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Original Articles

Case Report

Review Article

Letters to the Editor

Turkish Journal of Pediatric Disease

Original Article

Risk factors and outcomes of neonatal progressive hydrocephalus: A retrospective analysis

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ABSTRACT

Objective: Hydrocephalus is a complex neurological disorder affecting the central nervous system, which can lead to severe neurodevelopmental complications despite early diagnosis and treatment. Although advances in diagnostic and therapeutic methods have been achieved, managing hydrocephalus remains challenging. Neural tube defects are among the most common causes of hydrocephalus, highlighting the importance of prenatal diagnosis. Treatment often involves surgical intervention, making imaging techniques and timely surgical management critical. This study aimed to investigate the risk factors, etiologies, and treatment outcomes of neonates diagnosed with hydrocephalus.

Material and Methods: A retrospective study was conducted on neonates diagnosed with hydrocephalus and followed at Ankara Bilkent City Hospital Neonatal Intensive Care Unit between September 2019 and January 2023. Neonates who died in the delivery room or during transfer, whose records were incomplete, or whose families were unreachable were excluded. Clinical, demographic, and treatment data were obtained from hospital records and analyzed.

Results: Out of 115 patients screened, 104 met the inclusion criteria. Of these, 42% were born prematurely. The prevalence of congenital hydrocephalus was 74%, post-hemorrhagic hydrocephalus 24.1%, and post-infectious hydrocephalus 1.9%. Female infants comprised 58.7% of cases, and 87.5% were delivered via cesarean section. Among mothers, 42.5% reported regular folic acid intake during pregnancy. Parental consanguinity was noted in 24.5% of cases. Additional anomalies were present in 74% of patients, with 67.3% receiving an antenatal diagnosis. Epilepsy was observed in 36.5% of patients, and 39.9% of these were treated with antiepileptic drugs. Ventriculoperitoneal shunts were placed in many patients, with 44.7% requiring shunt revision, predominantly due to infection (33.7%). Referral cases accounted for 17.3%, mostly post-hemorrhagic hydrocephalus, with a 72% epilepsy rate and 25.3% antiepileptic treatment initiation in this subgroup.

Conclusion: This study provides comprehensive insights into the epidemiology, familial risk factors, etiological profiles, and treatment outcomes of progressive hydrocephalus diagnosed antenatally or postnatally. The findings offer valuable data to inform improved diagnostic and therapeutic strategies for neonates affected by hydrocephalus.

Keywords: Antenatal diagnosis, hydrocephalus, neonate, neural tube defects, risk factors, ventriculoperitoneal shunt

Introduction

Hydrocephalus is defined by the pathological accumulation of cerebrospinal fluid (CSF) within the cerebral ventricles and/or subarachnoid spaces due to impaired CSF circulation (1). The meninges—comprising the dura mater, arachnoid mater, and pia mater—together with CSF play a crucial role in protecting the central nervous system. CSF circulates continuously within the subarachnoid space, maintaining homeostasis and providing mechanical protection (2). Clinically, hydrocephalus is classified as obstructive (non-communicating) or communicating, depending on whether the impairment lies in CSF flow pathways or in the balance between CSF production and absorption. The condition is characterized by ventricular dilatation and increased intracranial pressure (ICP), resulting from complex pathophysiological mechanisms. Clinical manifestations are often non-specific and may occur irrespective of the underlying etiology (3).

The prevalence of congenital hydrocephalus in the United States and Europe is estimated at 0.5–0.8 per 1000 live and stillbirths. Approximately half of the cases are associated with meningomyelocele, although this proportion varies geographically (4). First described by Hakim and Adams in 1965, hydrocephalus has since been linked to potential genetic susceptibility, as suggested by its increased frequency in certain ethnic and regional populations. While no single causative gene has been identified, multiple genetic alterations are believed to contribute to its development (5,6). Several maternal risk factors have been implicated, including folic acid and zinc deficiency, fetal alcohol exposure, maternal obesity, antiepileptic drug use, and insulin-dependent diabetes mellitus. In the neonatal period, neural tube defects represent the most common etiology, with meningomyelocele being the predominant form. The extent of neurological impairment varies according to lesion level and is frequently permanent (7). Prenatal diagnosis, achievable in up to 90% of cases, allows for optimized delivery planning and early postnatal management. The primary goal in the management of meningomyelocele is to preserve neurological function at birth and prevent complications such as meningitis and sepsis. Early postnatal surgical repair of exposed neural tissue and closure of the defect remains the most effective intervention (8).

Diagnosis of hydrocephalus relies on imaging modalities such as ultrasonography, computed tomography, and magnetic resonance imaging. Treatment options include CSF diversion techniques, primarily ventriculoperitoneal shunting or endoscopic third ventriculostomy. Careful patient selection is essential, and differential diagnoses involving other neurodegenerative conditions must be excluded. Patients with shorter symptom duration and predominant lower extremity involvement are more likely to benefit from surgical intervention (9). Hydrocephalus remains a condition with significant morbidity despite advances in diagnosis and treatment. Early prenatal detection, identification of risk factors, and appropriate surgical management play a decisive role in improving outcomes. The aim of this study was to retrospectively evaluate risk factors, etiological causes, and treatment outcomes in newborns diagnosed with hydrocephalus and to propose recommendations for diagnostic, therapeutic, and follow-up strategies based on these findings.

Materials and Methods

This retrospective study analyzed a total of 104 newborns diagnosed with hydrocephalus at the Neonatal Intensive Care Units (NICU) of Ankara Bilkent City Hospital Children's Hospital between September 2019 and January 2023. Inclusion criteria comprised a diagnosis of hydrocephalus within the neonatal period (the first 28 days of life) confirmed via neuroimaging (ultrasonography, CT, or MRI), administration of medical or surgical treatment, and the availability of complete medical and follow-up records. Conversely, patients diagnosed after the neonatal period, those with insufficient imaging or incomplete follow-up data, and postmortem-diagnosed cases who did not receive treatment were excluded from the study. Demographic and clinical characteristics, laboratory findings, and follow-up data were retrospectively retrieved from the hospital's electronic medical record system.

The diagnosis of hydrocephalus was established based on neurological assessments and standard neuroimaging techniques, primarily including cranial ultrasonography (USG), magnetic resonance imaging (MRI), and computed tomography (CT). The presence of ventriculomegaly, elevated cerebrospinal fluid (CSF) pressure, and clinical symptoms—such as increased head circumference, persistent fontanelle patency, and neurological impairments—were considered in combination. Imaging findings were also used to classify the type of hydrocephalus as congenital, post-hemorrhagic, or post-infectious. Among the 104 patients included in the study, transfontanelle ultrasonography (TFUS) was performed in at least 88 patients (84.6%), while specific TFUS parameters were assessed in up to 95 patients (91.3%). The variation in patient numbers resulted from missing data or parameters that were not evaluated in all cases.

The decision to perform ventriculoperitoneal (VP) shunt placement was made by a multidisciplinary team, taking into account the patient's clinical status, imaging findings, and CSF pressure measurements. Indications for shunt surgery included elevated intracranial pressure, progressive ventricular dilatation, and worsening neurological symptoms. Post-treatment follow-up included regular assessment for complications, shunt revisions, and infection surveillance.

Statistical analysis

The data were analyzed using IBM SPSS Statistics for Windows (Version 24.0; IBM Corp., Armonk, NY, USA). As continuous variables did not show a normal distribution, they were summarized as median (interquartile range, Q1–Q3), minimum, and maximum values, while categorical variables were presented as counts and percentages. Comparisons between groups were performed using the Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test, as appropriate. A p value of ≤ 0.050 was considered statistically significant.

Results

This retrospective study included 104 neonates diagnosed with hydrocephalus. Of these, 41.3% were male and 58.7% were female. Regarding the mode of delivery, 87.5% were born via cesarean section (CS), while 12.5% were delivered through normal spontaneous vaginal delivery (NSVD). A total of 42% of the infants were preterm births. Among the mothers, 75% had no chronic disease before or during pregnancy, whereas 22.1% had a chronic condition. According to maternal medical history, the most frequent chronic condition among the mothers was hypothyroidism, followed by hypertension, diabetes mellitus, and asthma.

Table I: Gender distribution and maternal pregnancy characteristics of patients (n=104)

Characteristic	n (%)
Gender	
Male	43 (41.3)
Female	61 (58.7)
Delivery mode	
Cesarean section	91 (87.5)
Normal spontaneous vaginal delivery	13 (12.5)
Maternal chronic disease (n=101)	
Present	23 (22.1)
Absent	78 (75.0)
Medications during pregnancy (n=19)	
Levothyroxine	8 (36.3)
Anticoagulant	3 (13.6)
Insulin	2 (9)
Antihypertensive	2 (9)
Inhaled corticosteroid	2 (9)
Antibacterial	2 (9)
Urinary antispasmodic	1 (4.5)
Antiretroviral	1 (4.5)
Phlebotonic	1 (4.5)
Folic acid supplementation (n=94)	
Regular	40 (42.5)
Irregular	31 (32.9)
None	23 (24.4)
History of abortion (n=104)	
Present	37 (35.1)
Absent	67 (64.9)

Among the 19 mothers who used medication during pregnancy, the distribution was as follows: 36.3% used levothyroxine, 13.6% anticoagulants, 9% insulin, 9% antihypertensives, 9% inhaled corticosteroids, 9% antibacterials, 4.5% urinary antispasmodics, 4.5% antiretrovirals, and 4.5% phlebotonics (Table I).

While 42.5% of the mothers regularly used folic acid throughout pregnancy, 32.9% used it irregularly, and 24.4% did not use it at all. Additionally, 35.1% of the mothers had a history of at least one abortion. Table I summarizes the gender distribution of the patients and the pregnancy characteristics of the mothers.

The mean maternal age was 27.48±6.22 years, the mean birth weight of the infants was 2569.80±882.97 g, and the mean gestational age was 35.65±4.30 weeks. The mean number of pregnancies among the mothers was 2.95±2.06. The mean APGAR scores were 5.69±1.87 at 1 minute and 7.68±1.48 at 5 minutes postpartum. The mean time to symptom onset was 3.32 ± 9.64 days (Table II).

Among the patients, 67.3% had received an antenatal diagnosis. The rates of ventriculomegaly, meningomyelocele, and encephalocele were 56.3%, 43.6%, and 10.8%, respectively. While 81.8% of the patients were born in the hospital, 17.3% were referred from external centers. The rate of parental consanguinity was 24.5%, and 11.1% of the mothers reported a history of previous pregnancies affected by hydrocephalus or spina bifida.

Regarding hydrocephalus types, 74% had congenital hydrocephalus, and 24.1% had posthemorrhagic hydrocephalus.

Table II: Demographic and clinical characteristics of the study population

Variable	mean±SD	min-max
Maternal age (years)	27.48±6.22	17.00-42.00
Birth weight (g)	2569.80±882.97	700.00-4880.00
Gestational age (weeks)	35.65±4.30	24.00-41.00
Gravidity	2.95±2.06	1.00-11.00
APGAR 1	5.69±1.87	1.00-8.00
APGAR 5	7.68±1.48	4.00-9.00
Antenatal diagnosis week	24.15±6.04	10.00-39.00
Symptom onset (postnatal day)	3.32±9.64	0-61

The rate of additional anomalies was 92.3%. Among the 32 patients with facial anomalies, 59.3% had dysmorphic facial features, and 12.5% had scaphocephaly.

Epilepsy was present in 36.5% of the patients, and antiepileptic treatment was initiated in 39.9%. Shunt revision was performed in 44.7% of the patients, and shunt infection developed in 33.7%. The rate of central nervous system (CNS) infection was 28.8%, and cerebrospinal fluid (CSF) culture was positive in 33.7% of the cases.

Discussion

Hydrocephalus is characterized by abnormal cerebrospinal fluid (CSF) accumulation resulting from impaired production, circulation, or absorption. Sustained intracranial pressure elevation and ventricular dilatation adversely affect neuronal development; therefore, early diagnosis and timely intervention are critical to reducing morbidity and mortality (10). In this context, our findings provide insight into both etiological distribution and outcome patterns in a tertiary referral neonatal population.

In our cohort, congenital hydrocephalus was the predominant etiology (74%), followed by posthemorrhagic (24.1%) and postinfectious forms (1.9%). The overall incidence of neonatal hydrocephalus (1.52%) is consistent with reports from developed countries. However, the relatively high proportion of posthemorrhagic hydrocephalus likely reflects our center's role as a referral unit for extremely preterm infants. Importantly, this distribution suggests that local neonatal care characteristics substantially influence etiological patterns, emphasizing the need for center-specific management strategies (11,12).

Contrary to reports of male predominance in pediatric hydrocephalus, female infants constituted the majority of our cohort (13). We believe this finding may be related to a higher proportion of prenatally diagnosed congenital cases and referral bias, rather than a true gender-related biological difference. This observation highlights the impact of prenatal screening practices on postnatal epidemiological profiles.

Birth weight was comparable to previous studies; however, lower gestational age and earlier prenatal diagnosis were

notable findings (14). Earlier detection likely reflects increased antenatal surveillance of high-risk pregnancies and may contribute to improved perinatal stabilization. At the same time, the lower gestational age may explain the substantial burden of posthemorrhagic hydrocephalus observed, reinforcing the close relationship between prematurity and CSF circulation disorders.

The very high cesarean section rate (87.5%) and relatively low first-minute APGAR scores mirror findings from similar healthcare settings (15). In our opinion, these findings reflect the complex perinatal management of prenatally diagnosed hydrocephalus cases rather than inadequate obstetric care, as most neonates showed improvement by the fifth minute. Maternal age did not differ from national data and does not appear to be an independent risk factor (13,16). However, maternal comorbidities were common (22.1%) and may have contributed indirectly to hydrocephalus development by increasing the risk of prematurity and intraventricular hemorrhage (17–19). This supports the concept that maternal health optimization may play a role in preventive strategies (20).

Medication exposure during pregnancy was documented in nearly one-fifth of cases. Although most medications were clinically justified, this finding underscores the importance of careful pharmacological counseling during pregnancy, particularly during the organogenesis period, when the fetal brain is highly vulnerable to teratogenic effects (21–23). Suboptimal folic acid supplementation remains a significant concern. Similar to previous reports, irregular or absent folic acid use was common (24). While maternal risk factors alone may not fully explain hydrocephalus development, our findings suggest that inadequate preventive care may exacerbate underlying genetic or environmental susceptibility (25,26).

The predominance of congenital hydrocephalus in our cohort contrasts with studies reporting posthemorrhagic etiologies as the leading cause (25). We believe this difference reflects referral of antenatally diagnosed and structurally complex cases. Additionally, emerging evidence on genetic and molecular mechanisms affecting neurodevelopment and CSF regulation supports the possibility that undiagnosed genetic factors contributed to our high congenital case rate (26). A striking finding of our study was the very high rate of associated anomalies (92.3%), far exceeding previously reported rates (14). This may be explained by lower pregnancy termination rates and referral of multisystem anomaly cases. Clinically, this finding underscores the necessity of comprehensive prenatal counseling and multidisciplinary postnatal care.

Long-term neurological morbidity was considerable. Neuromotor impairment and epilepsy were frequent, with epilepsy observed in 36.5% of patients, exceeding rates reported in European cohorts (27). Although epilepsy was less frequent in congenital hydrocephalus than in secondary forms, the overall neurological burden highlights the need for structured long-term follow-up and early neurodevelopmental intervention. Shunt-related complications and epilepsy remain major determinants of quality of life (28). Our findings support the growing emphasis on individualized treatment strategies, early risk stratification, and advances in prenatal diagnosis to reduce shunt dependency and improve long-term outcomes (29).

Conclusion

This study is limited by its retrospective, single-center design, incomplete records, and lack of standardized neurodevelopmental and genetic assessments. Nevertheless, it provides valuable real-world data reflecting the impact of referral patterns, prenatal diagnosis, and maternal factors on neonatal hydrocephalus. Future multicenter prospective studies incorporating genetic analyses and long-term follow-up are essential to further clarify disease mechanisms and optimize management.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Bilkent City Hospital (15.03.2023, reference number: E2-23-3297).

Contribution of the authors

EK, DH: Collected and recorded the patients' data, were responsible for literature research, TC, DH: Followed patients, TC, EK: Took the lead in writing the manuscript. All authors discussed the results and contributed to the final manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Clinical and laboratory characteristics of nephropathic cystinosis in a resource-limited region

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ABSTRACT

Objective: Cystinosis remains a significant cause of morbidity in developing countries. Key challenges include limited access to specialized clinics, availability of cysteamine treatment, and difficulties in monitoring treatment efficacy, such as measuring leukocyte cystine levels. The aim of this study was to describe the clinical characteristics, growth patterns, and renal outcomes of pediatric patients with nephropathic cystinosis in a resource-limited region

Material and Methods: This retrospective study included 17 patients diagnosed with cystinosis who were followed in the Pediatric Nephrology Clinic of a tertiary care center between June 2016 and April 2023. Clinical and laboratory characteristics were evaluated, and statistical analyses were performed using IBM SPSS Statistics.

Results: After a median follow-up period of 69.24 months, no significant change was observed in weight SDS ((median [IQR]; baseline vs. follow-up; -3.6 [1.35] vs. -2.8 [1.55], p=0.255). However, height SDS significantly decreased (median [IQR]; baseline vs. follow-up; -2.8 [2.44] vs. -3.9 [2.35], p=0.034). Ocular involvement was present in all patients, and six were diagnosed with hypothyroidism. The majority of patients (n=9) exhibited biochemical features consistent with renal Fanconi syndrome. One patient initially presented with persistent hypochloremic hypokalemic metabolic alkalosis and subsequently developed Fanconi syndrome during follow-up, while another showed transient metabolic alkalosis at presentation. The median estimated glomerular filtration rate (eGFR) significantly declined from diagnosis (116.66 [62.69] mL/min/1.73 m^2) to the last follow-up (77.40 [95.18] mL/min/1.73 m^2, p=0.007). Twelve patients had an eGFR <90 mL/min/1.73 m^2; three progressed to stage 3 chronic kidney disease, and three required renal replacement therapy.

Conclusion: Growth retardation and progression to chronic kidney disease are significant challenges for cystinosis patients in resource-limited settings. Improving access to specialized care and monitoring is essential to enhance patient outcomes.

Keywords: Cystinosis, chronic kidney disease, cysteamine, nephropathic cystinosis, resource-limited settings

Introduction

Cystinosis is a rare disease caused by mutations in the CTNS gene, with an estimated incidence of 1 in 100000 to 1 in 200000 in the USA. It is characterized by the accumulation of intralysosomal cystine crystals due to dysfunction of cystinosin, a lysosomal transport protein (1). In regions with high rates of consanguineous marriages, such as Türkiye and various countries in the Middle East and East Mediterranean, the prevalence of cystinosis may be significantly elevated (1, 2). Given the high burden of autosomal recessive disorders in populations with elevated consanguinity rates, the regional prevalence of cystinosis is expected to surpass that reported in Western countries. The disease can affect multiple organs and is categorized into three distinct types: nephropathic, infantile, and ocular cystinosis (3-5). Nephropathic cystinosis, the most common form, is an orphan disease that necessitates early diagnosis and intervention due to its potential to progress to end-stage renal disease in childhood. Since cysteamine therapy functions by reducing intracellular cystine accumulation, its introduction in the 1980s has markedly improved renal survival and overall outcomes in affected patients. Cysteamine achieves this by converting intralysosomal cystine into metabolites that can exit the lysosome via alternative transport pathways, thereby preventing crystal formation and

reducing cellular toxicity (6). Despite these advancements, cystinosis continues to be a major cause of morbidity in developing countries compared to developed nations (7). In such settings, access to specialized metabolic and pediatric nephrology centers is often limited, cysteamine therapy may be difficult to obtain due to logistical or financial barriers, and regular monitoring—particularly leukocyte cystine measurement—is frequently unavailable. Socioeconomic challenges may further compromise treatment adherence and follow-up continuity. These factors collectively increase the risk of growth retardation, progression to kidney failure, and extrarenal complication (8). The study centre, located in a city in eastern Türkiye with a population of 1.1 million and a crude birth rate of 17.1 per 1000 inhabitants in 2023, serves as a focal point for pediatric nephrological consultations. Given the region's high natality rate and the relatively high prevalence of rare genetic disorders like cystinosis—likely due to elevated consanguinity rates—we manage a substantial number of these patients each year. The aim of this study was to evaluate the clinical characteristics of pediatric patients with cystinosis from a resource-limited region, with a particular focus on growth outcomes and progression to kidney failure.

Materials and Methods

This retrospective study included 17 patients diagnosed with cystinosis who were followed in the Pediatric Nephrology Clinic of a Van Research and Education Hospital between June 2016 and April 2023. The diagnosis of cystinosis is fundamentally based on clinical and laboratory criteria associated with renal Fanconi syndrome, including growth failure, polyuria, electrolyte imbalances, glucosuria, phosphaturia, and generalized proximal tubular dysfunction. The confirmation of cystinosis is established through the detection of corneal cystine crystals during ophthalmic examination and/or the measurement of elevated leukocyte cystine levels at an external centre (exceeding 2 nmol half-cystine per mg of protein) and/or the identification of mutations in the CTNS gene (3).

