIA: *Juvenile idiopathic arthritis,* ***CAFP:*** *Confounding/ Adjusted factors Other Parameters,* ***SLE:*** *Systemic Lupus Erythematosus,* ***DM:*** *Dermatomyositis,* ***IgAV-HSP:*** *IgA vasculitis Henoch-Schonlein Purpura,* ***KD:*** *Kawasaki disease, FMF: Familial Mediterranean Fever,* ***Ref.:*** *References,* ***GP:*** *Gestational and perinatal,* ***PRDs:*** *Pediatric rheumatic diseases,* ***sJIA:*** *Systemic JIA, M/G* ***Dis.:*** *Maternal/gestational diseases,* ***ESR:*** *Erythrocyte sedimentation rate,* ***UVR:*** *Ultraviolet radiation,* ***MEFV:*** *Mediterranean Fever*

between climate change and pediatric rheumatic diseases, with a particular focus on the most prevalent conditions (Table I).

Juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease among PRDs. It encompasses several subtypes and is primarily characterized by arthritis of unknown origin that begins before the age of 16 and persists for at least six weeks. JIA classification is based on factors such as the number of affected joints, extra-articular involvement (e.g., eyes, skin, internal organs), hereditary predisposition, and specific laboratory markers. The global prevalence of JIA is estimated to range between 3.8 and 400 cases per 100.000 individuals, with an incidence varying from 1.6 to 23 per 100.000 individuals (11). The development of JIA is influenced by both internal and external antigens that trigger an exaggerated inflammatory response (6,12).

The disease’s pathophysiological cascade begins with the abnormal activation of immune cells, including T cells, B cells, natural killer (NK) cells, dendritic cells (DCs), macrophages, and neutrophils. This dysregulation leads to the production of pro-inflammatory mediators, ultimately causing joint damage and systemic complications (6).

Environmental pollutants, particularly airborne contaminants [most known; PM10, PM2,5, nitrogen oxides (NOx), sulfur

dioxide (SO_2), ozone (O_3), lead, and carbon monoxide (CO)] are believed to induce oxidative stress or inflammation, which can result in systemic autoimmune disease like JIA. These effects may even be observed as early as the perinatal period (7, 13, 14). Some studies have reported that exposure to PM2.5 in early life (11–40 weeks of gestation and the first 14 weeks after birth; odds ratios range from 1.02 to 1.08) and during the preschool period (RR = 1.76, 95% CI 1.07–2.89, per 10 µg/m3 increase in 3-day lagged moving average PM2.5) is associated with an increased risk of JIA. Similarly, exposure to ozone in the second year of life (OR: 2.76, 95% CI: 1.20–6.37, p = 0.017) and SO2 (hospital admissions due to acute PRD episodes; OR: 1.98, 95% CI: 0.25–3.69) has been implicated in disease onset and exacerbation (5, 13, 15-17). In addition to air pollution, research indicates that reduced sunshine exposure may increase the risk of JIA (18), and extreme weather conditions, including sudden cold waves associated with climate change, may exacerbate joint pain. Studies have shown significant associations between cold weather events and increased pain severity ($p < 0.01$) (19). However, no convincing correlation was demonstrated between the disease process and the seasonal pattern (20, 21).

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that affects multiple organ systems and results from impaired immunological tolerance. The incidence of childhood-onset SLE ranges from 0.36 to 2.5 per 100,000 individuals, with prevalence estimates varying from 1.89 to 25.7 per 100.000 across different regions (22). While genetic factors contribute to disease onset and clinical presentation, the relatively low penetrance of SLE suggests that gene-environment interactions and environmental triggers play a crucial role in its etiology (23).

In genetically predisposed individuals, environmental factors can induce epigenetic modifications through multiple mechanisms. One key mechanism is altered DNA methylation either hypermethylation or hypomethylation which affects immune regulation, particularly in CD4+ T cells. These epigenetic modifications contribute to oxidative stress and upregulate inflammatory gene expression (24). Another pathway linking environmental exposure to autoimmunity involves the aryl hydrocarbon receptor (AhR), commonly known as the 'environmental receptor'. AhR acts as a transcriptional regulator, mediating cellular responses to environmental stimuli. Its influence on immune cell function has been associated with multiple autoimmune diseases, including SLE, underscoring the role of environmental factors in disease pathogenesis (25).

Studies investigating the adverse health effects of climate change on rheumatic disorders have identified several environmental factors that may exacerbate disease activity in SLE. Rising ambient temperatures, ultraviolet radiation, ozone levels, residual wind, relative humidity, wildfire smoke, and air pollution have been associated with increased disease flares. Specific associations have been reported between these environmental exposures and SLE flares. Exposure to $PM_{2.5}$ has been linked to an increased risk of rash flares (OR 1.03) and joint flares (OR 1.03). Higher ambient temperatures have been associated with rash flares (OR 1.07), joint flares (OR 1.05), and hematologic flares (OR 1.10). Elevated ozone levels have been correlated with an increased risk of rash flares (OR 1.013). Additionally, residual wind has been linked to joint (OR 1.04), neurologic (OR 1.10), renal (OR 1.03), and pulmonary flares (OR 1.14), while higher relative humidity has shown a significant association with joint flares (OR 1.16, $p<0.050$) (10,26,27).

Climate change-related factors are expected to influence solar ultraviolet (UV) radiation levels both directly and indirectly (28). UV radiation is known to exacerbate pre-existing SLE. Experimental studies suggest that UV-B radiation, in particular, may contribute to disease onset (OR 13.71, 95% CI 3.77–49.92) by inducing reactive oxygen species, promoting DNA damage, and altering T-cell and cytokine activity (13).

Exposure to $PM_{2.5}$, a key component of air pollution, has been associated with an increased risk of developing systemic autoimmune rheumatic diseases, including SLE (adjusted HR 1.12, 95% CI 1.08–1.15) (29). Similarly, research indicates that $PM_{2.5}$ exposure may increase respiratory and subsequent systemic inflammation in children with SLE, raising the risk of a high SLE Disease Activity Index 2000 (SLEDAI-2K ≥ 8; OR 1.47, 95% CI 1.10–1.84) (30). Furthermore, PM_{10} exposure has been linked to a 34% increased risk of heightened disease activity (SLEDAI-2K score >8; 95% CI 7.0–68.0) (31). Another study found that $PM_{2.5}$ exposure was associated with elevated anti-dsDNA levels (OR 1.34, 95% CI 1.02–1.77) and increased cellular casts (OR 1.28, 95% CI 0.92–1.80), suggesting it may trigger SLE activity (32). A study investigating the relationship between NOx, an air pollution marker, and SLE found it to be a significant risk factor, influencing both disease prevalence and mortality, especially in individuals with kidney involvement (33).

Juvenile dermatomyositis

Juvenile dermatomyositis (JDM) is an uncommon inflammatory autoimmune myositis whose cause remains unknown. Distinctive skin manifestations include calcinosis, Gottron papules, and heliotrope dermatitis. Symmetrical atrophy of the proximal muscles in children impairs daily functioning. In addition to muscle weakness, systemic symptoms, including anorexia, pain, and fever may also manifest. This condition involves multisystemic vasculitis and is likely to be accompanied by cardiovascular and cerebrovascular comorbidities, as well as pulmonary problems (34). Population-based studies estimate an annual incidence of two to three cases per million children. Although rare, JDM is the most common inflammatory myopathy in children (35).