The medical records of patients were obtained from the hospital patient records and the included patients were evaluated in terms of demographic, clinical, and laboratory data. The evaluated demographic characteristics included gender, age, body weight, weight standard deviation score (SDS), height, height SDS, body mass index (BMI), BMI SDS.

Clinical characteristics included eye involvement, hypothyroidism and hypophosphatemic rickets, existence of nephrocalcinosis, evolution of chronic kidney disease during follow up. Laboratory characteristics included serum creatinine at the time of first and last admission, estimated glomerular filtration rate (eGFR) at the time of first and last admission, blood gas status at admission and genetic testing if available.

Weight (kg), height (cm), and BMI (kg/m^2) values, along with their corresponding standard deviation scores (SDS), were obtained and assessed based on predefined reference ranges for Turkish children (9). Serum creatinine levels were measured using an enzymatic assay, and the estimated glomerular filtration rate (eGFR) was calculated utilizing the bedside Schwartz equation (10, 11).

Molecular genetic analyzes of the patients included in this study were performed at an external center. A clinical exome sequencing kit (SOPHIA GENETICS, Boston, MA, USA) was applied to patients using an NGS-based system (NextSeq 500 system Illumina, San Diego, CA, USA). Data analyzes were carried out with the help of the kit manufacturer's analysis program (SOPHIA DDM). Reported variants were identified using the Human Gene Mutation Database (HGMD) database. Other variants were classified according to American College of Medical Genetics (ACMG) criteria.

In our cohort, alkali therapy was administered using a citrate solution containing sodium citrate 100 g, potassium citrate 100 g, and citric acid 70 g per liter. This corresponds to a sodium dose of 1.16–4.65 mEq/kg/day and potassium dose of 0.98–3.92 mEq/kg/day when administered at 1–4 mL/kg/day.

Neutral phosphate supplementation was provided using Joulie solution ($Na_2HPO_4{\cdot}7H_2O$ 136 g + H_3PO_4 58.8 g per liter), corresponding to a sodium and phosphate dose of 1.02–4.07 mEq/kg/day each, administered at 1–4 mL/kg/day. Cysteamine bitartrate was prescribed to all patients at a dose of 60–90 mg/kg/day, and cysteamine eye drops were administered four times daily.

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, USA). The normality of the variables was assessed through both visual methods (histograms) and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests). Descriptive statistics for categorical variables were presented as frequencies. For variables that did not follow a normal distribution, medians and interquartile ranges (IQR) were reported. When evaluating differences between patients' weight SDS, height SDS, BMI SDS and eGFR values at the first and last admission, the Wilcoxon signed-ranks test was used. A p value <0.050 was considered statistically significant

Results

Primary complaints and epidemiological characteristics of the patients are summarized in Table I. Among the 17 patients, there were 8 girls (44.4%) and 9 boys (55.6%). The median age at presentation was 10.92 (IQR; 8.40) months, and the median follow-up time was 69.24 (IQR;61.20) months. Most patients were admitted with growth retardation, evidenced by a median weight SDS of -3.66 (IQR; 1.35), median height SDS of -2.89 (IQR; 2.44), and BMI SDS of -1.93 (IQR; 1.46). At the time of admission, the median serum creatinine (Cr) level was 0.33 (0.18) mg/dL, and the estimated glomerular filtration rate (eGFR) was 116.66 (IQR; 62.69) mL/min/1.73 m^2 (Table I).

After a median follow-up duration of 69.24 (IQR; 61.20) months, reassessment of height and weight showed no

Table I: Epidemiological properties of cytinosis patients

Variable	Values	p
Number of patients	17	-
Age at onset*	10.92 (8.40)	-
Follow up duration*	69.24 (61.20)	-
Gender (Female)†	8 (44.4)	-
Prensence of consanguinity†	13 (72.2)	-
Weight at onset (kg)*	6.6 (1.55)	-
Weight SDS at onset*	-3.66 (1.35)	-
Height at onset*	68 (7.5)	-
Height SDS onset*	-2.89 (2.44)	-
BMI at Oonset*	14.27 (1.53)	-
BMI SDS at onset*	-1.93 (1.46)	-
Creatinine levels*		
Diagnosis	0.33 (0.18)	0.001‡
Last visit	0.72 (0.87)	
eGFR*		
Diagnosis	116.66 (62.69)	0.007‡
Last Visit	77.40 (95.18)	
Primary complaints*		
Growth retardation	11 (64.7)	-
Vomiting	1 (5.9)	
Family history	4 (23.5)	
Walking difficulty	1 (5.9)	

: median (IQR), †: n(%), ‡: Wilcoxon signed-ranks test,* ***eGFR:* *estimated glomerular filtration rate,* ***SDS:*** *Standard deviation scrore,* ***BMI:*** *Body mass index*

statistically significant difference in weight standard deviation scores (SDS). Baseline median body weight SDS was -3.6 (IQR; 1.35), compared with -2.8 (IQR; 1.55) at follow-up (p = 0.255). However, height SDS significantly deteriorated from a baseline median of -2.8 (IQR; 2.44) to -3.9 (IQR; 2.35) (p=0.034), indicating a notable decline in lineer growth (Figure 1).

Among the initial laboratory data available for 11 patients, the following findings were noted. First, all patients demonstrated tubulopathy as anticipated. And also the majority (n=9) had profiles consistent with incomplete or complete renal Fanconi syndrome (Table II). Additionally, metabolic alkalosis was identified in two patients during blood gas analyses: one (P3) had transient alkalosis, while another (P12) exhibited persistent hypochloremic hypokalemic metabolic alkalosis without ocular cystine crystals, initially leading to a provisional diagnosis of Bartter syndrome. However, upon the development of renal Fanconi syndrome, cystine levels were assessed externally, confirming cystinosis (Table II).

During periodic follow-up evaluations, ocular involvement was documented in all patients. Additionally, hypothyroidism necessitating treatment was detected in six patients (35.2%), and clinical manifestations of rickets were observed in four patients (23.5%) (Table II). Nephrocalcinosis was identified in six patients (35.2%). Treatment adherence was assessed clinically; good adherence was documented in 9 (52.9%) patients, whereas poor adherence was noted in 8 (47.1%) patients (Table II). Poor adherence was more common among those who progressed to advanced CKD.

Table II: Clinical and laboratory characteristics of patients

Patient No	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Age at diagnosis (months)	13.9	6.9	24.6	10.9	14.7	7.9	7.6	9.9	9	15	7.08	26.4	15.3	22.9	17.0	6	10.9
Follow up time (months)	91.6	86.1	1	82.0	54.8	28.0	11.5	123.0	69.2	76.8	89.1	56.6	42.4	25.0	129.7	30.3	120.1
Tubulopathy at onset																	
Glycosuria	+	+	-	NA	+	+	-	NA	NA	+	+	-	+	NA	NA	+	NA
Hypophosphatemia	+	+	+	NA	+	+	+	NA	NA	+	+	+	+	NA	NA	+	NA
Metabolic acidosis	-	-	-	+	+	+	+	+	+	-	-	-	+	+	+	-	+
Metabolic alkalosis	-	-	+	-	-	-	-	-	-	-	-	+	-	-	-	-	-
Normal blood gas	+	+	-	-	-	-	-	-	-	+	+	-	-	-	-	+	-
Extrarenal Findings (during follow up)																	
Ocular involvement	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hypothyroidism	-	-	-	+	-	-	-	+	-	-	-	-	+	-	+	+	+
Rickets	-	-	-	-	-	-	-	-	-	-	-	+	-	-	+	+	+
Treatment Adherence	G	G	G	P	P	G	G	G	P	P	P	P	G	G	P	G	P
Nephrocalcinosis (Present)	+	-	-	+	-	+	-	+	+	-	-	-	-	-	-	-	+
Kidney function status/eGFR (Last)																	
eGFR	155.8	146.2	113.2	10.3	44.0	89.5	193.8	62.4	55.0	75.8	80.9	32.2	133.3	80.6	9.7	77.4	9.10
CKD stage (KDIGO)	G1	G1	G1	G5	G3	G2	G1	G2	G3	G2	G2	G3	G1	G2	G5	G2	G5

G: *Good* ***P:*** *Poor,* ***NA:*** *not avaliable,* ***CKD:*** *Chronic Kidney Disease,* ***KDIGO:*** *Kidney Disease: Improving Global Outcomes*

Table III: Genetic analysis of patients

Patient	Gene (Transcript)	Zygosity	Variation	R/N	ACMG	OMIM	IP
P1	CTNS (NM_001031681)	Homozygous	c.681G>A (p.Glu227Glu)	CS099126	P	Cystinosis (OMIM: 606272)	AR
P2	CTNS (NM_001031681)	Homozygous	c.681G>A (p.Glu227Glu)	CS099126	P	Cystinosis (OMIM: 606272)	AR
P6	CTNS (NM_001031681)	Homozygous	c.681G>A (p.Glu227Glu)	CS099126	P	Cystinosis (OMIM: 606272)	AR
P7	CTNS (NM_004937)	Heterozygous	c.681G>A (p.Glu227Glu)	CS099126	P	Cystinosis (OMIM: 606272)	AR
		Heterozygous	c.1015G>A (p.Gly339Arg)	CM980461	P		AR
P8	CTNS (NM_004937)	Homozygous	c.681G>A (p.Glu227Glu)	CS099126	P	Cystinosis (OMIM: 606272)	AR
P9	CTNS (NM_004937)	Homozygous	c.681G>A (p.Glu227Glu)	CS099126	P	Cystinosis (OMIM: 606272)	AR
P13	CTNS (NM_001031681)	Homozygous	c.681G>A (p.Glu227Glu)	CS099126	P	Cystinosis (OMIM: 606272)	AR
P16	CTNS (NM_004937)	Homozygous	c.18_21delGACT (p.Thr7Phefs*7)	CD982561	P	Cystinosis (OMIM: 606272)	AR

R/N: *reported/nove,* ***ACMG:*** *American College of Medical Genetics and Genomics,* ***OMIM:*** *Online Mendelian Inheritance in Man,* ***IP:****Inheritance pattern,* ***AR:***Autosomal reccessive***, P:*** *pathogenic,* ***CTNS:*** *cystinosis*

When comparing patients' eGFR values at diagnosis (116.66 [62.69] mL/min/1.73 m²) with those at the final follow-up (77.40 [95.18] mL/min/1.73 m²), the median eGFR at follow-up was significantly lower (p=0.007) (Table I). According to the KDIGO classification, 5 patients were in stage G1, 6 in G2, 3 in G3, and 3 in G5 at the final visit, with no patients in G4. In total, 12 patients had an eGFR below 90 mL/min/1.73 m², and 3 of them had progressed to stage 3 chronic kidney disease, while another 3 had developed end-stage kidney disease requiring renal replacement therapy (Table II). Genetic results were available for 8 of the 17 patients, with the identified genetic variants detailed in Table III.

Discussion

In this study, growth retardation, recurrent vomiting, and a positive family history were the most common presenting features that prompted referral to the nephrology clinic. The distribution of presenting symptoms was consistent with previous reports (2, 4). In addition to these primary complaints, parents frequently reported polyuria and polydipsia, reflecting the early onset of tubular dysfunction typical of nephropathic cystinosis. Older patients also described a pronounced tendency toward salt craving, which is commonly observed in the context of chronic electrolyte losses associated with the disease.

Bertholet-Thomas et al. (7) reported that in developing countries patients were slightly older at the time of diagnosis compared to patients diagnosed in developed countries, 1.5 years vs.1.3 years, respectively but the proportion of patients with a diagnosis before 2 years of age was not different between developing and develeped countries. Soliman et al. (12) reported that mean age at the time of diagnosis was above four years (52.7 months) and almost half (44%) of their patients were diagnosed after the age of five years. In our study median age at diagnosis was 10.9 months. Despite limited resources, the relatively younger age at diagnosis in this study group compared to other developing countries may be attributed to heightened clinical awareness, likely influenced by the increased prevalence of consanguineous marriages in the region and the consequent higher incidence of autosomal recessive disorders.

In this study, there were three patients without glucosuria at baseline. Of these, two were patients with a known family history of cystinosis in a sibling (P2, P7), and one presented with a phenotype of Bartter syndrome (P12). In other patients, glucosuria was observed as a reflection of generalized proximal tubular dysfunction. In the same patient group (P2 and P7), bicarbonate levels in blood gas at the time of diagnosis were within low-normal limits. Although renal Fanconi syndrome typically presents with pronounced clinical and laboratory findings, it should be noted that some cases may present with incomplete proximal tubular dysfunction, and it may take time for generalized tubular dysfunction findings to fully manifest (13, 14). In the presence of incomplete renal Fanconi syndrome or metabolic alkalosis instead of metabolic acidosis, diagnosis may delay (12-16).

Failure to thrive is almost a universal finding in cystinosis and other hereditary renal tubular disorders. On the other hand, it has been reported that effective and appropriate treatment can improve weight and height parameters and that catch-up growth can occur in these patients particularly in dRTA (17). However in more complex renal tubular disorders such as cystinosis and renal fanconi syndrome and proximal RTA achieving catch up growth may differ than other hereditary renal tubular disorders such as dRTA (17-20).

In this study, the significant decrease in median height SDS scores observed at the end of a median follow-up period of 69 months was notable. Although all patients included were receiving oral cysteamine therapy, the decline in height SDS scores may be attributed to several potential factors. Despite treatment, patients with renal Fanconi syndrome experience loss of final adult height, due to a variety of factors such as chronic hypokalemia, persistant metabolic acidosis and consequences, phospate loss and resultant defective bone mineralisation and inadequate intake of required daily energy due to polydypsia and loss of appetite (18-21). Also nutritional deficiencies and the effects of hormones such as growth hormone and thyroid hormones may play a role in growth retardation. Particularly in patients with cystinosis, the feeling of fullness and abdominal distention due to polyuria and polydipsia can restrict adequate caloric intake, leading to

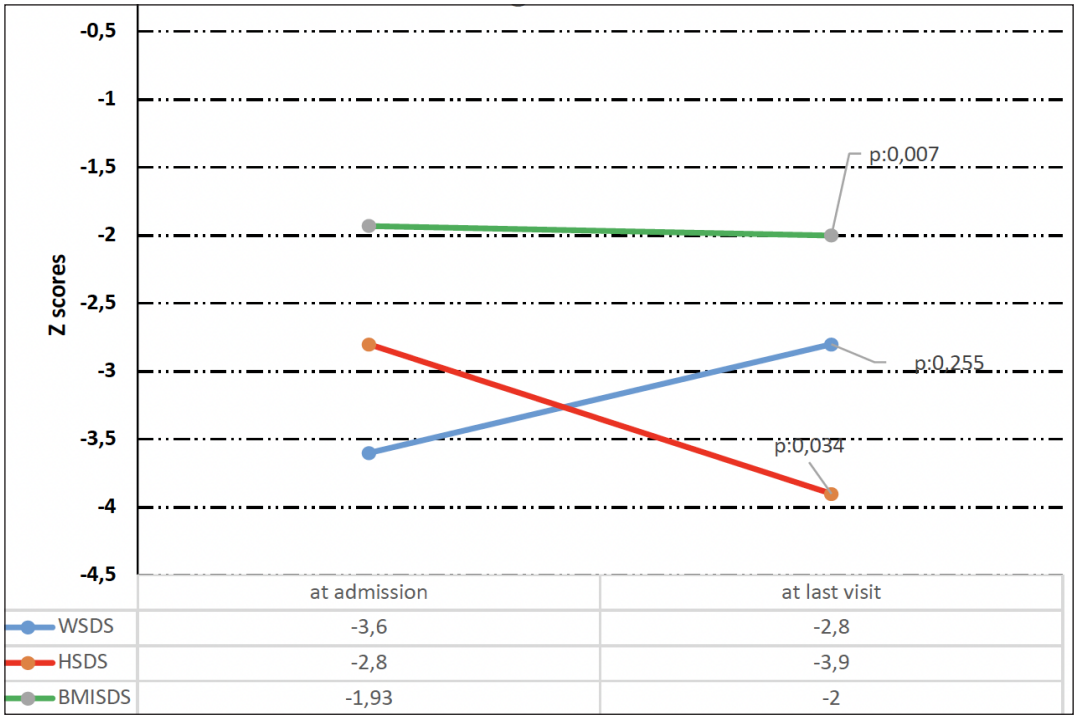

Figure 1: Changes in median weight for age,height for age and body mass index Z scores

nutrient deficiencies and anemia. Additionally, hypothyroidism is not uncommon in patients with cystinosis and may contribute to retarded growth (22). In our study, patients were screened for hypothyroidism during their follow-ups and 6 out of 17 patients were started on levothyroxine. Furthermore, given that 6 of the 17 patients had advanced-stage chronic kidney disease (3 patients with stage 3 CKD and 3 with end-stage renal disease requiring dialysis), we can speculate that the impact of hormonal factors, particularly within the growth hormone axis, becomes increasingly evident as chronic kidney disease progresses and renal function deteriorates.

In this study, nephrocalcinosis was detected in 6 patients. Nephrocalcinosis in patients with cystinosis may develop due to significant calcium and phosphorus loss and the balance between fluid intake and loss, but it can also arise as a complication related to supportive therapies containing active vitamin D, calcium, and phosphorus (23). Although this study does not permit definitive conclusions regarding the impact of nephrocalcinosis on renal function, we contend that it is essential to evaluate the relationship between nephrocalcinosis and GFR loss in larger cohorts.

Upon analysis of patients over the age of 1 at admission, a total of 8 patients exhibited eGFR greater than 90 ml/min/1.73 m^2 at baseline, which subsequently declined to below 90 at the final follow-up. Among these patients, 3 were undergoing peritoneal dialysis, while 3 had progressed to stage 3 chronic kidney disease in a pre-dialysis state. Despite all patients having initiated cysteamine therapy, the relatively high incidence of renal failure in this cohort is a matter of concern. We believe that this situation may be significantly related to the treatment adherence related with socioeconomic conditions and family structures in the region. Specifically, low literacy rates and large family sizes appear to be factors that reduce treatment adherence. From a clinician's perspective, the regular monitoring of leukocyte cystine levels, alongside essential clinical and laboratory parameters, is crucial for assessing treatment efficacy. Unfortunately, due to the inability to measure leukocyte cystine levels in the region, patients are required to seek care at larger centers for this assessment. This situation poses socioeconomic challenges for families and complicates optimal treatment monitoring. Additionally, side effects related to the medication, such as taste disturbances and vomiting, can hinder the attainment of effective dosing, potentially leading to treatment non-adherence.

Conclusion

While the progression to kidney failure in patients with cystinosis undergoing cysteamine treatment may be manageable the optimal management of these patients continues to pose a substantial challenge for clinicians, particularly in developing countries and in regions that are remote from major experienced medical centers. We think that, in light of the literature, cystinosis can be viewed as two distinct entities—before and after the initiation of cysteamine treatment—particularly in developed countries. However, in resource-limited settings, cystinosis remains an orphan condition and continues to be a significant cause of chronic kidney failure.

Limitations

The limitations of this study include its retrospective nature and the challenges in accessing data for some patients who were referred from different centers. Although all patients were followed periodically, treatment adherence was evaluated

subjectively, which may introduce potential misclassification bias. Additionally, the inability to routinely measure leukocyte cystine levels limited the objective assessment of metabolic control and prevented a more accurate correlation between adherence and renal outcomes. The relatively small sample size, inherent to the rarity of the disease, may also restrict the generalizability of our findings.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Van Research and Education Hospital (15.09.2023, number: 2023/09-06).

Contribution of the authors

Study conception and design: AY, OG; data collection: AY; analysis and interpretation of results: AY,OG; draft manuscript preparation: AY. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

The hidden costs of seizure control: Metabolic and hormonal effects of anti-seizure medications in children

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ABSTRACT

Objective: This study aimed to evaluate the metabolic and hormonal effects of anti-seizure medications (ASMs) in children with epilepsy by comparing serum levels of vitamin D, calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), vitamin B12, folate, thyroid-stimulating hormone (TSH), and free thyroxine (fT4) between ASM-treated patients and healthy controls. A secondary aim was to investigate differences between patients treated with valproate (VPA) and those treated with levetiracetam (LEV).

Materials and Methods: A total of 106 pediatric epilepsy patients undergoing ASM therapy were included in the study, with 93 on monotherapy and 13 on polytherapy for at least six months. Additionally, 80 age- and sex-matched healthy controls were included. Serum biochemical parameters were analyzed retrospectively. Subgroup analyses compared patients on VPA and LEV monotherapy. Statistical comparisons and correlation analyses assessed relationships between drug exposure and biochemical values.

Results: Vitamin D levels were significantly lower in ASM-treated patients compared to controls ($p<0.001$). TSH levels were higher in the VPA group than in the LEV group ($p<0.001$), although there were no significant differences in thyroid hormone levels between ASM-treated patients and the healthy control group overall. No significant differences were observed in calcium, phosphorus, ALP, vitamin B12, or folate levels between the groups. The duration of ASM use was not correlated with any of the biochemical parameters.

Conclusion: Vitamin D deficiency and changes in thyroid function may occur in children treated with ASMs, especially VPA. However, vitamin B12 and folate levels tend to stay stable. Given the ongoing fluctuations in vitamin D and thyroid hormone levels, more frequent monitoring of these parameters may be warranted in pediatric epilepsy patients on ASM therapy. In contrast, less frequent assessment of vitamin B12 and folate may be enough unless there are clinical reasons to test further. More prospective studies are needed to determine the best monitoring approaches.

Keywords: Antiepileptic drug, children, folate vitamin D, thyroid hormones, vitamin B12

Introduction

Epilepsy is a chronic disorder characterized by recurrent, unprovoked seizures caused by abnormal electrical activity (1). Its prevalence is approximately 0.5–1%, making it one of the most common chronic illnesses in childhood (2). Seizure control may require long-term use of anti-seizure medications (ASMs), which have been shown in the literature to potentially affect thyroid function, bone health, and vitamin levels (3, 4). Sodium valproate (VPA) is a traditional ASM that has been used for many years to treat epilepsy (5), while levetiracetam (LEV) is considered one of the newer drugs that has become increasingly preferred for seizure control in recent years (6). Both medications are commonly used to manage epilepsy in the pediatric population. The primary aim of our study was to evaluate serum levels of 25-hydroxyvitamin D (25-OHD), calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), vitamin B12, folate, thyroid-stimulating hormone (TSH), and free thyroxine (fT4) in children undergoing ASM therapy for epilepsy compared to healthy controls. The secondary aim was to examine the relationship between these vitamin and hormone levels among patients with epilepsy treated with either VPA or LEV.

Materials and Methods

The retrospective study was conducted between January 1, 2022, to February 1, 2023, involving children aged 1 to 18 years who visited the pediatric neurology outpatient clinic at Atatürk Sanatoryum Training and Research Hospital. A total of 106 children participated in the study, all diagnosed with epilepsy according to the definitions and classifications of the International League Against Epilepsy (ILAE) (7). These patients had no known chronic illnesses besides epilepsy and had been treated with either VPA or LEV, in monotherapy or polytherapy, for at least six months due to generalized or focal epilepsy. Furthermore, all participants had been seizure-free for a minimum of six months before enrollment. Of these, 93 children were on these medications as monotherapy, while the remaining 13 patients were also taking one or more additional ASMs, such as carbamazepine, clobazam, or other ASMs. Eighty healthy children, without any known chronic illnesses, and matched in terms of age and gender to the study group, were included as the control group in the study. Serum levels of 25-OHD (µg/L), P (mg/dL), ALP (U/L), Ca (mg/dL), vitamin B12 (ng/L), folate (µg/L), TSH (mU/L), and fT4 (ng/dL) in the children were retrospectively reviewed from the hospital's information management system records. Because this was a retrospective study, the exact timing of blood sampling in relation to ASM administration and diurnal variation could not be standardized; however, samples were obtained during routine outpatient visits in the morning hours (08:00–12:00) following the hospital's standard laboratory protocol. This condition should be considered when interpreting the results. Participants with chronic diseases other than epilepsy, those who had used ASMs for less than six months, individuals with clinical seizures during the follow-up period, those with known thyroid disorders or undergoing thyroid hormone replacement therapy, and individuals receiving vitamin B12, folate or vitamin D supplementation were excluded from the study.

The primary comparisons were made between children receiving ASM treatment for epilepsy and healthy controls. Secondarily, comparisons were conducted between 29 patients receiving VPA monotherapy and 57 patients receiving LEV monotherapy. Patients using carbamazepine, clobazam, or other treatments were excluded from the drug comparison analysis due to their small sample sizes. The demographic characteristics of the patients, along with their levels of 25-OHD, vitamin B12, folate, and thyroid hormones, were compared between groups. The levels of 25-OHD (30-100 µg/L), vitamin B12 (200-883 ng/L), folate (3.1-20.5 µg/L), fT4 (0.7-1.48 ng/dL), TSH (0.35-4.94 mU/L), Ca (9-11 mg/dL), P (4-9 mg/dL), and ALP (75-316 u/L) were considered within normal reference ranges. In the literature, vitamin D levels below 20 are considered deficient (8).

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics, version 30.0 software package (New York, USA: IBM Corp.). Descriptive statistics were used to summarize the demographic and clinical characteristics of the participants. Continuous variables were presented as mean and standard deviation (SD), and categorical variables were expressed as frequencies and percentages. The data distribution normality was assessed with the Kolmogorov-Smirnov test and Shapiro–Wilk test. For comparisons between two independent groups, the Mann-Whitney U test was applied for non-normally distributed variables. To evaluate differences in serum levels of 25-OHD, Ca, P, ALP, vitamin B12, TSH, fT4, and folate between the epilepsy and healthy control group, independent sample tests were applied accordingly. Comparisons between patients on VPA monotherapy and those on LEV monotherapy were conducted similarly. Correlation analyses were performed using Spearman's correlation coefficients, depending on the distribution of data, to assess the relationship between the duration of anti-seizure medication use and serum levels of 25-OHD, Ca, P, ALP, vitamin B12, TSH, fT4, and folate. A p-value of less than 0.050 was considered statistically significant for all analyses.

Results

A total of 106 pediatric patients diagnosed with epilepsy (88 with generalized epilepsy and 18 with focal epilepsy; 53 males and 53 females) were included in the study. The mean age was 11.8±1.2 years (range; 1–18 years). In the control group, consisting of 80 healthy children (38 females and 42 males), the mean age was 11.3±3.2 years. The average duration of ASM use when blood sampling was 21.6±14.9 months among the patient group. Demographic characteristics are summarized in Table I. In children undergoing ASM treatment, the mean serum 25-OHD level was 12.5±5.1 µg/L, compared to 19.5±8.6 µg/L in healthy controls, with this difference being statistically significant ($p<0.001$). Among those on medication, the mean serum Ca level was 9.8±0.4 mg/dL, P level was 4.5±0.7 mg/dL, and ALP level was 201±90.9 U/L. In the healthy control group, these values were 9.8±0.5 mg/dL, 4.7±0.5 mg/dL, and 224.6

Table I: Demographic data of epilepsy patients and the control group

	Epilepsy Patients	Control Group
Number of total patients	106	80
Age (year)*	11.8±1.2	11.3±3.2
Gender†		
Girl	53 (50.0)	38 (47.5)
Boy	53 (50.0)	42 (52.5)
Epilepsy Type†		
Generalized	88 (83.0)	-
Focal	18 (17.0)	-
Medication used†		
Levetiracetam	65 (61.3)	-
Valproate	41 (38.7)	-
Carbamazepine	8 (7.5)	-
Clobazam	7 (6.6)	-
Other	3 (2.8)	-
Polytherapy†	13 (12.3)	-
Duration of medication (month)*	21.6±14.9	-

**: mean±SD, †: n(%), ‡: month± SD*

Table II: Laboratory values of epilepsy and control groups

	Epilepsy (n=106)			Control (n=80)			p†
	mean±SD	median (min-max)	IQR* 25-75	mean±SD	median (min-max)	IQR* 25-75	
Calcium (mg/dL)	9.8 ± 0.4	9.8 (8.8-10.8)	9.5-10.1	9.8 ± 0.5	9.8 (8.2-11.2)	9.5-10.1	0.526
Phosphorus (mg/dL)	4.5 ± 0.7	4.8 (3.2-6.0)	4.5-5.2	4.7 ± 0.5	4.8 (3.1-6.0)	4.4-5.1	0.752
Alkaline Phosphatase (U/L)	201 ± 90.9	175.5 (63.0-555.0)	140.5-250.8	224.6 ± 99.1	219 (5.9-592.0)	176.8-278.5	0.061
25-OH Vitamin D (µg/L)	12.5 ± 5.1	12.3 (3.5-27.0)	9.0-16.5	19.5 ±8.6	18.0 (6.1-61.0)	14.0-24.7	<0.001
TSH (mU/L)	2.44 ± 2.66	1.71 (0.41-25.78)	1.16-2.98	2.34 ± 1.48	1.96 (0.02-61.00)	1.23-3.20	0.655
Free T4 (ng/dL)	0.95 ± 0.14	0.96 (0.66-1.70)	0.87-1.03	0.95 ± 0.11	0.95 (0.65-1.20)	0.89-1.03	0.502
Vitamin B12 (ng/L)	347 ± 111	342 (140-634)	273-445	373 ± 139	355 (172-826)	280-414	0.347
Folate (µg/L)	8.2 ± 3.2	8.0 (2.1-12)	6.6-8.5	8.3 ± 2.7	8.2 (4-11.5)	7.6-9.0	0.481

***IQR:** Interquartile Range, †: Mann–Whitney U test*

Table III: Laboratory values of levetiracetam and valproate groups

	Levetiracetam (n=57)			Valproate (n=29)			p†
	mean±SD	median (min-max)	IQR* 25-75	mean ± SD	median (min-max)	IQR* 25-75	
Calcium (mg/dL)	9.7 7±0.42	9.8 (8.8-10.5)	9.5-10.1	9.82±0.46	9.8 (8.9-10.8)	9.5-10.1	0.704
Phosphorus (mg/dL)	4.75±0.67	4.8 (3.2-6.0)	4.4-5.3	4.63±0.58	4.7 (3.3-5.5)	4.5-5.0	0.334
Alkaline Phosphatase (U/L)	208.16±96.48	195 (63-555)	144-263	183.24±71.38	166 (71-328)	129-247	0.311
25-OH Vitamin D (µg/L)	13.11±4.6	12.3 (6.2-27.0)	9.2-16.5	12.71±4.74	12.1 (3.5-20.3)	8.3-17.1	0.833
TSH (mU/L)	1.66±1.09	1.35 (0.41-6.75)	1.02-2.12	4.07±4.39	3.19 (1.00-25.78)	2.09-4.35	<0.001
Free T4 (ng/dL)	0.97±0.14	0.96 (0.76-1.70)	0.87-1.04	0.93±0.12	0.95 (0.66-1.18)	0.86-1.02	0.346
Vitamin B12 (ng/L)	351.53±119.95	342 (140-634)	255-448	364.26±94.84	330 (217-621)	299-444	0.565
Folate (µg/L)	8.71±3.2	8.5 (6.0-12.7)	7.1-9.2	7.32±2.81	7.4 (3.4-10.1)	6.7-8.5	0.793

***IQR:** Interquartile Range, †: Mann–Whitney U test*

±99.1 U/L, respectively. There were no significant differences between the two groups in Ca, P, and ALP levels (p = 0.526, p = 0.752, p = 0.061, respectively). In our study, we also compared ALP values in patients with vitamin D levels below 20 between groups treated and not treated with ASMs. The ALP level was 202.5±92.8 U/L in the epilepsy group and 230.6±115.8 U/L in the control group; the difference was not statistically significant (p=0.090). TSH and fT4 levels were measured at 2.44±2.66 mU/L and 0.95±0.14 ng/dL, respectively, in the ASM-treated group, and 2.34±1.48 mU/L and 0.95±0.11 ng/dL in the control group. These differences were not statistically significant (p =0.655 and p =0.502, respectively). Similarly, the mean vitamin B12 level was 347±111 ng/L in the epilepsy group and 373±139 ng/L in the control group, with no statistically significant difference observed (p =0.347). The folate levels in the epilepsy and control groups were 8.2±3.2 and 8.3±2.7, respectively; the difference was not statistically significant (p= 0.481) (Table II). No significant correlation was found between the duration of medication use and the levels of vitamin D (p=0.612), vitamin B12 (p=0.920), folate (p= 0.54) or thyroid hormones (TSH p= 0.072, sT4 p=0.786). Correlations between medication duration and laboratory parameters were assessed using Spearman's rank correlation test due to non-normal data distribution.

Discussion

ASMs affect thyroid hormone levels through various mechanisms. Most increase the clearance of thyroid hormones by inducing hepatic microsomal enzymes, while others exert their effects via the hypothalamic-pituitary axis (9). It has been suggested that VPA may increase TSH levels due to its gamma-aminobutyric acid (GABA)-like effects.

GABA inhibits somatostatin release, which in turn suppresses TSH secretion; thus, reduced somatostatin activity may lead to increased TSH levels. Additionally, VPA might impair thyroid hormone production by causing zinc and selenium deficiencies. Magnesium deficiency may also contribute by reducing iodine uptake and thyroxine (T4) synthesis, thereby triggering increased TSH secretion. Furthermore, magnesium deficiency may reduce the physiological effects of thyroid hormones (10). VPA extensively binds to plasma proteins and may displace T4 from its binding sites, potentially altering circulating free hormone levels (11).

Several studies in the literature have shown that VPA can have variable effects on thyroid hormones. In line with our results, the survey conducted by Güngör et al. (12) reported elevated TSH levels in patients using VPA, without any significant alteration in fT4 levels (13). When examining studies on patients using VPA, while one study reported an increase in TSH levels along with a reduction in fT4, whereas another did not find significant changes in thyroid hormone levels (14-17). These varying results may be attributed to differences in methodologies and study populations across the respective studies. Moreover, some studies have also demonstrated that the duration of VPA treatment may influence thyroid function during therapy (18). However, in our study, no association was found between the duration of medication use and thyroid function.

LEV exerts its effects through synaptic vesicle glycoprotein 2A (SV2A), which is expressed in both the central nervous system and endocrine tissues. (19). However, in our study, no changes were observed in thyroid hormone levels in patients using LEV.

This finding is consistent with numerous studies in the literature, which include both short- and long-term treatment durations, where similar results have been reported (12, 15, 20, 21). In our study, although higher thyroid hormone levels were observed in the group treated with ASMs, no significant difference was observed in thyroid hormone levels between ASM-treated patients and the healthy control group. While a difference in thyroid hormone levels was observed between the groups using VPA and LEV, the lack of a significant difference between ASM-treated and non-ASM-treated patients overall may be attributed to the fact that the majority of patients in the ASM-treated group were receiving LEV, which doesn't affect thyroid function in our study.

ASMs may negatively impact bone health by decreasing bone quality and increasing the risk of fractures. This effect is thought to originate from disruptions in vitamin D metabolism, decreased osteoblast activity, and changes in collagen production (22). Many traditional ASMs, such as phenytoin, carbamazepine, and phenobarbital, act as inducers of the hepatic cytochrome P450 enzyme system, potentially leading to vitamin D deficiency (23). Widely used in children with epilepsy, VPA is not typically classified as a hepatic enzyme inducer; however, some studies have reported its ability to induce CYP3A4 and CYP24A1, enzymes involved in vitamin D catabolism (24). LEV is an ASM primarily metabolized through enzymatic hydrolysis of its acetamide group (27%), while the hepatic cytochrome P450 (CYP) system contributes only minimally (approximately 2.5%) (25). Despite its growing use in pediatric and adult epilepsy management, clinical evidence regarding its effect on vitamin D metabolism and bone health remains limited. Animal studies have provided some insight into the possible skeletal impacts of LEV. In a study by Nissen-Meyer et al. (26), LEV treatment in rats was linked to microstructural changes in the bone matrix, although bone mineral density (BMD) stayed the same.

Conversely, some experimental studies have found that long-term administration of LEV may lead to a significant decrease in bone mineral content in rat models, indicating potential adverse effects on bone quality with prolonged use (27). In the study by Vijayakumar et al. (28), patients receiving ASMs therapy exhibited significantly lower serum levels of 25-OHD, Ca, and P compared to the control group. In contrast, their ALP levels were significantly elevated. In the meta-analysis by Zhang et al. (29) evaluating the effects of ASMs on bone mineral metabolism, a decrease in 25-OHD levels was observed. Additionally, ALP levels increased, while no significant changes were found in Ca and P levels. In the study conducted by Yıldız et al. (30), which compared values before and after the use of ASMs, a significant decrease in vitamin D levels was observed, whereas no significant changes were observed in Ca, P, and ALP levels. The results of the study by Yıldız et al. (30) were consistent with ours. The presence of conflicting results in the literature regarding Ca, P, vitamin D, and ALP metabolism may be due to individual factors such as sun exposure, as well as underlying mechanisms that are not yet fully understood.

According to the Endocrine Society Guidelines, vitamin D levels should be monitored in children with epilepsy receiving ASM therapy, including those treated with VPA or LEV (31,32). Considering the high prevalence of vitamin D deficiency observed in our cohort, routine assessment of vitamin D levels should be included in the standard management of pediatric patients receiving ASM treatment.

Vitamin B12 levels in patients using ASMs remain a topic of debate in the literature. While some studies have reported decreased levels, others have found elevated or normal levels (4,33-37). Linnebank et al. (37) reported that, among patients receiving ASM monotherapy, neither the mean serum vitamin B12 levels nor the prevalence of subnormal vitamin B12 values differed significantly from those of untreated individuals or healthy controls. Notably, patients treated with valproate monotherapy exhibited higher mean serum vitamin B12 levels than untreated patients and controls, with this increase showing a dose-dependent pattern. In our study, as reported above, there was no significant difference in vitamin B12 levels observed between the groups that received and those that did not receive ASMs. However, unlike this study, we also found no significant difference in vitamin B12 levels between patients treated with VPA and those not treated with VPA. Conflicting findings in the literature on vitamin B12 levels may be attributed to differences in therapy duration, drug types used, dietary intake, or genetic factors that influence vitamin metabolism. Therefore, although our findings did not show a significant change in serum vitamin B12 levels, based on the data mentioned earlier, routine

monitoring of vitamin B12 levels in patients on long-term ASM therapy may be advisable. ASMs are known to impact folate metabolism, but the degree of this effect seems to differ based on the medication. VPA, a commonly used AED, has been associated with reduced serum folate levels in some studies. Sharma et al. (38) and Linnebank et al. (37) reported a significant decrease in folate levels in children receiving VPA therapy. On the other hand, several studies, including those by Geda et al. (39) and Özdemir et al. (40), found no significant changes in folate levels, suggesting that the impact of valproate may vary depending on factors such as dosage, treatment duration, and individual differences. LEV, a newer ASM, seems to have little to no impact on folate levels, as noted by Linnebank et al.(37). Reflecting these mixed results, our own study found no significant difference in serum folate levels between the ASM-treated group—most of whom were on LEV therapy—and healthy controls. These findings highlight that ASMs do not uniformly affect folate metabolism and reinforce the importance of personalized monitoring approaches in clinical practice.

Conclusion

In conclusion, while our study found that vitamin D levels and thyroid hormones were affected in children receiving ASMs, vitamin B12 and folate levels remained stable. However, previous studies in the literature have reported that each of these parameters can be influenced by ASMs. Considering our findings and the existing evidence, we suggest that clinicians stay alert to potential changes in these biochemical markers in children receiving ASM therapy, while emphasizing that our results are based on single-time-point measurements and do not allow for definitive recommendations on monitoring frequency. Nevertheless, given the ongoing fluctuations in vitamin D and thyroid hormone levels, more frequent monitoring of these parameters may be warranted. In contrast, vitamin B12 and folate levels could be assessed at longer intervals unless clinically indicated. Early detection and proper supplementation in deficiency cases are crucial, as they can help prevent long-term complications and support optimal growth and neurological development in children with epilepsy. Therefore, further studies are needed to determine the optimal duration and frequency of monitoring.

Limitations

The limitations of our study include neglecting confounding factors such as nutrition and age, measuring values at only one time point, the retrospective design, lack of standardization in the timing of blood sampling relative to ASM administration and diurnal variation, a small sample size, and limited diversity of treatment regimens. However, despite these limitations, the consistency of our findings with the literature indicates that our study group is homogeneous and that our data are accurate

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Atatürk Sanatoryum Training and Research Hospital (June 26, 2024, reference number: 2024 BÇEK/97).

Contribution of the authors

Study conception and design: ÖA, ANC, BD, ADB; data collection: ÖA, ANC, BD, AP; analysis and interpretation of results: ÖA, ANC, AP; draft manuscript preparation: ÖA, ANC, ADB. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Bowel habit changes in children with PFAPA Syndrome: Before and after treatment evaluation with the Bristol Stool Scale

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ABSTRACT

Objective: Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis (PFAPA) syndrome is one of the most common autoinflammatory diseases of childhood. Although gastrointestinal system (GIS) complaints are reported, bowel habits have not been objectively evaluated in these patients. This study investigated changes in bowel habits before and after treatment in children with PFAPA using the Bristol Stool Scale and daily stool frequency.

Materials and Methods: We included 101 children diagnosed with PFAPA according to the EUROFEVER/PRINTO criteria. Clinical, laboratory, daily stool frequency, and stool form were evaluated during febrile attacks before and after treatment. Stool form was evaluated using the Bristol Stool Scale and classified as hard (types 1–3), normal (type 4), and loose (types 5–7).