A case-control study identified air pollutants, particularly carbon monoxide exposure during the third trimester (OR 12.21, 95% CI 1.28–115.96, p=0.030) and maternal smoking during pregnancy (OR 13.26, 95% CI 1.21–144.29, p=0.030),

as potential in utero risk factors for JDM, likely mediated by epigenetic alterations and microchimerism (36). Another multicenter myositis analysis study demonstrated that the clinical and immunological manifestations of autoimmune muscle diseases, including dermatomyositis (weighted r= 0.939, p<4 x 10-7) could be modulated by ultraviolet radiation intensity in different regions. Additionally, the study identified a strong positive correlation between dermatomyositis incidence and both temperature and altitude (37). Sun exposure, and the resulting UV radiation, is a well-established environmental factor that may contribute to DM development and exacerbation. Climate change leads to stratospheric ozone depletion, which causes a rise in UV-B radiation reaching the Earth's surface. This may contribute to the development and exacerbation of DM (38,39). In a separate study, sun exposure was found to be associated with exacerbation of dermatomyositis; patients experiencing flare were found to have a greater propensity to spend time outdoors in comparison to those who did not (OR 2.0, 95% CI:1.1-3.7, p=0.030) (40). Since children spend more time outdoors than adults, those with JDM may be particularly vulnerable to the harmful effects of solar radiation (41). A study investigating the association between climate change and dermatomyositis, using meteorological parameters, found that being exposed to low temperatures and excessive relative humidity was linked to a higher likelihood of outpatient visits for dermatomyositis (42). This suggests that both extreme heat and cold may influence disease activity through different mechanisms.

Immunoglobulin A vasculitis

Immunoglobulin A (Ig A) vasculitis (previously referred to as Henoch Schonlein Purpura (HSP)) is a prevalent form of vasculitis observed in childhood, impacting individuals from diverse ethnic backgrounds globally. Its reported incidence rate ranges from 10 to 30 cases per 100.000 children, with 90 percent occurring in children under 10 years of age (43,44). In the majority of patients, the diagnosis is established upon the observation of a rash and symptoms in the gastrointestinal, musculoskeletal, and renal systems. Children present clinically with findings of palpable purpura more prominent in the lower part of the body, abdominal pain, arthralgia or arthritis, and renal involvement, including proteinuria or hematuria (45).

The etiology of IgA vasculitis seems to be influenced by a combination of environmental, genetic, and antigenic factors. Recent research has suggested that epigenetic mechanisms, such as changes in DNA and histones, may contribute to the development of IgA vasculitis and worsen inflammatory reactions (46). While epidemiological studies consider environmental factors such as seasonal and geographical diversity, the predominant focus is on infectious agents, particularly those that induce upper respiratory tract diseases, when examining the triggers of IgA vasculitis (44,47). From a climate change perspective, alterations in temperature, precipitation, relative humidity, and air pollution are expected to influence bacterial and viral activity. Furthermore, given the susceptibility of children's immune systems to the fluctuations caused by climatic changes, shifts in both the severity and frequency of respiratory tract infections could have an adverse impact on the epidemiology and prognosis of IgA vasculitis (48). An important factor impacting the prognosis is that 30-50 % of children with IgA vasculitis suffer renal involvement, which can vary in severity from mild to end-stage renal failure. IgA vasculitis-associated renal involvement is a significant contributor to chronic kidney disease (CKD) in pediatric patients (49). Exposure to elevated levels of air pollution, particularly $PM_{2.5}$ and NO_2, over a moderate to short duration is linked to a decline in eGFR and the development of CKD (50). This situation may pose a risk for childhood rheumatic patients such as IgA vasculitis with kidney involvement.

Kawasaki disease

Kawasaki disease (KD) is an acute vasculitis that predominantly impacts arteries of the small to medium size, with a predilection for in children under five (51). While the prevalence of this condition is higher in Asian countries, particularly Japan, it can manifest in children from many ethnic backgrounds, exhibiting a worldwide distribution (52). The disease is characterized primarily by mucocutaneous changes and lymphadenopathy, accompanied by a persistent fever that lasts for a minimum of five days. In the absence of proper management and treatment, KD may result in coronary artery abnormalities, which can subsequently give rise to acquired heart disease (53).