Results: Following treatment, median daily stool frequency during attacks decreased (2 [0.25–10] vs. 1 [0.25–6]; p=0.008), while stool form assessed by the Bristol Stool Scale remained unchanged (4 [1–7] vs. 4 [1–7]; p=0.943). No significant difference was observed in stool consistency categories (p=0.174). In the probiotic group, patients with normal stool form increased from 53.6% (n=15) pre-treatment to 57.1% (n=16) post-treatment.

Conclusion: To our knowledge, this study is the first to objectively evaluate bowel habits in children with PFAPA syndrome. Following treatment, stool frequency during episodes decreased significantly, while stool form remained unchanged. These results indicate that post-treatment alterations in bowel habits are primarily related to stool frequency. Future studies incorporating fecal biomarkers may provide further insights into gastrointestinal involvement and potential subclinical intestinal inflammation in PFAPA.

Keywords: Aphthous, colchicine, fever, pharyngitis, probiotics, stomatitis

Introduction

Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis (PFAPA) syndrome is one of the most common autoinflammatory diseases of childhood. This syndrome generally manifests before the age of five and is characterized by recurrent febrile episodes occurring at regular intervals (1,2). These episodes may be usually observed pharyngitis, aphthous stomatitis, and cervical lymphadenitis, whereas children remain entirely asymptomatic between episodes. In addition to the classical clinical features, children with PFAPA may present with gastrointestinal system (GIS) complaints, such as diarrhea, abdominal pain, nausea, and vomiting. Although PFAPA follows a generally self-limited course, recurrent attacks are known to adversely affect the quality of life of both the patient and their families (3-6).

The Bristol Stool Scale is a diagnostic tool that classifies stool form into seven categories and is widely used in clinical practice for the objective assessment of bowel habits in children (7,8). Although GIS complaints have been described in the existing literature on PFAPA syndrome, to our knowledge, no study has evaluated stool form using the Bristol Stool Scale in these patients. In this study, we aimed to objectively evaluate changes in bowel habits during PFAPA attacks by assessing stool form with the Bristol Stool Scale and the average daily defecation frequency during pre-treatment and post-treatment attack periods.

Materials and Methods

This study was conducted at the Department of Pediatric Rheumatology, Istanbul Medeniyet University Göztepe Prof. Dr. Süleyman Yalçın City Hospital between January 2022 and June 2024. between January 2022 and June 2024. A total of 152 children who were classified as PFAPA syndrome according to the EUROFEVER/PRINTO criteria were initially enrolled (9). In our clinic, all patients presenting with GIS symptoms are routinely evaluated with additional tests for differential diagnosis, including celiac disease screening and fecal calprotectin testing. After excluding patients with incomplete data, concomitant GIS diseases, use of medications that could affect bowel habits, or secondary causes of diarrhea, 101 children constituted the final study cohort. Before treatment initiation, all families were informed about the international consensus recommended therapeutic options for PFAPA, and treatment decisions were made jointly with parents (10). Accordingly, patients were started on either colchicine or probiotic prophylaxis, and treatment was maintained throughout the follow-up period. In patients receiving probiotic prophylaxis, Streptococcus salivarius K12 (Bactoblis®) was administered orally once daily. The study flow diagram is presented in Figure 1.

Demographic information, clinical characteristics, and laboratory data of the patients were obtained from their medical records. Disease activity in PFAPA patients was assessed using the Autoinflammatory Diseases Activity Index (AIDAI) (11). Stool form was assessed using the Bristol Stool Scale and classified as hard (types 1–3), normal (type 4), or loose (types 5–7) (12).

To establish pre-treatment status, patients were evaluated during the month prior to treatment initiation, and data on clinical features, AIDAI scores, stool form assessed by the Bristol Stool Scale, average daily stool frequency, and inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were recorded during febrile attacks. After treatment initiation, patients were followed with regular follow-up visits over a 6-month period. During this follow-up, the same parameters were reassessed during febrile attacks, and the mean values obtained across this period were calculated for each patient. These post-treatment averages were then compared with the baseline pre-treatment values to evaluate treatment outcomes.

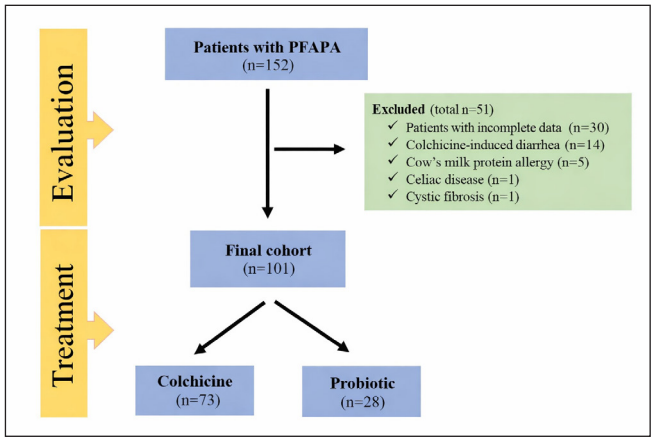

Figure 1: Flowchart illustrating the patient selection process (PFAPA: Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis).

In addition, to investigate the association between disease activity and stool form assessed by the Bristol Stool Scale, correlation analyses were performed using pre-treatment and post-treatment average values.

Statistical analysis

Statistical analyses were performed using SPSS for Windows, version 26.0 (SPSS Inc., Chicago, IL, USA). The distribution of continuous variables was assessed with the Kolmogorov–Smirnov test. Continuous variables were expressed as mean and standard deviation when normally distributed and as median (minimum–maximum) when non-normally distributed, while categorical variables were presented as frequencies and percentages. Comparisons of pre-treatment and post-treatment values within the same group were performed using the paired t-test for normally distributed data or the Wilcoxon signed-rank test for non-normally distributed data. For comparisons between two independent groups, Student's t-test was applied to normally distributed variables, while the Mann-Whitney U test was used for non-normally distributed variables. Correlation analyses were conducted using Spearman's correlation test, given the non-normal distribution of the variables. Categorical stool form, which was categorized into three groups according to the Bristol Stool Scale (hard: types 1–3, normal: type 4, loose: types 5–7), was analyzed using the McNemar–Bowker test to evaluate pre- and post-treatment changes. This test was selected to determine whether stool form categories differed between two time points within the same individuals in the presence of more than two categorical outcomes. A p value of less than 0.050 was considered indicative of statistical significance in all analyses.

Results

The study cohort consisted of 101 patients, of whom 73 (72.3%) were female. The median age at symptom onset was 30 (2–92) months, and the mean age at diagnosis was 52.9±24.4 months. Parental consanguinity was present in 18 (17.8%) patients. A family history of periodic fever syndromes was observed in 61.3% (n=62) of the patients, while a family history of tonsillectomy was reported in 41.4% (n=42). During febrile attacks prior to treatment, the most common clinical manifestation was sore throat in 100 (99%). This was followed by lymphadenitis in 79 (78.2%), fatigue in 60 (59.4%), oral aphthae in 53 (52.5%), abdominal pain in 50 (49.5%), myalgia in 47 (46.5%), arthralgia in 44 (43.6%), nausea/vomiting in 31 (30.7%), headache in 30 (29.7%), diarrhea in 18 (17.8%), constipation in 6 (5.9%), chest pain in 5 (5%), and conjunctivitis in 5 (5%). Colchicine was administered to 73 patients (72.3%), whereas 28 patients (27.7%) received probiotic therapy.

Comparison of pre-treatment and post-treatment findings during attacks

In the total cohort, following treatment, a significant reduction was observed in the median number of stools per day (2 [0.25–10] vs. 1 [0.25–6]; p=0.008). In contrast, stool

Table I: Comparison of laboratory and clinical findings during attacks before and after treatment

	Pre-treatment*	Post-treatment*	p‡
Total Cohort (n=101)			
Duration of attacks†	4 (1-10)	3 (0-10)	<0.001
Interval between attacks†	20 (7-90)	30 (7-180)	<0.001
Number of stool/day	2 (0.25-10)	1 (0.25-6)	0.008
Bristol Stool Scale	4 (1-7)	4 (1-7)	0.943
AIDAI score	24 (0-128)	3 (0-60)	<0.001
CRP (mg/l)	54.9 (7.9-191)	46.9 (2.2-212)	0.050
ESR (mm/h)	32 (12-63)	21 (5-46)	0.080
Colchicine Group (n=73)			
Duration of attacks†	4 (2-10)	3 (1-10)	<0.001
Interval between attacks†	20 (10-90)	30 (7-180)	<0.001
Number of stool/day	2 (0.25-10)	1 (0.25-6)	0.034
Bristol Stool Scale	4 (1-7)	4 (1-7)	0.675
AIDAI score	24 (0-80)	4.5 (0-60)	<0.001
CRP (mg/l)	51.5 (7.9-190)	46 (2.2-208)	0.062
ESR (mm/h)	39 (12-63)	19 (5-46)	0.655
Probiotic Group (n=28)			
Duration of attacks†	4.5 (1-10)	2 (0-4)	<0.001
Interval between attacks†	15 (7-60)	30 (10-90)	0.001
Number of stool/day	1.5 (0.33-5)	1 (0.33-3)	0.078
Bristol Stool Scale	4 (1-7)	4 (2-7)	0.776
AIDAI score	27.5 (6-128)	2 (0-15)	<0.001
CRP (mg/l)	87.7 (8.7-191)	48 (11.5-212)	0.062
ESR (mm/h)	22 (12-47)	22 (21-39)	0.655

: median (min-max), †: days, ‡: Wilcoxon signed-rank test,* ***AIDAI:* *Auto-Inflammatory Diseases Activity Index,* ***CRP:*** *C-Reactive Protein,* ***ESR:*** *Erythrocyte sedimentation rate*

form assessed by the Bristol Stool Scale showed no significant change (4 [1–7] vs. 4 [1–7]; p=0.943). Similarly, in the colchicine group, a significant reduction was observed in the median number of stools per day following treatment (2 [0.25–10] vs. 1 [0.25–6]; p=0.034), while stool form assessed by the Bristol Stool Scale showed no significant change (4 [1–7] vs. 4 [1–7]; p=0.675). In the probiotic group, however, no significant change was observed following treatment in either the median number of stools per day (1.5 [0.33–5] vs. 1 [0.33–3]; p=0.078) or stool form assessed by the Bristol Stool Scale (4 [1–7] vs. 4 [2–7]; p=0.776). Detailed results for the total cohort and subgroups are presented in Table I.

Similarly, no significant difference was observed in stool consistency categories in both the colchicine and the probiotic group (p=0.247 vs. p=0.311). The number of patients with hard stools decreased from 9 (8.9%) in the pre-treatment period to 6 (5.9%) post-treatment, while patients with normal stools decreased from 65 (64.3%) to 63 (62.4%). In contrast, the number of patients classified as having loose stools increased from 27 (26.7%) before treatment to 32 (31.7%) after treatment. Nevertheless, in the probiotic group, the proportion of patients with normal stool form showed an increase from 53.6% (n=15) pre-treatment to 57.1% (n=16) post-treatment. The detailed data are given in Table II. No significant difference was observed between the colchicine and probiotic groups in the difference of daily stool frequency from pre- to post-treatment (Colchicine groups: 0 (–2 to 6); Probiotic groups: 0 (–0.5 to 3); p=0.957).

In the total cohort, no significant association was found between AIDAI scores and Bristol Stool Scale values at pre-

Table II: Stool form categories pre-treatment and post-treatment in the Colchicine and Probiotic groups

	n	Post-treatment†			p‡
		Hard	Normal	Loose	
Colchicine Group*	73	5	47	21	0.247
Hard	6	5 (6.8)	0 (0)	1 (1.3)	
Normal	50	0 (0)	46 (63)	4 (5.4)	
Loose	17	0 (0)	1 (1.3)	16 (21.9)	
Probiotic Group*	28	1	16	11	0.311
Hard	3	1 (3.5)	0 (0)	2 (7.1)	
Normal	15	0 (0)	14 (50)	1 (3.5)	
Loose	10	0 (0)	2 (7.1)	8 (28.5)	

**: Pre-treatment, †: n%), ‡: McNemar–Bowker test*

treatment (r=0.043, p=0.667) or at post-treatment average values (r=–0.044, p=0.665). Similarly, no significant association was observed between AIDAI scores and Bristol Stool Scale values in the colchicine or probiotic groups at pre-treatment (colchicine group r=–0.015, p=0.899; probiotic group: r=0.132, p=0.512) or at post-treatment average values (colchicine group r=–0.004, p=0.974; probiotic group: r=–0.001, p=0.997).

Discussion

In our study, patients were evaluated during attack periods both before and after treatment. Following treatment, a significant decrease was observed in attack frequency and in AIDAI scores reflecting disease activity. With this clinical improvement, there was a significant reduction in daily stool frequency, but no change in stool form as assessed by the Bristol Stool Scale. A statistically significant reduction in stool frequency was observed in the colchicine group. Although not significant, a similar trend was noted in the probiotic group. Moreover, the proportion of patients classified as normal according to the Bristol Stool Scale (type 4) increased after treatment in this group. However, this change also did not reach statistical significance, which may be partly attributable to the smaller sample size in the probiotic group. Overall, these findings suggest that the post-treatment changes in bowel habits in PFAPA are primarily related to stool frequency, and that probiotic treatment may also exert a more favorable effect in achieving normal stool form.

Although aphthous stomatitis is defined to be one of the typical features of PFAPA syndrome, GIS symptoms such as diarrhea, abdominal pain, nausea, and vomiting have been reported during PFAPA attacks (5,13). Oral ulcers and GIS symptoms are well-documented manifestations of diseases such as Crohn's disease (CD) and Behçet's disease (BD), which may overlap and mimic each other (14-17). Moreover, significant genetic similarities indicating common mechanisms between PFAPA syndrome and BD were discovered (18). These similarities and overlapping clinical features raise the question of whether the GIS complaints observed in PFAPA represent merely transient symptoms or reflect an underlying intestinal involvement resembling colitis, an issue that warrants further investigation.

One of the most noteworthy findings of our study is that the post-treatment increase in the proportion of patients with normal stool form represents, to our knowledge, the first report suggesting that probiotic therapy may have a

beneficial effect on bowel habits during PFAPA attacks. This finding is consistent with the literature reporting that probiotics may be beneficial in the regulation of GIS symptoms. Indeed, probiotics have been shown to strengthen the intestinal mucosal barrier, modulate immune responses, and possess significant potential in the prevention and treatment of various diseases (19,20). Therefore, we suggest that probiotics may be considered as an option, particularly for PFAPA patients with gastrointestinal complaints. However, it should be emphasized that the mechanisms of action of colchicine and probiotics differ: colchicine exerts a direct anti-inflammatory effect in autoinflammatory diseases, whereas probiotics primarily act through immunomodulatory pathways linked to the gut microbiota. Although probiotics are not approved for autoinflammatory diseases, clinical studies have demonstrated that they can reduce attack frequency and provide clinical benefit in PFAPA (20-22).

In the colchicine group, there was an observed increase in the proportion of patients experiencing loose stools following treatment. This phenomenon may be attributed to diarrhea being reported as one of the GIS side effects associated with colchicine (22). However, since patients who had diarrhea due to colchicine were excluded from our study, the observed increase is more likely to reflect a softening of stool consistency rather than a true adverse event. This finding suggests that the effect of colchicine on stool form may exist along a spectrum, with only some patients progressing to clinically overt diarrhea.

Overall, our findings indicate that post-treatment changes in bowel habits in PFAPA are primarily related to daily stool frequency. In both treatment groups, a decreasing trend in stool frequency during attacks was observed after treatment, but a statistically significant reduction was noted only in the colchicine group. Nevertheless, no significant difference was found between the colchicine and probiotic groups in terms of the change in daily stool frequency from pre- to post-treatment. This suggests that, independent of stool form categories, both treatments may exert similar effects on bowel habits.

Limitations

Our study has certain limitations. The Bristol Stool Scale may be useful in collecting information on bowel habits; however, it does not provide information on intestinal inflammation. In addition, we did not include fecal biomarkers, which could have provided a more objective assessment of GIS involvement in PFAPA. Moreover, dietary intake during attacks was not assessed in detail, even though certain foods are known to predispose to diarrhea or constipation and thereby influence stool consistency. Nevertheless, to our knowledge, this study is the first to objectively evaluate changes in bowel habits during attacks in children with PFAPA syndrome through pre- and post-treatment comparisons of stool frequency and stool form assessed using the Bristol Stool Scale.

Conclusion

In conclusion, we demonstrated that, in children with PFAPA syndrome, treatment resulted in a significant reduction in attack frequency and disease activity during febrile episodes, along with a decrease in daily stool frequency. While stool form assessed by the Bristol Stool Scale showed no overall significant change, our data revealed an increase in the proportion of patients with normal stool form after treatment, in the probiotic group. These findings suggest that post-treatment changes in bowel habits in PFAPA are primarily related to stool frequency. Future studies incorporating fecal biomarkers may help to better elucidate gastrointestinal involvement in PFAPA syndrome, as well as possible subclinical intestinal inflammation.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by İstanbul Medipol University (18/07/2024, reference number: 725).

Contribution of the authors

Study conception and design: ZA, FH, KO; Data collection: ZA, ESYE, FK, EK, LK, END, HKD, MOB, UFO; Analysis and interpretation of results: ZA, FH, KO; Literature search: ZA, ESYE, FK, EK, LK, END, HKD, MOB, UFO; Draft manuscript preparation: ZA, FH, KO. All authors reviewed the results and approved the final version of the article

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

First aid knowledge among caregivers of children receiving home health care

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ABSTRACT

Objective: Parents of children receiving home health care must possess adequate first aid knowledge to manage emergencies effectively. This study aimed to assess the level of first aid knowledge among caregivers of pediatric patients receiving home health care and to identify factors associated with knowledge gaps.

Materials and Methods: This cross-sectional study was conducted with 66 caregivers of children aged 1 month-18 years registered at the Home Health Services Unit of Prof. Dr. Cemil Tascioglu City Hospital between November 2024 and February 2025. Data were collected through face-to-face interviews using a 20-item first aid knowledge questionnaire developed from a literature review. Demographic and clinical characteristics were recorded.

Results: The average first aid knowledge score was 8.18±4.88 (range: -4 to 18), indicating a 39.0% success rate. Most participants were mothers (86.4%) with elementary or middle school education (65.2%). Significant positive correlations existed between first aid knowledge and both education level (rho=0.290, p=0.019) and age group (p=0.030), with caregivers aged 35-45 showing higher knowledge scores than those aged 18-25 (p=0.015). Critical gaps in knowledge were seen in poison control hotline awareness (4.5%), fall-from-height intervention (16.7%), and unconscious child assessment (27.3%). Despite low knowledge levels, 87.9% of participants were willing to receive first aid training.

Conclusion: Caregivers of children receiving home health care show inadequate first aid knowledge, especially in critical emergencies. Lower education levels and younger age are linked to reduced knowledge. The strong motivation for training among caregivers offers a chance for targeted educational efforts. Urgent, comprehensive, and customized first aid training programs are necessary, particularly for caregivers of medically complex children using specialized medical devices.

Keywords: Caregivers, child,first aid, home health care, pediatrics

Introduction

Home Health Services (HHS) is a community-based care model that provides medical and supportive services to home-bound individuals in order to ensure continuity of care and improve quality of life (1). In our country, legislation related to HHS was first defined on March 10, 2005 (2). In recent years, advances in medicine have reduced mortality rates, increasing the number of children with life-limiting illnesses (3). Pediatric palliative care (PPC) takes a multidisciplinary approach, integrating medical, psychological, and rehabilitative support for children with complex healthcare needs and their families, both in hospital and home settings. HHS follows many PPC patients with complex requirements in concordance with hospital-based care teams. The use of HHS by these children with chronic illnesses requiring care improves the quality of life for both the child and the caregiver, and also contributes to reducing healthcare costs by decreasing the use of intensive care beds, the risk of infection, and complication rates (4,5). In Türkiye, pediatric HHS predominantly serve children with chronic neurological conditions and complex care needs, many of whom are dependent on medical devices such as tracheostomy, mechanical ventilation, or gastrostomy, with mothers being the primary caregivers in the vast majority of cases, as previously reported (6). In children receiving HHS, it is important for caregivers to know how to approach the patient and manage emergencies that may occur outside the hospital in order to reduce mortality in such situations.

Despite the essential importance of emergency awareness in home care contexts, there is a lack of evidence about the first aid knowledge and capability of caregivers who overlook medically demanding children outside hospital settings. This disparity is especially worrying given that these youngsters frequently utilize specialized medical devices (tracheostomies, mechanical ventilators, gastrostomy tubes) and encounter elevated rates of emergencies necessitating prompt attention. This study aimed to evaluate the first aid knowledge of caregivers of children receiving HHS and to identify demographic and clinical characteristics linked to knowledge gaps, to inform targeted educational interventions.

Materials and Methods

This study was designed as a cross-sectional research study. The study was conducted to assess the first aid knowledge level of parents of children aged 0-18 receiving HHS. Caregivers of neonates <1 month and incomplete medical records, temporary caregivers, and individuals who declined participation were excluded. Written informed consent was obtained from all participants.

The study was conducted at Prof. Dr. Cemil Tascioglu City Hospital Hospital, a tertiary care center. The HHS Unit provides comprehensive medical support, including medication administration, wound care, nasogastric tube replacement, blood sampling, physical therapy, respiratory support management (tracheostomy care, mechanical ventilation), and nutritional support (gastrostomy tube management). Data collection took place between November 1, 2024, and February 1, 2025. Researchers collected data via face-to-face interviews during house visits. The researchers completed the questionnaires during the interviews, which averaged 10 to 15 minutes in duration. The study population consisted of parents of 92 children aged 0-18 years who were registered in the HHS unit. The sample size was calculated using the Cochran formula with a 95% confidence interval and a 5% margin of error. When the finite population correction was applied, the minimum required sample size was determined to be 75. The study was conducted with 66 parents, representing 71.7% of the population. Post-hoc power analysis revealed that the current sample size had 62.4% statistical power, which is acceptable for descriptive and correlational analyses.

The functional dependency status of children was classified based on functional mobility and caregiving needs, independent of medical diagnosis, using a functional care-based approach. Children who were bedbound, had no independent mobility, and required complete assistance for all activities of daily living, including those dependent on medical devices such as tracheostomy or mechanical ventilation, were classified as fully dependent. Children who were able to get out of bed and had limited or assisted mobility within the home environment but required caregiver support for certain daily activities or outdoor mobility were classified as partially dependent. Children who were not bedbound and had functional mobility within the home but whose participation outside the home was restricted due to conditions such as autism spectrum disorder, psychiatric disorders, or epidermolysis bullosa were classified as independent. Although these children were not physically dependent on caregivers for daily activities, they were considered home-bound because of clinical or safety-related limitations. This classification was intended to reflect functional caregiving burden rather than disease-specific severity.

Caregivers' first aid knowledge was assessed using a 20-item multiple-choice questionnaire developed based on the literature (7,8). The questionnaire addressed common pediatric emergency situations, including trauma and falls, bleeding control, loss of consciousness, poisoning, electrical injuries, and basic emergency response principles. The content and clinical relevance of the questionnaire were reviewed by two pediatric emergency medicine specialists. Correct answers were scored as +1, "I do not know" responses as 0, and incorrect answers as –1, resulting in a total score ranging from –20 to +20, with higher scores indicating better first aid knowledge.

Statistical analysis

Data analysis was performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics are presented as mean and standart deviation, median (minimum and maximum), and number (percentage). The distribution of continuous variables was assessed using the Shapiro–Wilk normality test. Multivariate linear regression analysis was performed to jointly evaluate the demographic and clinical variables that could affect caregivers' first aid knowledge scores. Categorical variables were compared using the chi-square test. Differences in continuous variables between groups were evaluated using the Mann–Whitney U test or the Kruskal–Wallis test, as appropriate. The relationship between education level and first aid knowledge score was assessed using Spearman's correlation analysis. Multivariate linear regression analysis was performed to evaluate the independent effects of demographic and clinical variables on caregivers' first aid knowledge scores. A p value <0.050 was considered statistically significant.

Results

A total of 66 caregivers participated in the study, with women constituting the vast majority of participants (93.9%). The educational level of participants was predominantly elementary school (27.3%) and middle school (25.8%).

When examining the age distribution of the 66 caregivers who participated in the study, it was found that more than half of the participants were in the 35–45 age range (57.6%), followed by the 26–35 (18.2%) and 45–55 age groups (18.2%), the least represented group was individuals aged 55 and over (1.5%). The socio-demographic characteristics of participants are shown in Table I.

The mean age of the children was 9.33±5.10 years, with a median age of 8 years (min–max; 1–17). Regarding clinical diagnoses, the most common conditions were cerebral palsy (30.3%), epidermolysis bullosa (16.7%), and spinal muscular atrophy type 2 (4.5%). Among the children, 56.1% were classified as fully dependent, 30.3% as independent, and

Table I: Socio-demographic characteristics of the participants

Category	n (%)
Age group	
18–25	3 (4.5)
26–35	12 (18.2)
35–45	38 (57.6)
45–55	12 (18.2)
55 and above	1 (1.5)
Gender	
Female	62 (93.9)
Male	4 (6.1)
Relationship to the child	
Mother	57 (86.4)
Father	4 (6.1)
Other	5 (7.6)
Education level	
Not completed primary school	8 (12.1)
Primary school	18 (27.3)
Secondary school	17 (25.8)
High school	10 (13.6)
Associate degree	1 (1.5)
University	11 (16.7)
Postgraduate	1 (1.5)
Occupation	
Housewife	56 (81.8)
Other	12 (18.2)

13.6% as partially dependent. In terms of medical device usage, 62.1% of children used at least one specialized medical device: 10.6% required mechanical ventilation with tracheostomy and gastrostomy tube, while 37.9% had no device-related special health conditions. The average first aid knowledge score of caregivers was 8.18±4.88, with scores ranging from –4 to 18. The percentage of correct answers to knowledge questions ranged from 28.2% to 92.4%. When examining the distribution of first aid knowledge scores according to age, gender, and occupational groups, no statistically significant difference was found between the groups (p>0.712).

When examining the relationship between the child's bedridden status and caregivers' first aid knowledge levels, no statistically significant difference was found between the groups (p = 0.740). When evaluating the average knowledge scores, it was observed that the scores of caregivers of partially dependent children were slightly higher than those of caregivers of fully dependent and independent children (9.11±4.97 vs. 8.32±4.83 vs. 7.50±4.88, p=0.740). However, this difference did not reach a statistically significant level. When examining the relationship between the child's specific health condition (tracheostomy, PEG tube, etc.) and caregivers' first aid knowledge levels, no statistically significant difference was found between the groups (p = 0.500). Among the least correctly known topics were the National Poison Control Center number to call in case of poisoning (28.2%), the information that the head should not be tilted back in case of a nosebleed (33.3%), and the information that direct contact should not be made with a child who has been electrocuted (36.4%).

In contrast, the statement that participants knew most correctly was "A child who has suffered a head injury should be kept awake," with a correct answer rate of 92.4%. This result indicates that caregivers have relatively higher awareness of trauma and basic first aid topics, but not poisoning and electric shock.

Multivariate linear regression analysis was performed to jointly evaluate the demographic and clinical variables that could affect caregivers' first aid knowledge scores. The variables included in the model were age, gender, education level, occupation, the child's dependency status, and the child's specific health condition. The analysis found that the age variable was a significant predictor (Table II). Specifically, caregivers aged 35–45 had significantly higher knowledge scores than those aged 18–25 (B=6.05; β=0.62; 95% CI: 0.49–11.60; p=0.048). Specifically, caregivers aged 35–45 had significantly higher knowledge scores than those aged 18–25 (p=0.048). Although there was a trend toward higher scores in other age groups, these differences did not reach statistical significance. The relationship between participants' demographic and clinical characteristics and their first aid knowledge score was evaluated using univariate analyses, and the results are presented in Table III. The study revealed a statistically significant relationship between age group (p = 0.030) and education level (p = 0.023) and first aid knowledge score. The post-hoc analysis revealed that participants aged 35-45 exhibited significantly higher first aid knowledge ratings compared to those aged 18-25 (p=0.015) (Table III). Participants in the 35-45 age group had the highest mean knowledge score (9.42±4.02), followed by the 45-55 age group (8.17±4.00).

A positive and significant correlation was found between education level and first aid knowledge score (rho=0.290, p=0.019). A noticeable correlation was discovered between an elevated level of education and an increase in first aid knowledge scores. The score of participants with postgraduate education was 12.00, the average score of high school graduates was 8.78±2.54, that of primary school graduates was 7.72±4.85, and that of individuals who did not complete primary school was 5.25±4.37. Gender (p=0.549), occupation (p=0.712), and the child's dependency status (p=0.740) were found to have no significant effect on the level of first aid knowledge.

When participants' desire to receive first aid training was evaluated, it was determined that the vast majority (87.9%) wanted to receive training. Only 12.1% stated that they did not want to receive first aid training. When comparing participants' desire to receive first aid training with their current knowledge levels, the average knowledge score for those who wanted to receive training was 7.95±5.01, while for those not wishing to receive training, it was 9.88±3.56. The variation between the groups was not found to be statistically significant (p=0.324). Notably, a small group of participants who did not wish to receive training (n = 8) had a higher average knowledge level. The knowledge levels of this group were above the overall average (8.18±4.88), while a few participants (12–14 points) exhibited significantly high knowledge levels.

Discussion

Our findings show that caregivers of children receiving HHS have poor first aid knowledge, which aligns with previous

Table II: Univariate and multivariate linear regression analysis of factors associated with first aid knowledge scores

Predictor	Univariate				Multivariate				
	B	SE	95% CI	p	B	SE	β	95% CI	p
Age group (ref: 18–25)				0.030*					
26–35 years	2.83	2.98	-3.13–8.79	0.346	2.32	2.97	0.18	-3.63–8.27	0.439
35–45 years	6.09	2.77	0.55–11.63	0.032*	6.05	2.77	0.62	0.49–11.60	0.048*
45–55 years	4.83	2.98	-1.13–10.79	0.110	4.99	3.05	0.40	-1.13–11.10	0.108
≥55 years	-3.33	5.33	-14.00–7.33	0.534	-3.27	5.54	-0.08	-14.37–7.84	0.558
Gender (male)	-1.52	2.53	-6.57–3.53	0.549	-1.34	2.74	-0.07	-6.83–4.14	0.625
Education level	0.74	0.36	0.02–1.46	0.023*	0.73	0.44	0.25	-0.14–1.61	0.100
Occupation	0.73	1.68	-2.64–4.09	0.712	-1.19	2.11	-0.09	-5.41–3.04	0.576
Child dependency status	0.36	0.68	-0.99–1.71	0.740	0.47	0.68	0.09	-0.91–1.84	0.500
Child specific health condition	-0.61	1.24	-3.10–1.88	0.500	-1.39	1.36	-0.14	-4.12–1.33	0.310

***B:** Unstandardized regression coefficient, **SE:** Standard error, **β:** Standardized regression coefficient, **CI:** Confidence interval. (Multivariate model summary: $R^2 = 0.241$, Adjusted $R^2 = 0.119$, $F(9, 56) = 1.97$, $p = 0.060$, $N = 66$.)*

Table III: Comparison of mean first aid knowledge scores by sociodemographic characteristics

Variables	n	Values*	p
Age group			
18–25 years	3	4.0 (0–6)	0.030†
26–35 years	12	6.0 (–4–15)	
35–45 years	38	9.0 (0–18)	
45–55 years	12	8.5 (0–15)	
55 years and above	1	0.0 (0–0)	
Gender			
Female	62	8.0 (–4–18)	0.549‡
Male	4	7.5 (0–12)	
Education level			
Not completed primary school	8	6.0 (–1–12)	0.023†
Primary school	18	8.0 (–4–14)	
Secondary school	17	7.0 (0–17)	
High school	10	8.5 (6–15)	
Associate degree	1	11.0 (11–11)	
University	11	10.0 (–3–18)	
Postgraduate	1	12.0 (12–12)	
Occupation			
Housewife	56	8.0 (–4–17)	0.712†
Officer	2	11.0 (10–12)	
Other	8	9.5 (–3–18)	
Child's dependency status			
Fully dependent	37	8.0 (–3–17)	0.740†
Partially dependent	9	10.0 (0–16)	
Independent	20	7.5 (–4–18)	
Willingness to receive first aid training			
Yes	58	8.0 (–4–18)	0.324‡
No	8	10.0 (5–14)	

: median (min-max), †: Kruskal–Wallis test, ‡: Mann–Whitney U test

Turkish studies that report low training rates and widespread knowledge gaps among parents (9,10). The children in our study are at higher medical risk and have complex care needs. Therefore, the consequences of lacking first aid knowledge may be more serious for this group.

This study identified a link between education level and first aid knowledge, aligning with previous research that connects health literacy to emergency preparedness (11). Likewise, Dinçer et al. (9) found that parents with university education were more likely to have received first aid training, which helped them feel more confident during emergencies. Notably, 65.2% of our participants had education levels of middle school or lower. It is well established that lower educational attainment negatively impacts both health literacy and first aid knowledge (11). This underscores the importance of carefully designing educational programs for this group. Educational materials should be visually engaging, written in simple language, and include practical demonstrations.

Caregivers aged 35-45 years showed significantly higher knowledge scores than those aged 18-25 years. Similar age-related trends have been documented in a previous study (12). The greater knowledge level among middle-aged parents can be attributed to their additional life experience and exposure to various health issues during child-rearing. However, the notably lower knowledge level among the younger group is concerning. This underscores the importance of creating targeted first aid training programs for young parents.

Research in the literature explores the relationship between caregiving burden and knowledge level. Studies on caregivers of patients receiving HHS have shown that increasing caregivers' knowledge can reduce their burden and improve patient care quality (13). In this context, providing thorough first aid training to parents of children with all levels of dependency could both enhance the quality of care and boost parents' self-confidence and psychological well-being.

Our study found that the questions with the highest success rates were "Children who have suffered head trauma should be kept awake" (92.4%), "The emergency number in Türkiye is 112" (90.9%), and "Apply direct pressure to the wound site in case of bleeding" (89.4%). The high success rate on these topics can be explained by the fact that this information is generally widespread in society and frequently emphasized through the media.

The fact that 90.9% of respondents correctly knew the emergency number (112) demonstrates the success of awareness campaigns in Türkiye. However, the 9.1% of the group who did not know this vital information remains concerning. The high rate of correct knowledge about bleeding injury intervention (89.4%) is encouraging, as bleeding control is a critical first aid skill of vital importance.

It is very concerning that the questions with the lowest success rates were the poison control hotline number (4.5%), intervention for falls from heights (16.7%), assessment sequence for an unconscious child (27.3%), and intervention for animal bites/insect stings (30.3%).

Only 4.5% of participants knew the correct number for the poison control hotline (114), while 63.6% responded "I don't know," indicating a severe lack of awareness on this issue. Childhood poisonings represent a significant portion of emergency department visits (14). Knowing the poison control hotline number can be life-saving, especially for children who are at high risk of coming into contact with medications, cleaning products, and other chemicals at home. This finding underscores the urgent need for comprehensive awareness campaigns promoting the poison control hotline.

Only 27.3% correctly answered the question about the order of assessment in an unconscious child, highlighting a significant knowledge gap. While first aid education is important for the general population, the importance of proper ABC (airway, breathing, circulation) assessment and management is particularly evident in the patient profile followed in home healthcare. Changes in consciousness are especially common in children with epilepsy, cerebral palsy, or metabolic disorders, making accurate ABC assessment crucial (15). A lack of knowledge in this area may lead to incorrect or delayed emergency interventions.

Only 16.7% of respondents answered the question about intervention in falls from height correctly, which is a serious concern. InHHS patients, first aid knowledge is particularly important given the risk of falls and related complications associated with inadequate or insufficient use of protective bed or edge barriers. In cases of falls from height, due to the risk of cervical spine injury, it is crucial not to move the child and to stabilize the head and neck while waiting for professional help (16). Lack of knowledge in this area may result in permanent neurological damage due to inappropriate interventions.

In our study, 62.1% of participants' children used at least one medical device, such as a tracheostomy, mechanical ventilator, or gastrostomy tube. Our findings highlight insufficient basic first-aid knowledge among caregivers managing these devices, underscoring an urgent need for training. Although discharge education on device use is routinely provided in many centers, the need for repetition, reinforcement, and hands-on practice remains evident. Moreover, this training is generally limited to device-specific management and does not include first aid education. Life-threatening complications such as tracheostomy tube obstruction or decannulation, gastrostomy tube dislodgement or blockage, and ventilator failure require rapid and appropriate intervention (17). Therefore, caregivers of children using medical devices should be trained not only in device-related care but also in basic first aid and emergency response.

The literature highlights that proper caregiver training is essential for ensuring patient safety and quality of care in the home care of children with complex medical needs (18). However, our findings indicate that caregivers of children who use medical devices still have insufficient first-aid knowledge. Training provided to families generally focuses on device management and does not include first-aid education; therefore, incorporating structured first-aid training into existing caregiver education programs would provide meaningful additional benefit.

Our study found that the most common diagnoses were cerebral palsy. These conditions present distinct emergency risks, seizures and aspiration in cerebral palsy, skin breakdown and infection in epidermolysis bullosa, and respiratory failure in SMA (19-21). Similar to our findings, a recent Turkish study on pediatric palliative care patients reported that neurological disorders, particularly cerebral palsy, constitute the majority of children requiring home-based complex care, emphasizing the need for comprehensive caregiver education in managing disease-specific emergencies (22). Each of these disorders needs specific first aid knowledge. These different situations suggest that first aid training needs to include both basic first aid and diagnosis-specific emergency protocols.

One of the most positive findings of our study is that the vast majority of participants (87.9%) expressed a desire to receive first aid training. This increased determination is an important factor that increases the chance of success in training programs.

The literature shows that first aid training programs provided to families of children with special needs increase parents' knowledge levels, strengthen their self-confidence, and reduce their anxiety levels (23).

In a study, though primarily focused on adult patients, evaluating the effectiveness of basic life support training provided to home caregivers, a significant increase in knowledge levels was found after training, and it was determined that organizing these trainings in a practical, hands-on manner increased their effectiveness (24). These findings indicate that parents' high motivation should be assessed through well-planned training programs.

Limitations

The relatively small sample size limited the statistical power for subgroup analyses. In addition, as the study was conducted in a single HHS unit, the findings may not be generalizable to all regions of Türkiye. This study assessed only caregivers' theoretical first-aid knowledge; practical application skills were not evaluated, and a discrepancy between knowledge and practice may exist. Furthermore, emergency management skills specific to medical devices such as tracheostomy, mechanical ventilation, and gastrostomy tube were not assessed. Finally, the predominance of female participants limited the evaluation of fathers as caregivers.

Conclusion

This study revealed that the first aid knowledge level of parents of pediatric patients receiving HHS is inadequate. There are serious knowledge gaps, particularly in critical areas such as the poison control hotline, assessment of unconscious patients, and intervention for falls from heights. There is a positive correlation between educational level and first aid knowledge, with parents with low educational levels constituting a particularly at-risk group.

Our study aims to emphasize the importance of comprehensive emergency training programs for patients monitored by HHS, the desire of the vast majority of participants (87.9%) to receive training, and the provision of first aid training to these patients, anticipating the potential success of interventions in this area. Additionally, studies on home care populations, though primarily focused on adult patients, highlight an urgent need for pediatric-specific research on the effectiveness of first-aid training programs for caregivers of children with complex healthcare needs.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Prof. Dr. Cemil Taşcıoğlu City Hospital (21.10.2024 reference number: 242).

Contribution of the authors

Study conception and design: AB, BA; data collection: AB; analysis and interpretation of results: AB, BA, SA; draft manuscript preparation: AB, BA. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Pediatric unintentional injuries in emergency care: A three-year retrospective study from a tertiary care center

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ABSTRACT

Objective: Pediatric unintentional injuries are a major public health concern, as most are preventable. This study aimed to assess emergency department cases by etiology, demographics, seasonal distribution, and outcomes, to define the regional profile and guide prevention.

Material and Methods: This retrospective study included 2524 children aged 0–18 years admitted with unintentional injuries between January 2021 and June 2024. Cases were classified as trauma, poisoning/aspiration, environmental injuries, or other causes.

Results: Of the cases, 1454 (57.6%) were male, median age 47 months. Poisoning/aspiration was most common (n=1153; 45.6%), followed by trauma (n=840; 33.2%), environmental injuries (n=473; 18.7%), and others (n=62; 2.4%). Poisonings predominated in 0–5 years, while trauma was more frequent in adolescents. Leading poisoning causes were drugs (n=516; 20.4%) and corrosives (n=441; 17.5%). Carbon monoxide poisoning was notable among environmental injuries (n=267; 10.6%). Most patients were discharged (80.6%), while 14.5% were hospitalized, 3.7% required intensive care, and 5.5% underwent surgery. Mortality and sequelae were each 0.3%. Seasonal variation was evident: poisonings in spring–summer, trauma in summer–autumn, and carbon monoxide in winter.

Conclusion: Poisonings were the leading cause in early childhood, while trauma predominated in adolescents. Preventive strategies, including parental education, household safety, and region-specific policies, are essential to reduce morbidity and mortality.

Keywords: Accident, adolescent, child, poisoning, wounds and injuries

Introduction

Unintentional injuries are defined as physical harm occurring without intent, most commonly resulting from road traffic accidents, falls, burns, drownings, and poisonings (1). They are a major cause of morbidity and mortality in childhood and account for nearly 5 million deaths worldwide each year, most of which occur in low- and middle-income countries (2-4). Such injuries also constitute about 10% of pediatric outpatient visits, placing a considerable burden on healthcare systems (5,6).