In genetically predisposed individuals, KD is thought to result from an abnormal inflammatory response to an infectious trigger or other stimuli (51,54). Changes in climate and environmental factors have been linked to an increased risk of inflammatory and atopic diseases, including Kawasaki disease, in children exposed to pollution, allergens, and dust (55). Based on extensive epidemiological analyses of Japanese data, certain studies suggest that airborne biological or chemical particles transported by tropospheric wind over extensive distances might induce KD (52). In line with this notion, an additional study investigated the correlation between the initiation of KD and environmental variables including daily precipitation, observed local surface temperature, upper air wind regimes, and local air pollution. The results suggest that particular wind conditions may foster the dissemination of airborne agents that could potentially be linked to the initiation of the disease (56). Studies investigating elevated levels of atmospheric pollutants, which are considered to cause excessive oxidative stress and inflammatory responses in the vascular system, have shown that higher levels of $PM_{2.5}$ were associated with an increased risk of KD (OR 1.02; 95% CI 1.00–1.03). Additionally, a 1-μg/m^3 increase in NO and SO2 concentrations correlated with higher KD incidence (NO: OR 3.94; 95% CI 0.04–7.98; SO2: OR 3.60; 95% CI 1.12–6.14). Elevated temperatures (RR 1.76; 95% CI 1.01–3.07) and short-term exposure to ozone (each IQR increase in O_3 concentration at lag 0 day increased the risk of KD onset by 16.2%; 95% CI 3.6%–30.3%) were also associated with a higher likelihood of KD (51,57-59). A longitudinal study

investigating air pollution exposure during the prenatal and postnatal periods reported that there was a positive correlation between particulate air pollution exposure during pregnancy (OR 2.02, 95% CI 1.13, 3.61) and the incidence of hospital admissions related to Kawasaki disease in early childhood (60).

Familial mediterranean fever

Familial Mediterranean fever (FMF) is the most prevalent autoinflammatory disease, with individuals of Mediterranean and Middle Eastern heritage being disproportionately affected. The condition is distinguished by recurrent, self-limiting episodes of fever that are accompanied by polyserositis (61). Mutations in the MEFV gene lead to excessive inflammation, a hallmark of this autosomal recessive disorder (62). The genotype-phenotype link in FMF is not linear, and patients with the same MEFV mutations may exhibit different clinical characteristics, despite belonging to the same family (63). Since disease severity is influenced more by geographic region than by MEFV mutations, this phenotypic variability suggests a role for environmental factors in modulating symptoms (64). Episodes of FMF are often preceded by emotional or physical stress (65). In a few limited studies investigating climate-related factors or living conditions that trigger FMF attacks, humidity has been identified as a trigger for FMF attacks in individuals with exon 2 mutations (p=0.023). Seasonal changes were significantly associated with increased attacks in patients with the homozygous M694V mutation (p=0.036). Similarly, exposure to cold was linked to FMF exacerbations in those with exon 10 mutations (p=0.044) and in individuals homozygous for M694V (p=0.016). In addition, long-term travel, relocation and hunger may be triggers, depending on the underlying mutation type (66,67). The significance of cold exposure, specifically hypothermia, as an environmental component has been substantiated to be on scale with physical stress as a catalyst. Conversely, reduced cold stress due to climate change and global warming has been linked to a temporary decline in the frequency and severity of FMF attacks (66,68). In another longitudinal study, it was shown that there was no significant seasonal variation in disease activity for FMF. However, it was noticed that the frequency of attacks increased during the winter season and reduced during the summer season (69).

CONCLUSION

In conclusion, when reviewing the existing body of literature, substantial evidence emerges that highlights the adverse impacts of climate change and global warming on the well-being of children. These effects manifest through alterations in seasonal patterns and atmospheric conditions, raised pollution levels, and the consequential influence on our biological, physical, and chemical surroundings. Rheumatic disorders chronically affect the life of children, rendering them more susceptible to fragility. Thus, in order to figure out the elements that delineate the onset and progression of these diseases and to develop strategies for long-term prevention and individualized therapeutic approaches, further investigation is required to analyze consequences of climate change, which stands as one of the most significant challenges of our era.

Contribution of the authors

Yaman Artunç N: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***Yalçin S:*** Constructing the hypothesis or idea of research and/or article Planning methodology to reach the conclusions, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Reviewing the article before submission scientifically besides spelling and grammar.

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Conflict of interest

The authors declare that there is no conflict of interest.

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