According to the Turkish Statistical Institute, children aged 1–17 comprise 25.5% of Türkiye population, a proportion notably higher than in European countries (14.6%) (7).

In Van city province, this rate reaches 65.7%, ranking fourth nationally, and accidents and poisonings represent the leading causes of mortality in this age group (8). Globally, approximately 15.3% of children and adolescents experience at least one injury annually, with adolescents sustaining more severe injuries due to risk-taking behaviours and access to firearms, alcohol, and drugs, while younger children are particularly vulnerable because of curiosity and incomplete physical development (4,9,10).

Socioeconomic status and parental education have consistently been shown to inversely affect the incidence of childhood injuries (4,11-13). Van city, located in eastern Türkiye, ranks lowest in the national socioeconomic development index (14).

The aim of this study was to describe the age, gender, seasonal, and temporal characteristics of childhood unintentional injuries in Van city, thereby contributing to the limited literature and supporting the development of preventive policies and child health protection strategies.

Materials and Methods

This study included 2524 children and adolescents (0–18 years) with unintentional injuries admitted to the Pediatric Emergency Department of Van Training and Research Hospital between January 2021 and June 2024. As the largest tertiary care center in eastern Türkiye, the hospital serves approximately six neighboring provinces.

The study was retrospectively designed using Electronic Medical Records (EMR). Since data were anonymized, individual consent was not required. However, families had been informed at admission that their records might be used for research, and written consent was obtained.

Patients admitted by self-presentation, ambulance, or referral from other healthcare centers were included. Initial screening was performed via ICD-10 codes, but due to inconsistencies, cases registered as "forensic" in the pediatric emergency EMR were used. Intentional injuries (suicide attempts, abuse, assaults) were excluded. Accidental genital trauma was classified as unintentional and included. Total of 4.500 forensic cases were referred to the Pediatric Emergency Department. Of these, 1976 were intentional and excluded; 2524 unintentional cases were analyzed.

Recorded variables were age, gender, admission date, season, weekday/weekend, public/religious holidays, and school status at the time of admission. Patients discharged with residual dysfunction were defined as having physical impairment. Mortality referred to in-hospital deaths during the index admission only (15,16).

Cases were categorized into four groups according to the nature of the incident:

Group 1 : Trauma-related injuries [e.g., traffic accidents, falls, head injuries, major long bone or pelvic fractures, thoracic trauma, hand or foot trauma, abdominal injuries from sharp objects, firearm injuries, ocular foreign bodies, earthquake-related injuries].

Group 2 : Poisonings and aspiration [drug ingestion, non-drug ingestions (e.g., mushrooms or toxic plants) and corrosive substance ingestions (e.g., chemical agents such as detergents), foreign body ingestion or aspiration].

Group 3 : Environmental injuries [burns, electric shock, frostbite, carbon monoxide poisoning].

Group 4 : Other injuries and conditions [snake/insect bites, drowning, asphyxia, animal attacks].

Final clinical outcomes were categorized as emergency department discharge, hospitalization, intensive care unit admission, death, or referral to a higher-level center, while surgical interventions were documented separately. All cases were stratified into three age groups: 0–5, 6–12, and 13–18 years. Poisoning cases were specifically classified according to the American Association of Poison Control Centers system, and a comparable classification approach was applied to the other injury groups for consistency (14).

Statistical analysis

Analyses were performed with IBM SPSS Statistics v26 (IBM Corp., Armonk, NY, USA), and figures generated using GraphPad Prism v9 (GraphPad Software, San Diego, CA, USA). Categorical variables were summarized as frequencies and percentages, and continuous variables as medians with interquartile ranges. Group comparisons used the Kruskal-Wallis test for continuous data and Pearson's chi-square or Fisher's exact test for categorical data (when expected counts <5). Subgroup analyses were conducted by etiology and age, with Bonferroni-adjusted post-hoc tests applied where global significance was found. Etiology Group 4 was excluded from comparisons due to small numbers and overlapping categories. A two-sided $p<0.050$ was considered significant.

Results

Males accounted for 1454 (57.6%) cases, with a median age of 47 months (IQR; 25–107). Group 2 was the most common etiology (n= 1153; 45.6%), followed by Group 1 (n = 840; 33.2%), Group 3 (n = 473; 18.7%), and Group 4 (n = 62; 2.4%).

Most presentations occurred on weekdays (n = 1873; 74.2%), while 651 (25.8%) were on weekends; 85 (3.4%) were during religious and 31 (1.2%) during official holidays. Injury type differed by day of the week (χ^2 = 22.261; p = 0.043). No significant association was found with school periods (χ^2 = 2.119; p = 0.333). Seasonal variation was evident (χ^2 = 132.439; p <0.001): Group 1 peaked in fall and summer, Group 2 in spring and summer, and Group 3 in winter but declined in summer (Table I). Group 2 was significantly more frequent on weekends (χ^2 = 21.568; p=0.043).Regarding outcomes, 2034 (80.6%) patients were discharged, 366 (14.5%) hospitalized, and 94 (3.7%) admitted to PICU. Surgical intervention was required in 139 (5.5%). Seven (0.3%) were discharged with sequelae, and 7 (0.3%) died.

Trauma-related injuries were frequent: head trauma (n= 164; 6.5%) and traffic accidents (n= 142; 5.6%) predominated, followed by bone fractures (n= 94; 3.7%) and genital trauma (n= 88; 3.5%). Other injuries included hand trauma (2.3%), sharp object injuries (1.5%), ocular foreign bodies (1.1%), foot trauma (1.0%), firearm injuries (0.8%), pelvic fractures (0.6%), and thoracic trauma (0.4%). Rare events were earthquake-related (0.2%) and occupational injuries (0.2%) (Table II).

Ingestion and intoxication were also common. Drug intoxication was the leading cause (n= 516; 20.4%), followed by corrosive ingestion (n= 441; 17.5%). Non-drug intoxications occurred in 115 cases (4.6%). Foreign body ingestion was less frequent: non-battery objects (2.6%), batteries (0.5%), and aspiration (0.1%) (Table II). Among environmental exposures, CO poisoning (n= 267; 10.6%) was most common, followed by burns (4.8%), electrocution (3.2%), and frostbite (0.3%). Other external causes were animal attacks (1.3%), drowning (0.6%), snake/insect bites (0.3%), and asphyxia (0.2%) (Table II). Gender was

Table I: Demographic and clinical characteristics of pediatric forensic cases

Variable	Values*
Gender	
Female	1070 (42.4)
Male	1454 (57.6)
Day of the week	
Monday	367 (14.5)
Tuesday	379 (15)
Wednesday	390 (15.5)
Thursday	386 (15.3)
Friday	351 (13.9)
Saturday	298 (11.8)
Sunday	353 (14)
Season	
Fall	545 (21.6)
Spring	701 (27.8)
Summer	724 (28.7)
Winter	554 (21.9)
Holiday name	
Week-day	1794 (71.1)
Weekend	614 (24.3)
New Year's Day	5 (0.2)
National Sovereignty and Children's Day	5 (0.2)
Labor and Solidarity Day	11 (0.4)
Commemoration of Atatürk, Youth and Sports Day	3 (0.1)
Democracy and National Unity Day	2 (0.1)
Victory Day	2 (0.1)
Republic Day	3 (0.1)
Ramadan Feast (Eid al-Fitr)	26 (1)
Sacrifice Feast (Eid al-Adha)	59 (2.3)
Holiday category	
Religious	85 (3.4)
Official/Administrative	31 (1.2)
School holiday status	
Closed	730 (28.9)
Open	1794 (71.1)
Final outcome	
Discharge to outpatient clinics	2034 (80.6)
Hospitalization (Ward)	366 (14.5)
Intensive care unit admission	94 (3.7)
Underwent surgery	139 (5.5)
Physical impairment	7 (0.3)
Mortality	7 (0.3)

**: n(%)*

significantly associated with injury distribution (χ^2=10.250; p=0.006); males predominated in Group 1, while females were more frequent in Group 3. Age group was also strongly associated with etiology (χ^2 = 573.920; p< 0.001). Group 2 was most common in 0–5 years, Group 1 in 6–12 years, and Groups 1 and 3 in adolescents (Table III).

By age, 1486 (58.9%) cases were 0–5 years, 618 (24.5%) were 6–12 years, and 420 (16.6%) were 13–18 years. The clinical outcomes exhibited variability according to age, as evidenced by the statistical analysis (Table IV). The discharge of patients as outpatients (χ^2 = 6.794; p = 0.033), admission to the Pediatric Intensive Care Unit (PICU) (χ^2 = 7.455; p = 0.024), the necessity for surgical intervention (χ^2 = 45.502; p < 0.001), and the season of presentation (χ^2 = 35.485; p < 0.001) were found to be statistically significant. Post-hoc tests indicated that outpatient treatment and PICU admissions were more prevalent in children aged 0–5 years, whereas surgical interventions were more common in older children (see Table IV and Figures 1). The seasonal peaks differed according to age group, with peaks of 0–5 years in spring/summer and 13–18 years in fall/winter. The detailed associations are illustrated in Table IV.

Table II: Etiological distribution of pediatric forensic cases

Variable	n (%)
Group 1	840 (33.2)
Traffic accident	142 (16.9)* (5.6)†
Head trauma	164 (19.5)* (6.5)†
Major bone fracture	94 (11.2)* (3.7)†
Pelvic ring injury	14 (1.7)* (0.6)†
Thoracic trauma	9 (1.1)* (0.4)†
Hand trauma	58 (6.9)* (2.3)†
Injury by sharp or piercing object	38 (4.5)* (1.5)†
Foot trauma or laceration	26 (3.1)* (1)†
Foreign body in the eye	29 (3.5)* (1.1)†
Firearm injury	20 (2.4)* (0.8)†
Genital trauma	88 (10.5)* (3.5)†
Other trauma	252 (30)* (10)†
Occupational injury	4 (0.5)* (0.2)†
Earthquake-related injury	5 (0.6)* (0.2)†
Group 2	1153 (45.6)
Drug intoxication	516 (44.8)* (20.4)†
Non-drug intoxication	115 (10.0)* (4.6)†
Corrosive substance ingestion	441 (38.2)* (17.5)†
Foreign body aspiration	3 (0.3)* (0.1)†
Foreign body (non-battery) ingestion	65 (5.7)* (2.6)†
Foreign body (battery) ingestion	13 (1.1)* (0.5)†
Group 3	473 (18.7)
Electrocution	80 (16.9)* (3.2)†
Frostbite	7 (1.5)* (0.3)†
Burn injury	120 (25.4)* (4.8)†
CO Poisoning	267 (56.4)* (10.6)†
Group 4	62 (2.4)
Drowning	16 (25.8)* (0.6)†
Asphyxia	4 (6.5)* (0.2)†
Animal attack	33 (53.2)* (1.3)†
Snake/insect bite or sting	9 (14.5)* (0.3)†

**: within the subgroup, †: within the whole study group*

Discussion

Injuries continue to be a leading cause of morbidity and mortality in childhood in both developed and developing countries. Although recent trends show a decline in overall rates, injury types vary significantly by age, gender, and region, and further progress is needed to protect children's health (17,18). Although preventive measures have historically reduced pediatric poisonings, recent evidence indicates a resurgence in certain types, and injuries and poisonings are once again among the leading factors threatening child health. This situation highlights the need for sustainable preventive strategies and a closer assessment of emerging risk factors, particularly in older children (19,20). This study examined the types and demographic characteristics of pediatric accidental injuries, their distribution by age group and season, and found that poisoning ranked first among unintentional injuries in childhood, followed by trauma.

Table III: Comparison of demographic and clinical variables across unintentional injury groups

Variable	Group 1	Group 2	Group 3	Test Statistic	p
Number of patients	840	1153	473	-	-
Age (months)*	90 (46-148)	31 (20-47)	73 (30-145)	511.052†	<0.001
Age group‡					
0-5 Years	279 (19)	970 (66.2)	216 (14.7)	573.920§	<0.001
6-12 Years	341 (57.4)	115 (19.4)	138 (23.2)		
13-18 Years	220 (54.1)	68 (16.7)	119 (29.2)		
Gender‡					
Female	326 (30.9)	504 (47.8)	225 (21.3)	10.250§	0.006
Male	514 (36.4)	649 (46)	248 (17.6)		
Day of the week‡					
Monday	119 (32.9)	177 (48.9)	66 (18.2)	21.568§	0.043
Tuesday	140 (37.4)	158 (42.2)	76 (20.3)		
Wednesday	120 (31.3)	202 (52.6)	62 (16.1)		
Thursday	134 (36)	159 (42.7)	79 (21.2)		
Friday	120 (35.4)	164 (48.4)	55 (16.2)		
Saturday	93 (32.2)	123 (42.6)	73 (25.3)		
Sunday	114 (32.9)	170 (49.1)	62 (17.9)		
Season‡					
Fall	226 (42.7)	215 (40.6)	88 (16.6)	139.785§	<0.001
Spring	200 (29.3)	343 (50.2)	140 (20.5)		
Summer	285 (40.1)	358 (50.4)	67 (9.4)		
Winter	129 (23.7)	237 (43.6)	178 (32.7)		
Holiday category‡					
Religious	33 (39.2)	42 (50)	9 (10.7)	9.438§	0.307
Week-day	602 (34.4)	824 (47)	326 (18.6)		
Official/ administrative	12 (38.7)	14 (45.2)	5 (16.1)		
Weekend	193 (32.2)	273 (45.6)	133 (22.2)		
School holiday status‡					
Closed	238 (33.3)	329 (46.1)	147 (20.6)	1.294§	0.524
Open	602 (34.4)	824 (47)	326 (18.6)		
Final outcome‡					
Discharge to outpatient clinics	558 (28)	1089 (54.6)	346 (17.4)	268.342§	<0.001
Hospitalization (Ward)	206 (57.2)	46 (12.8)	108 (30)	196.185§	<0.001
Intensive care unit admission	73 (85.9)	6 (7.1)	6 (7.1)	105.813§	<0.001
Underwent surgery	114 (83.8)	16 (11.8)	6 (4.4)	158.691§	<0.001
Physical impairment	6 (100)	0	0	-	-
Mortality	2 (66.7)	0	1 (33.3)	-	-

**: median (Q1-Q3), † : Kruskal–Wallis test ‡: n (%), § : Pearson Chi-square Test (Post-hoc Bonferroni correction)*

In our cohort, poisonings were particularly concentrated in the 0-5 age group. Young children are particularly vulnerable to accidental poisoning due to their curiosity and exploratory behavior (21). According to the World Health Organisation, approximately 45000 children and adolescents die each year from acute poisoning, with mortality rates four times higher in low-income countries (22,23). Similar to our findings, a study conducted in Vietnam reported that 65.6% of acute poisoning cases occurred in the 1-5 age group, while a study conducted in Nigeria found that 78.4% of poisoning cases occurred in children aged 5 years and under, particularly in boys from low socioeconomic backgrounds (24,25). In our study, medication ingestion was the most common cause of poisoning, followed by corrosive substance ingestion. Enboklang et al. (21) also emphasised that prescription and non-prescription medications are the most common causes of acute poisoning in children under 12 years of age. Contrary to previous reports showing higher rates of accidental poisoning in boys and higher rates of intentional poisoning in adolescent girls, we observed a higher prevalence of poisoning in girls aged 0-5 years (26). This may reflect region-specific sociocultural and household exposure factors. Previous studies have shown that boys generally spend more time outdoors than girls. Young girls may remain at home for longer periods, which may increase their risk of exposure to medicines and corrosive substances in the home (27,28).

Ingestion of corrosive substances also constituted a significant proportion of the cases in our study. In the United States, more than 100000 cases of corrosive substance poisoning are reported in children each year (29). Although parental education was not evaluated in our study, the fact that Van city province has the lowest socioeconomic status among Türkiye six most socioeconomically developed regions may be related to inadequate parental supervision and unsafe home environments, particularly among young children (30).

Trauma was the second most common cause and was the main cause of accidental injuries in adolescents. Previous studies have shown that trauma is more common in males, that traffic accidents are the main cause, and that a significant

Table IV: Comparison of variables across age groups in pediatric forensic cases

Variable	0-5 Years*	6-12 Years*	13-18 Years*	Test Statistic†	p
Number of patients	1486 (58.9)	618 (24.5)	420 (16.6)	-	-
Gender					
Female	651 (60.8)	258(24.1)	161 (15)	4.160	0.125
Male	835 (57.4)	360 (24.8)	259 (17.8)		
Day of the week					
Monday	228 (62.1)	87 (23.7)	52 (14.2)	8.160	0.772
Tuesday	216 (57)	97 (25.6)	66 (17.4)		
Wednesday	239 (61.3)	84 (21.5)	67 (17.2)		
Thursday	220 (57)	92 (23.8)	74 (19.2)		
Friday	209 (59.5)	89 (25.4)	53 (15.1)		
Saturday	168 (56.4)	81 (27.2)	49 (16.4)		
Sunday	206 (58.4)	88 (24.9)	59 (16.7)		
Season					
Fall	297 (54.5)	138 (25.3)	110 (20.2)	35.485	<0.001
Spring	446 (63.6)	153 (21.8)	102 (14.6)		
Summer	446 (61.6)	191 (26.4)	87 (12)		
Winter	297 (53.6)	136 (24.5)	121 (21.8)		
Holiday category					
Religious	53 (62.3)	21 (24.7)	11 (12.9)	9.674	0.289
Week-day	1061(59.1)	426 (23.7)	307 (17.1)		
Official/ administrative	21 (67.7)	9 (29)	1 (3.2)		
Weekend	351 (57.2)	162 (26.4)	101(16.4)		
School holiday status					
Closed	425 (58.2)	192 (26.3)	113 (15.5)	2.291	0.318
Open	1061 (59.1)	426 (23.7)	307 (17.1)		
Final outcome					
Discharge to outpatient clinics	1219 (59.9)	494 (24.3)	321 (15.8)	6.794	0.033
Hospitalization (Ward)	201 (54.9)	93 (25.4)	72 (19.7)	3.653	0.161
Intensive care unit admission	44 (46.8)	26 (27.7)	24 (25.5)	7.455	0.024
Underwent surgery	47 (33.8)	45 (32.4)	47 (33.8)	45.502	<0.001
Physical impairment	4 (57.1)	1 (14.3)	2 (28.6)	-	-
Mortality	5 (71.4)	1 (14.3)	1 (14.3)	-	-

: n (%) , †: Pearson Chi-square Test (Post-hoc Bonferroni correction

proportion of cases require major surgical intervention (31). Large cohort studies have also reported that head trauma is the most severe type of trauma and that mortality is higher in children under five years of age (32). Similarly, our findings show that trauma is more common in adolescent males and that hospitalisation and surgical intervention rates are higher than for other types of accidental injury, highlighting the significant burden of trauma on healthcare services. These cases typically require multidisciplinary treatment, including surgery and intensive care, highlighting the need for well-trained healthcare providers, adequate infrastructure, and preventive measures (33-35).

On February 6, 2023, two powerful earthquakes of magnitude 7.7 and 7.6 struck southeastern Türkiye, causing massive destruction and affecting millions in Türkiye and Syria (36). In our cohort, five patients (0.6%) presented with earthquake-related injuries, underscoring the impact of large-scale disasters on the pediatric injury burden.

Seasonal variations were also evident. Trauma was more common in summer and during weekdays, consistent with reports linking increased cases to school and outdoor activities (36). Children spend much of their time at school during weekdays and engage in various activities that carry a risk of injury, which may contribute to the higher number of weekday injury cases (37). In our cohort, the higher incidence of environmental events during winter months may be attributed to carbon monoxide poisoning due to the use of stoves and solid fuels in the region (38). Carbon monoxide poisoning accounted for more than 10% of all cases. This indicates that the use of stoves and solid fuels in the region is a significant public health issue. Therefore, preventive policies at the public health level are necessary, in addition to clinical approaches. Strengthening stove and chimney safety standards, educating the community on ventilation, promoting the widespread use of affordable carbon monoxide detectors, and providing government support for safe heating systems for disadvantaged families can reduce these preventable deaths and morbidity in childhood (39,40). These findings indicate that preventive strategies should take seasonal and regional risk factors into account.

Even minor injuries can negatively affect children's health and reveal underlying environmental risks. Many of these risks can be reduced through anticipatory guidance and

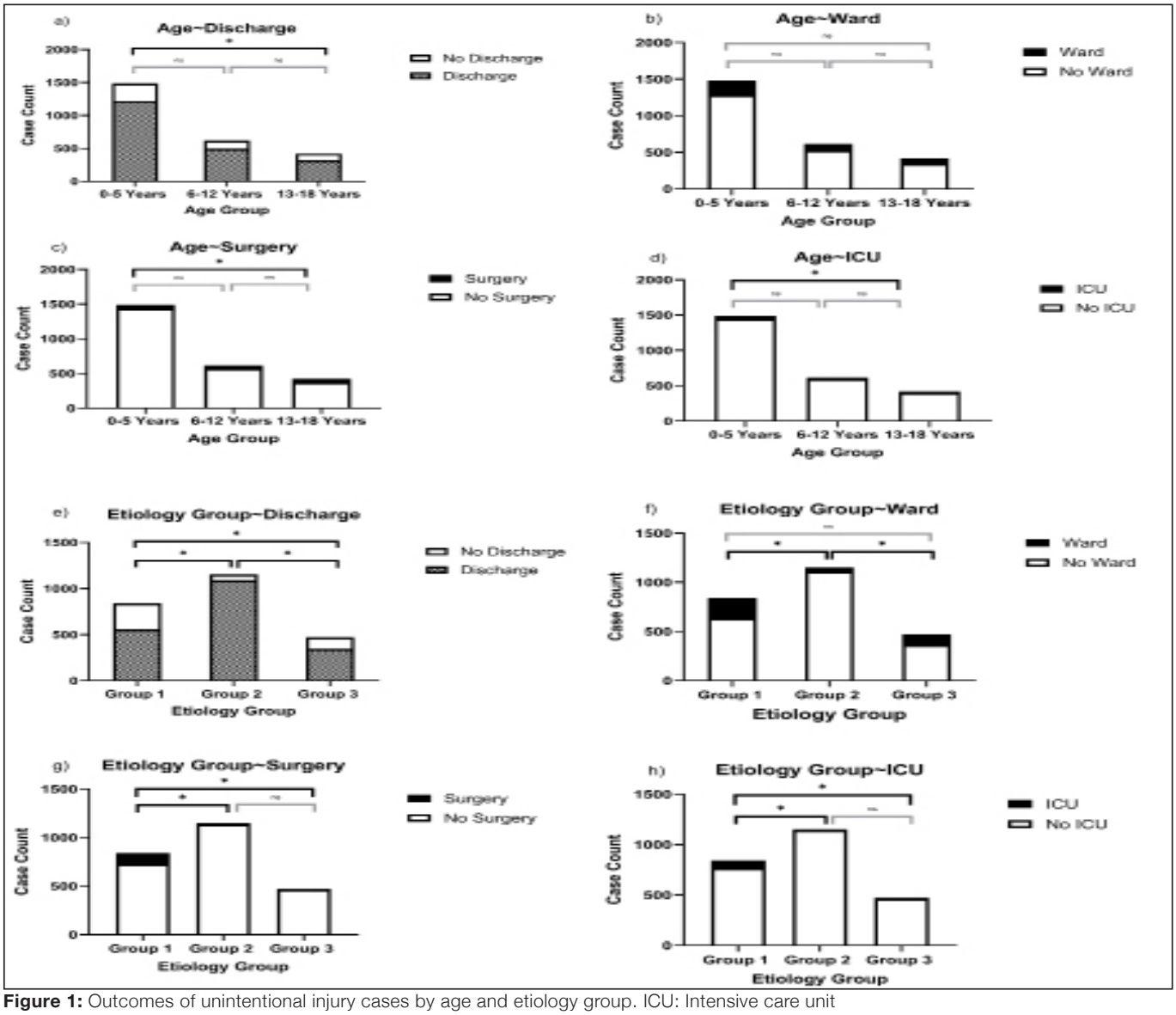

Figure 1: Outcomes of unintentional injury cases by age and etiology group. ICU: Intensive care unit

parental education provided by pediatricians in primary care. The American Academy of Pediatrics emphasizes safety promotion and injury prevention as key elements of child health supervision and recommends that counseling on unintentional injury prevention be offered at every health visit. In addition, family education programs, stronger household safety measures, and community-based awareness initiatives play a crucial role in reducing childhood poisonings and injuries (6).

Although most patients in our cohort were discharged from the emergency department without major health consequences, this does not indicate that pediatric forensic cases are clinically insignificant. Similar discharge rates have been reported in international studies (35). In a study from the United States, approximately 86% of pediatric poisoning cases were discharged from the emergency department (20). However, even cases with favorable clinical outcomes require substantial resource utilization, including prolonged observation, repeated laboratory testing, imaging, and antidote therapy. Therefore, despite low mortality and high discharge rates, pediatric unintentional injuries remain an important public health concern (25).

Limitations

Its retrospective design, based on forensic case records, may have led to underreporting of minor injuries. Analyses were restricted to demographic, seasonal, and temporal variables, without incorporating detailed clinical or sociodemographic factors such as parental education, income, residence, mechanism of injury, or treatments received. The low in-hospital mortality observed in our cohort likely underestimates the true burden, as fatalities before hospital arrival, severe cases directly admitted to intensive care, and long-term sequelae such as developmental or functional impairments were not systematically captured (3). Furthermore, post-discharge outcomes were unavailable, and the single-center design limits generalizability; however,

the hospital's role as a regional referral center enhances the representativeness of the findings. Despite these constraints, this study provides one of the largest datasets from a socioeconomically disadvantaged region of Türkiye, offering valuable evidence for pediatric emergency care and preventive policy development.

Conclusion

In this study evaluating 2524 pediatric forensic cases, poisonings were identified as the most common cause, predominantly affecting the 0–5 years age group. Trauma was more frequent among adolescents and was associated with higher rates of hospitalization and surgical intervention compared with other groups. In addition, the notable frequency of carbon monoxide poisoning in Van city highlights the significance of regional environmental risks.

These findings indicate that most pediatric forensic cases are largely preventable. Increasing parental awareness, strengthening household safety measures, and developing protective strategies tailored to regional risks are essential steps for ensuring the safety and well-being of children and adolescents.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Van Training and Research Hospital (01.11.2023, reference number: 2023/23-04).

Contribution of the authors

Study conception and design: ÖT, OS, ŞET; data collection: MÇK; analysis and interpretation of results: ÖT, OS, ŞET, MÇK; draft manuscript preparation: ÖT, ŞET. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Prevalence and clinical predictors of sleep disturbances in children with seasonal allergic rhinitis

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ABSTRACT

Objective: Seasonal allergic rhinitis (SAR) is one of the most common allergic diseases in childhood and is characterized by nasal congestion, rhinorrhea, sneezing, and itching. Beyond these classical nasal symptoms, SAR may also be associated with sleep disturbances. The present study aimed to determine the prevalence of sleep disturbances in children with SAR and to evaluate potential clinical predictors, including symptom severity, symptom timing, and comorbid allergic diseases.

Material and Methods: Children aged 6–16 years with seasonal allergic rhinitis (SAR) who were followed at the Pediatric Allergy and Immunology Department of Ankara City Hospital were enrolled in the study. An age- and demographically matched control group was also recruited. Sleep disturbances were assessed using the Sleep Disturbance Scale for Children (SDSC). SAR severity was classified according to the Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines, and symptom intensity was further evaluated using a visual analog scale (VAS). Logistic regression analysis was performed to identify independent predictors of SDSC-defined sleep disturbances.

Results: A total of 115 children with SAR (mean age: 11.6±3.2 years; 61.7% male) and 115 healthy controls were included. According to SDSC, 43.3% of children with SAR had clinically significant sleep disturbances. Compared with controls, children with SAR had significantly higher SDSC total scores (63.4±15.5 vs. 53.9±12.2; $p < 0.001$) and higher scores across all subscales. In multivariate logistic regression, an elevated nasal VAS score remained an independent predictor of sleep disturbances (OR: 1.86; 95% CI: 1.06-2.41; p=0.020).

Conclusion: Sleep disturbances were more prevalent in children with SAR than in healthy controls, and greater nasal symptom severity was independently associated with impaired sleep quality. Incorporating routine sleep quality assessment into the clinical evaluation of children with SAR may improve disease management and contribute to better overall quality of life.

Keywords: Seasonal allergic rhinitis, sleep disturbances, visual analogue scale

Introduction

Allergic rhinitis (AR) is an IgE-mediated inflammatory condition characterized by one or more symptoms, including nasal congestion, rhinorrhea (anterior or posterior), sneezing, and nasal itching (1,2). When accompanied by ocular symptoms, the condition is referred to as allergic rhinoconjunctivitis (ARC).

AR is a common disease. Its prevalence has been reported to range from 10% to 30% in children and adults (3,4). Findings indicate that in the majority of cases, AR symptoms begin before the age of 20, and in almost half of patients, the first symptoms appear around the age of 6 (5).

AR imposes a substantial disease burden and has been associated with fatigue, attention and learning difficulties, memory problems, and depressive symptoms (6,7). Previous studies have demonstrated that AR-related nasal obstruction contributes to sleep-related breathing disorders (8,9). Quality of life has been shown to be reduced in adolescents with AR or ARC, largely due to increased nasal symptoms, nasal congestion, impaired daily functioning,

and sleep disturbances (10,11). In addition, AR is frequently associated with asthma, another condition that may adversely affect sleep (12). In patients with AR, treatments targeting nasal congestion and inflammation have been shown to improve sleep quality and daytime alertness (8,13). Collectively, these findings underscore the clinical importance of assessing sleep disturbances in children with seasonal allergic rhinitis (SAR).

The aim of this study was to evaluate sleep disturbances in children with SAR and to examine their relationship with disease severity and associated clinical factors.

Materials and Methods

A total of 115 children aged 6–16 years with pollen sensitization who were diagnosed with seasonal allergic rhinitis (SAR) and followed at the Pediatric Allergy and Immunology Department of Ankara Bilkent City Hospital between May and July 2025 were included in the study. Patients with chronic or psychiatric diseases were excluded. All participants were evaluated during the same pollen season to minimize the potential impact of seasonal variations in pollen exposure on symptom severity and sleep outcomes. The control group consisted of children within the same age range and with comparable demographic characteristics who had no history of chronic, allergic, or psychiatric diseases. These children were recruited from the general pediatric outpatient clinic during routine health examinations

Demographic and clinical characteristics

Patients were evaluated during routine follow-up visits using the Sleep Disturbance Scale for Children (SDSC) and the Visual Analog Scale (VAS) to assess the severity of nasal and ocular symptoms (14,15). Medical histories were obtained, and physical examination findings were recorded.

The diagnosis and classification of SAR were made according to the Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines, based on symptom duration (intermittent or persistent) and severity (mild or moderate–severe). Symptoms occurring on fewer than four days per week or for less than four weeks were classified as intermittent, whereas symptoms present on more than four days per week and for more than four weeks were classified as persistent. Disease severity was categorized as mild in the absence of impaired sleep quality, impairment of daily activities, work or school performance, and troublesome symptoms. Moderate-to-severe disease was defined by the presence of at least one of the following: impaired sleep quality, limitation of daily activities, work or school impairment, or troublesome symptoms (16).

Demographic characteristics, exposure to cigarette, concomitant atopic diseases, aeroallergen sensitization, peripheral blood eosinophil counts, and total immunoglobulin E (IgE) levels were obtained from the patients' medica records.

Aeroallergen sensitivities

Aeroallergen sensitivities were determined by specific IgE (sIgE) and/or skin prick testing (SPT).

SPTs were performed in accordance with the guidelines of the European Academy of Allergy and Clinical Immunology (EAACI) (17). Antihistamines were discontinued at least 10 days prior to testing. DPTs were applied to the flexor surface of the forearm using commercial extracts (Lofarma, Milan, Italy, 1945). Grass pollens, rye, Aspergillus, Alternaria, tree mix (oak, maple, hazel), olea, birch, Artemisia, Dermatophagoides farinae, Dermatophagoides pteronyssinus, cat and dog epithelia, and cockroach extracts were used. The manufacturer's diluent (sodium chloride, sodium bicarbonate, phenol, and glycerol) was used as the negative control, and histamine as the positive control. Results were evaluated 15–20 minutes after application. Induration with a diameter of at least 3 mm surrounded by erythema was considered positive.

Serum sIgE levels were measured using the Immulite 2000 Immunoassay System (Siemens Healthcare Diagnostics, Tarrytown, NY, USA). A result equal to or greater than 0.35 kU/L was considered positive.

Sleep Disturbance Scale for Children (SDSC)

Sleep disturbances were assessed using the Sleep Disturbance Scale for Children (SDSC), developed by Bruni et al.(18) and validated in Turkish. The SDSC is a 26-item Likert-type questionnaire completed by parents to assess sleep disturbances in children aged 6–16 years over the previous six months. It comprises six subscales: disorders of initiating and maintaining sleep (DIMS) (items 1, 2, 3, 4, 5, 10, and 11), sleep breathing disorders (SBD) (items 13, 14, and 15), disorders of arousal (DA) (items 17, 20, and 21), sleep–wake transition disorders (SWTD) (items 6, 7, 8, 12, 18, and 19), disorders of excessive somnolence (DOES) (items 22, 23, 24, 25, and 26), and sleep hyperhidrosis (SHY) (items 9 and 16). Each item is scored on a 5-point Likert scale (1 = never, 5 = always), yielding total scores ranging from 26 to 130. A T-score is calculated based on the total score, with higher scores indicating more severe sleep disturbances. A T-score above 70 is considered indicative of clinically significant sleep disturbances (14,18).

Visual Analogue Scale (VAS)

Symptom severity was assessed using a 10-cm VAS, as recommended by the ARIA guidelines, where 0 indicated "no symptoms" and 10 represented "maximum severity" (15,16).

Statistical Analysis

Data obtained from medical records were analyzed using IBM SPSS Statistics 26.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics (frequency, percentages, mean, standart deviation, median and interquartile range) were calculated for demographic variables. The percentage of patients meeting the threshold value for sleep disorders on the SDSC was determined. Data were presented as mean and standard deviation (SD) or median [25–75% interquartile range (IQR)]. Groups were compared using the Mann–Whitney U test. Logistic regression analysis was performed to identify risk factors for sleep disorders. Variables with $p \leq 0.200$ in univariate analysis were included in the multivariate model. Results were reported as odds ratios (Exp(B)) with 95% confidence intervals. Statistical significance was set at $p < 0.050$.

Results

Demographic and clinical characteristics of patients

A total of 115 patients diagnosed with SAR were included in the study during the study period. The mean age of the patients was 11.6±3.2 years, and 61.7% (n=71) were male. Sensitization to aeroallergens other than pollen was detected in 46.1% of patients (n = 53), most commonly to cat dander (33.0%, n=38) and house dust mite (13.9%, n=16). At least one concomitant allergic disease was present in 48.7% of patients (n=56), with asthma (34.8%, n=40) and atopic dermatitis (13.9%, n=16) being the most common. Cigarette exposure was reported in 53.9% of patients (n=62), and a family history of allergic disease was present in 49.6% (n=57).

According to the ARIA classification, 54.8% of patients (n=63) had moderate-to-severe persistent rhinitis. The most commonly used treatments were nasal steroids (73.9%, n=85) and oral antihistamines (66.9%, n=77). The median absolute eosinophil count was 280 cells/mm³ (IQR: 142.5–440), and the total IgE level was 216 kU/L (IQR: 108–677.5). According to the SDSC, sleep disorder was detected in 44.3% of patients (n=51) (Table I).

Table I: Demographic and clinical characteristics of patients with seasonal allergic rhinitis

Variables	Values
Total number of patients	115
Male*	71 (61.7)
Age(year)†	11.6±3.2
Polisensitizatiion*	53 (46.1)
Cat	38 (33.0)
House Dust Mite	16 (13.9)
Dog	10 (8.7)
Mold	4 (3.5)
Cochroach	1 (0.9)
Concomitant allergic disease*	56 (48.7)
Asthma	40 (34.8)
Atopic dermatitis	16 (13.9)
Food allergy	4 (3.5)
Chronic urticaria	2 (1.7)
Drug allergy	1 (0.9)
Passive smoking exposure*	62 (53.9)
Familial history of allergic disease*	57 (49.6)
ARIA Classification*	
Moderate-severe/ persistant	63 (54.8)
Mild/ intermittant	32 (27.8)
Mild/persistant	11 (9.6)
Moderate-severe/intermittant	9 (7.8)
Treatment*	
Intranasal corticosteroids	85 (73.9)
Antihistaminic	77 (67.9)
Montelukast+levocetirizin combination	18 (15.7)
Oculer antihistaminic	12 (10.4)
Montelukast	6 (5.2)
Immunotherapy	1 (0.9)
AEC, cells/mm³‡	280 (142.5-440)
Total IgE,kU/L‡	216 (108-677.5)
Sleep disturbances according to SDSC*	51 (44.3)

***: n(%), †: mean± SD, ‡:** median (IQR), **AEC:** Absolute eozinophil count, **SDSC:** Sleep disturbance scale for children*

A control group consisting of 115 individuals was included in the study. The mean age of the control group was 11.3±3.4 years, and 59.1% (n=68) were male. The age and gender characteristics of the control group were similar to those of the patients (p=0.510 and p=0.590, respectively).

Comparison of sleep disorders between SAR patients and healthy controls

When comparing the SAR group with healthy controls in terms of SDSC total scores and subscale scores, significantly higher

Table II: Comparison of SDSC scores between children with SAR and healthy controls

Variable	SAR*	Control*	p†
Total number of patients	115	115	-
DIMS T score	15.2 ±4.7 56.2±10.5	13.8±4.6 53.2±10.4	0.310
SBD T score	7.2±3.3 66.1±10.3	4.3±2.1 51.4±11.5	<0.001
DA T score	5.1±2.4 64.2±17.2	4.0±1.5 55.2±13.8	<0.001
SWTD T score	11.8±4.7 57.1±14.2	10.2±3.9 52.4±12.6	<0.001
DOES T score	10.4±4.2 59.5±13.9	8.8±4.1 53.8±13.6	0.030
SHY T score	4.8±2.4 56.9±11.3	3.3±1.5 49.4±8.1	<0.001
Total score T score	54.8±16.6 63.4±15.5	44.8±12.3 53.9±12.1	<0.001

***: mean± SD, †: Mann Whitney U test, SDSC:** Sleep disturbance scale for children, **SAR:** Seasonal allergic rhinitis, **DIMS:** disorders of initiating and maintaining sleep, **SBD:** sleep breathing disorders, **DA:** disorders of arousal, **SWTD:** sleep–wake transition disorders, **DOES:** disorders of excessive somnolence, **SHY:** sleep hyperhidrosis*

Table III: Comparison of clinical parameters according to the presence of sleep disorders in patients with seasonal allergic rhinitis

Variable	Sleep Disorders		p
	Yes	No	
Number of total patients	51	64	-
Male*	30 (58.8)	41(64.6)	0.700
Passive smoking exposure*	30 (58.8)	32 (50)	0.100
Polisensitization*	27 (52.9)	26 (40.6)	0.250
Concomitant allergic disease*	26 (50.9)	30 (46.8)	0.710
Asthma*	16 (31.3)	24 (37.5)	0.550
Moderate-severe rhinitis*	38 (74.5)	34 (53.1)	0.020
Persistant rhinitis*	39 (76.4)	35 (54.6)	0.020
Familial history of allergic disease*	25 (49.1)	32 (50)	1.000
AEC, cells/mm³†	305 (143-357)	255(140-430)	0.190
Total IgE,ku/L†	227(115.1-796.7)	216(93.2-639.4)	0.810
Nasal VAS score†	7 (5-8)	4 (3-6)	<0.001
Ocular VAS score†	7 (3-8)	2 (1-5)	<0.001

***: n(%), †: median(IQR), AEC:** Absolute eozinophil count*

Table IV: Risk factors for sleep disorders in patients with seasonal allergic rhinitis

	Univariate			Multivariate		
	OR	CI (95%)	p	OR	CI (%95)	p
Gender	1.28	0.78– 1.71	0.800	-	-	-
Asthma	0.76	0.35-1.65	0.490	-	-	-
Concomittant allergic disease	1.17	0.56-2.46	0.660	-	-	-
Passive smoking exposure	1.42	0.68-3.0	0.340	-	-	-
Polisensitization	1.76	0.92-2.98	0.190	1.08	0.62-1.72	0.210
Moderate-severe rhinitis	1.25	1.02-1.40	0.020	1.07	0.40-2.85	0.830
Persistant rhinitis	1.49	1.13-1.91	0.010	1.03	0.35-3.05	0.780
Nasal VAS score	2.79	1.19-6.87	<0.001	1.86	1.06-2.41	0.020
Ocular VAS score	2.57	1.16-5.37	0.020	1.12	0.89-1.42	0.320

scores were observed in the SAR group. The SBD (p<0.001), DA (p<0.001), SWTD (p<0.001), DOES (p=0.03), and SHY (p <0.001) subscales were significantly higher in the SAR group. The total SDSC score was 54.8±16.6 in the SAR group and 44.8±12.3 in the control group (p<0.001) (Table II).

Comparison of SAR Patients with and without Sleep Disorders

When SAR patients were divided into two groups based on the presence of sleep disorders (those with sleep disorders: 44.3%, n=51; those without: 55.7%, n=64), the group with sleep disorders had a higher prevalence of moderate-severe rhinitis [74.5% (n=38) vs. 53.1% (n=34); p=0.020], persistent rhinitis [76.4% (n=39) vs. 54.6% (n=35); p=0.020], nasal VAS score [median: 7 (IQR: 5–8) vs. 4 (IQR: 3–6); p<0.001], and ocular VAS score [median: 7 (IQR: 3–8) vs. 2 (IQR: 1–5); p<0.001)] were significantly higher (Table III).

Risk Factors for Sleep Disorder

In univariate analysis, moderate-severe rhinitis (OR=1.25; 95% CI: 1.02–1.40; p=0.020), persistent rhinitis (OR=1.49; 95% CI: 1.13–1.91; p=0.010), nasal VAS score (OR=2.79; 95% CI: 1.19–6.87; p<0.001), and ocular VAS score (OR=2.57; 95% CI: 1.16–5.37; p=0.020) were significantly associated with sleep disorder. In multivariate analysis, only the nasal VAS score was identified as an independent risk factor (OR=1.86; 95% CI: 1.06–2.41, p=0.020) (Table IV).

Discussion

Allergic rhinitis in childhood is not limited to nasal and ocular symptoms but can also have adverse effects on sleep (8,9). As disease severity increases, problems such as sleep-related breathing disorders and decreased daytime performance are reported to occur more frequently (10,11). This finding indicates that the burden of AR on quality of life in children extends beyond what was previously recognized. In our study, sleep disturbances were detected in nearly half of the children diagnosed with SAR. Notably, sleep disturbances were more common in this group compared with a similar group of children without chronic or allergic diseases. Similar findings have been reported in the literature. In a study conducted by Roxbury et al. (19) in an adult population in the United States, individuals with allergic rhinitis were found to have longer sleep onset latency and significantly higher rates of insomnia, sleep apnea, nighttime awakenings, excessive daytime sleepiness, and sleep medication use. Similarly, in a study by Meltzer et al.(5), 40% of parents reported that their children's nasal allergies negatively affected sleep; 32% reported difficulty falling asleep, 26% reported nighttime awakenings, and 29% reported insufficient sleep quality. Comparable results were also observed in a study conducted in Latin America (20). In addition, a meta-analysis by Liu et al. (21) demonstrated poorer sleep quality and a higher prevalence of sleep disorders among individuals diagnosed with AR. Collectively, these findings indicate that allergic rhinitis has a significant impact on sleep quality and that consistent results have been observed across different populations.

When the SAR group was compared with healthy controls, significant differences were observed in the SDSC total score as well as in the subscales of sleep-related breathing disorders, disorders of arousal, sleep–wake transition disorders, excessive daytime sleepiness, and sleep-related excessive sweating. Obstructive sleep apnea (OSA) is the sleep pathology most frequently associated with SAR in the literature, and numerous studies have demonstrated this relationship (22,23). However, current evidence indicates that sleep impairment in SAR is not limited to OSA. Previous studies have shown that allergic rhinitis in children is associated with multidimensional sleep disturbances, ranging from difficulties in initiating and maintaining sleep to excessive daytime sleepiness, as well as arousal disorders, parasomnias, and sleep-related sweating (24). The higher scores observed in multiple SDSC subscales in the SAR group compared with healthy controls support the notion that sleep disturbances in SAR manifest across a multidimensional spectrum. This finding extends beyond studies in the literature that focus primarily on obstructive sleep apnea, underscoring the need for a comprehensive assessment of sleep health in children with SAR.

Our study found that the most important determinant of sleep disturbances in children with SAR was the severity of nasal symptoms. Specifically, higher nasal VAS scores were significantly associated with higher SDSC total scores. The key role of nasal symptoms has also been demonstrated in previous studies. In a randomized controlled trial involving children with sleep-related breathing disorders, intranasal budesonide treatment was shown to improve symptoms and quality of life, along with significant improvements in sleep parameters (25). Similarly, nasal irrigation has been reported to improve sleep quality in children with rhinitis symptoms, highlighting the importance of controlling nasal congestion for sleep health (26). Mansfield et al.

(27) also reported significant improvements in both sleep-related breathing disorders and daytime quality of life in children with SAR treated with intranasal corticosteroids. Collectively, these findings suggest that nasal symptom severity plays a central role in the pathophysiology of sleep disturbances in SAR and that effective symptom control directly contributes to improved sleep health.

Our study also demonstrated that ocular symptoms increase the risk of sleep disturbances in children with SAR. Li et al. (28) reported impaired sleep quality, more frequent nighttime awakenings, and increased daytime fatigue in patients with allergic conjunctivitis. These findings indicate that ocular symptoms adversely affect not only daytime quality of life but also sleep integrity. Consistently, our results show that the presence of ocular symptoms in children with SAR is associated with an increased risk of sleep disturbances, supporting the importance of the multidimensional symptom burden of SAR in the impairment of sleep health.

Our finding that persistent and moderate–to–severe rhinitis in children with SAR is associated with increased risk of sleep disturbances highlights the importance of disease severity in sleep health. Lee et al. (29) reported that sleep problems were more common in children with moderate–to–severe AR and that symptom severity was a key determinant of sleep quality. Similarly, Da Silva et al. (30) demonstrated that sleep-related breathing disorders were both more frequent and more severe in cases of moderate–to–severe rhinitis. When considered together with our results, these findings indicate that sleep disturbances become more pronounced in persistent and severe forms of SAR and that effective disease control plays a critical role in maintaining sleep health.

Limitations

Our study has several limitations. First, its single-center design and the assessment of sleep disturbances using a questionnaire, without objective methods such as polysomnography, may limit the strength of the findings. In addition, as our institution is a tertiary care center, the higher prevalence of persistent and more severe SAR phenotypes in our study population may limit the generalizability of the results. However, the use of standardized data collection forms and the evaluation of all patients by the same allergy–immunology specialists helped minimize potential measurement and assessment variability.

Conclusion

Sleep disturbances are common and multidimensional in children with SAR. Persistent and more severe rhinitis phenotypes, as well as ocular symptoms, were identified as risk factors for sleep disturbances, with nasal symptom severity playing a particularly important role. These findings suggest that childhood SAR is not limited to nasal and ocular complaints but also imposes a substantial burden on sleep health. In clinical practice, incorporating the assessment of sleep disturbances into routine follow-up for children with SAR may facilitate more comprehensive disease management.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Bilkent City Hospital (12.03.2025, reference number: TABED 1-25-1104).

Contribution of the authors

Study conception and design: EDM, ZŞE, FAG; Data collection: EKK, AKK, TTKG, FAG; Analysis and interpretation of results: FAG, EDM, ZŞE; Draft manuscript preparation: FAG, EDM, ZŞE; All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Anxiety disorder of hypertensive children and burnout levels of their families

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ABSTRACT

Objective: Our study focused on assessing the anxiety levels of children and adolescents being monitored for hypertension (HTN), as well as the burnout levels experienced by their caregivers.

Material and Methods: The study included 67 patients, aged 12 and older, who were monitored for HTN as the study group, and 60 children and adolescents, matched for gender and age, without chronic illnesses, were selected from the pediatric outpatient clinic for routine check-ups to serve as the control group. The State Anxiety Inventory (STAI-1), Trait Anxiety Inventory (STAI-2), and Beck Anxiety Inventory (BAI) were applied to the children, while the Maslach Burnout Inventory (MBI) was applied to their parents.

Results: We found the mean STAI-1 scores of the study group lower than the control group (43.6±6.4 vs. 51.6±15.4; p <0.001). However, no difference was detected between these groups in terms of the STAI-2 scores (p= 0.140). The median BAI scores were higher in study group than control group (10.0 vs.6.5; p=0.010) but no significant difference have been found in terms of severity of anxiety (p=0.170). There was no difference in caregivers between the emotional exhaustion (MBI-EE) and personal accomplishment (MBI-PA) subscale scores of the MBI of the caregivers (p=0.280, p=0.340 respectively).

Conclusion: Our study revealed low anxiety levels among HTN patients and low burnout scores in their families. However, we believe that continuous psychiatric support for both patients and their families may be essential for managing chronic conditions, indicating the need for further research in this area regard.

Keywords: Anxiety, caregiver burden, children, hypertension

Introduction

Hypertension (HTN) in children is defined as systolic or diastolic blood pressure (BP) in three different measurements over the 95th percentile, by age, gender, and height (1). The frequency of HTN is approximately 2–4% among children (2). In our country, the prevalence of hypertension in children aged 6 to 15 years ranges from 8.5% to 15% (3). Although it is rarely seen compared to adults, it is a significant chronic disease due to its complications and lays the groundwork for atherosclerosis in adulthood (4).

Hypertension can further be classified by etiology: essential or primary HTN (where an underlying cause cannot be identified) and secondary HTN (where an organic cause is established) (5). Essential hypertension is rarely seen in infants and young children, but its prevalence increases significantly in adolescence. A good general rule to follow is that the likelihood of identifying a secondary cause of hypertension is inversely related to the age of the child and directly related to the degree of BP elevation (6, 7).

Anxiety is a normal reaction to the stress factors and uncertainties in life; however, because the frequency and severity of this condition affect the quality of life, it is considered a pathological condition (8). Anxiety causes psychological symptoms, such as tension, worrying, crying attacks, and fear, as well as physiological symptoms, like tachycardia, tachypnea, vomiting, insomnia, anorexia, and tremors (9).

Although there is no standard definition of burnout, it is

described as mental and physical exhaustion caused by work (10). Like work-related burnout, it has been shown that parenting can also cause burnout in individuals. It is found that parents can feel a lot of stress while taking care of their children (11).

This study aimed to investigate the effect of HTN on the anxiety levels of children and the burnout levels of their families. Children with HTN and their families were compared with children who did not have a chronic disease and their families. At the end of the study, we aimed to determine the anxiety levels of hypertensive children and the burnout levels of their families.

Materials and Methods

The State-Trait Anxiety Inventory (STAI) scale is designed for children aged 12 and older. Therefore, between July 2017 and July 2018, we identified 67 patients aged 12 and above who visited our Ankara Pediatrics Hematology Oncology Research and Training Hospital, Pediatric Nephrology Outpatient Clinic for hypertension, along with their parents, as the study group. For the control group, we selected 60 children aged 12 and older who visited the pediatric outpatient clinic without any known chronic illnesses, along with their parents included.

All patients with hypertension were evaluated with a 24-hour ambulatory blood pressure monitorization (ABPM). The appropriate-sized cuff was attached to the non-dominant arm, and measurements were made every 20 minutes during wakefulness and every 30 minutes during sleep (12). For ABPM, an Erkameter 24 ABPM (Bad Tölz, Germany) device was used. The mean systolic and diastolic blood pressure measurements of 24-hour, daytime, and night-time, as well as systolic and diastolic blood pressure loads, were evaluated. These evaluations were compared with the mean blood pressure measurements of healthy children by Soergel et al. (13) and coordinated by Wühl et al. (14).

The demographic information of all children was recorded. Age, gender, height, weight, age at diagnosis, antihypertensive medications, and duration of use were recorded for the study group, while age and gender were recorded for the control group. STAI forms TX 1–2 and BAI were given to all children in the study, and MBI was given to their parents.

State-Trait Anxiety Inventory is an inventory used to measure the state and trait anxiety levels (15). It consists of two forms, STAI form TX-1 and STAI form TX-2, with 20 statements each. STAI form TX-1 inventory measures the subjective anxiety an individual feels due to stressful situations. STAI form TX-2 inventory measures the individual's predisposition to experiencing anxiety. This is the tendency of a person to perceive or interpret a situation as stressful.

The Beck Anxiety Inventory (BAI) is a self-assessment inventory developed by Beck et al. (16) and used to determine the frequency of anxiety symptoms experienced by individuals. It consists of 21 items, scored between 0–3; "none" is 0 points, "mild" 1 point, "moderate" 2 points, and "severe" is 3 points. The points are tallied after 21 items are marked, with 0–7 points indicating no anxiety, 8–15 indicating mild anxiety, 16–25 indicating moderate anxiety, and 26–63 points indicating severe anxiety symptoms.

The Maslach Burnout Inventory (MBI) is today's most widely accepted burnout description (17). It is comprised of 22 total items, and its results are evaluated in three dimensions. There are nine items in the "emotional exhaustion" (EE) dimension, eight items in the "personal accomplishment" (PA) dimension, and five items in the "depersonalization" dimension. Although it was expected that the MBI, originally designed to measure job burnout, could also assess parental burnout, validation studies found that the depersonalization subscale was not appropriate for this purpose. However, the emotional exhaustion and personal accomplishment subscales were deemed usable for assessing parental burnout (18). In national and international studies, it was deemed appropriate to evaluate the inventory for parents in two dimensions, which are personal accomplishment and emotional exhaustion (18-20). Individuals may score 0–52 points for the emotional exhaustion dimension and 0–32 points for the personal accomplishment dimension. High scores are interpreted in the same direction in the emotional exhaustion dimension regarding parental burnout and the opposite direction in the personal accomplishment dimension.

Statistical analysis

Statistical Package for Social Sciences (SPSS), version 22.0 for Windows (SPSS Inc. Chicago, USA) computer package program was used for statistical analysis of the research data. In the descriptive statistics section, categorical variables were presented as numbers and percentages, and continuous variables were presented as mean and standard deviation and median (minimum-maximum value). The conformity of continuous variables to normal distribution was evaluated using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Independent sample t-test was used for the comparison analysis between the two groups for the data of continuous variables that were found to be normally distributed between the groups as a result of the normality analysis. For the data that did not fit the normal distribution, the Mann-Whitney U test was used for the comparison analysis between two groups. Pearson chi-square test were used in the comparison analysis for categorical variables between independent groups. The relationship between independent predictors that did not fit the normal distribution was evaluated by Spearman correlation analysis. The absolute value of the correlation coefficient (rho) $r \leq 0.30$ indicates a weak relationship, 0.30-0.50 indicates a moderate relationship and $r \geq 0.50$ indicates a strong relationship (21). Statistical significance level was accepted as $p<0.050$.

Results

The general characteristics of the study group

In the study group of 67 patients, 45 (67.2%) were male, while 22 (32.8%) were female. The median age of the patients was 16.5 (IQR; 3.3), and the median age at diagnosis was 14.3 (IQR; 4) years. The mean follow-up period due to HTN of the study group in our hospital was 26.6±22.4) months. Thirty-

two (47.8%) patients were obese, and the median body mass index (BMI) was 25.7 (IQR; 7.5) kg/m². A total of eight patients (11.9%) required follow-ups for secondary hypertension. Of the 67 patients in the study group, 11 (16.4%) did not receive medical treatment, and blood pressure was monitored with lifestyle changes. There were 34 (50.7%) patients using one drug, 17 (25.4%) using two drugs, two (3%) using three drugs, and three (4.5%) using four drugs. The mean duration of the first line medical treatment was found to be 25.9± 21.5 months.

Comparison of the inventory scores:

The study group's mean STAI-1 score was lower than control group's score (43.6±6.4 vs. 51.6±15.4; p <0.001) (Table I). When the STAI-2 scores were compared, no significant difference was found between the two groups (p=0.140).

The study group's median BAI score was significantly higher than the control group (p = 0.012) (Table I). However, no difference was found when the anxiety levels (none, mild, moderate, severe) of the study and control groups were compared (p=0.170). There was no difference in the MBI-EE and MBI-PA median scores between the parents of the two groups (p=0.282, p=0.340) (Table I).

The MBI scores of the parents were compared, the median scores of the emotional exhaustion in male patients' parents were higher than those of the parents of the female patients (p =0.040) (Table II). As in the relationship between age and inventory scores, the STAI-1 score increases for both the study and control groups as the age decreases, while the BAI score increases as the age increases for all children (Table III). No differences were observed when comparing organ damage and STAI-1 (p=0.820), STAI-2 (p=0.990), BAI (p=0.430) scores in the study group. When assessing the patients' obesity and STAI-1 (p=0.470), STAI-2 (p=0.970), BAI (p=0.390) scores, no differences were found.

There was no difference between the follow-up periods (compared ≤12 months and >12 months) and STAI-1 (p=0.810), STAI-2 (p=0.830), BAI (p=0.610) scores of the patients and their parents' MBI-EE (p=0.240) and MBI-PA (p=0.900) scores .

The inventory scores of the study group using antihypertensive drugs were compared with the control group, we found the STAI-1 scores were higher in the control group (p=0.010). On the other hand, when the BAI scores were compared, the scores of patients using antihypertensive drugs were higher than the control group (p=0.009) (Table IV).

Table I: Comparison of inventory scores between the study and control groups (n=127)

	Control group	Study group	p
Number of patients	60	67	-
STAI-1 Score*	51.6±15.4	43.6±6.4	<0.001
STAI-2 Score*	49.4±11.4	46.9±7.1	0.140
BAI Score†	6.5 (0–39.0)	10.0 (0–4.0)	0.010
BAI State‡			
No anxiety	32 (53.3)	26 (38.8)	
Mild	18 (30.0)	19 (28.4)	0.170¶
Moderate	6 (10.0)	15 (22.4)	
Severe	4 (6.7)	7 (10.4)	
MBI-EE†	7.0 (0–2.0)	8.00 (0–47.00)	0.280
MBI-PA†	24.0 (1.0–32.0)	25.0 (1.0–36.0)	0.340

:** *mean±SD (Independent Sample T-test),* **†:** *median(min-max) (Mann–Whitney U test),* **‡:** *n(%) (Pearson Chi-Square test),* ***MBI-EE: *Maslach Emotional Exhaustion Score,* ***MBI-PA:*** *Maslach Personal Accomplishment Score*

Table II: Comparison of inventory scores by gender in the study group (n=67)

	Male	Female	p
Number of patients*	45 (67.2)	22 (32.8)	-
STAI-1 Score†	44.27±6.15	42.32±6.92	0.350
STAI-2 Score†	46.56±7.14	47.73±6.92	0.520
BAI Score‡	10.00(0–44.00)	10.00(0–33.00)	0.840
BAI State*			
No anxiety	18 (40.0)	8 (36.4)	
Mild	13 (28.9)	6 (27.3)	0.940
Moderate	10 (22.2)	5 (22.7)	
Severe	4 (8.9)	3 (13.6)	
MBI-EE‡	11.00(0–47.00)	5.00(0–20.00)	0.040
MBI-PA‡	25.00(1.00–35.00)	23.50(6.00–36.00)	0.920

:** *n(%) (Pearson Chi-Square test,)* **†:** *mean± SD (Independent Sample test) ,* **‡:** *median(min-max) (Mann–Whitney U test),* ***MBI-EE: *Maslach Emotional Exhaustion Score,* ***MBI-PA:*** *Maslach Personal Accomplishment Score,* ***BAI:*** *Beck Anxiety Inventory,* ***STAI-1:*** *The State Anxiety Inventory,* ***STAI-2:*** *Trait Anxiety Inventory*

Table III: Comparison of inventory scores by age in the study and control groups

	Age Total n=127		Age No HT n=60		Age Yes HT n=67	
	r	p	r	p	r	p
STAI-1 Score	-0.257	0.003	-0.319	0.010	-0.184	0.130
STAI-2 Score	-0.172	0.050	-0.232	0.070	-0.088	0.470
BAI Score	0.180	0.040	0.201	0.120	0.126	0.300
MBI-EE Score	-0.032	0.720	-0.084	0.520	-0.019	0.870
MBI-PA Score	-0.093	0.290	-0.037	0.770	-0.113	0.360

r: *rho,Spearman Correlation Coefficient,* ***MBI-EE:*** *Maslach Emotional Exhaustion Score,* ***MBI-PA:*** *Maslach Personal Accomplishment Score,* ***BAI:*** *Beck Anxiety Inventory,* ***STAI-1:*** *The State Anxiety Inventory,* ***STAI-2:*** *Trait Anxiety Inventory*

Discussion

In our study, we hypotized that HTN patients would have higher anxiety levels, and their families would have higher burnout scores. However, we found the mean STAI-1 scores of the study group lower than the control group, the median BAI scores were higher in study group and there was no difference in caregivers between the emotional burnout (MBI-EE) and personal success (MBI-PA) subscale scores of the MBI of the caregivers.

Hypertension is a chronic disease and requires long-term treatment and follow-up. Patients need to take medication every day, follow a special diet, and exercise regularly.

Table IV: Comparison of the study group using antihypertensive drugs and control group's inventory scores (n=116).

	Control group	Study group	p
Number of patients	60 (64.2)	56 (35.8)	-
STAI-1 Score*	51.6±15.4	43.5±6.7	0.010
STAI-2 Score*	49.4±11.4	47.6±7.1	0.280
Beck Anxiety Score†	6.5 (0–39.0)	10.50 (0–44.0)	0.009
Beck Anxiety State‡			
No anxiety	32 (53.3)	22 (39.3)	
Mild	18 (30.0)	14 (25.0)	0.120
Moderate	6 (10.0)	14 (25.0)	
Severe	4 (6.7)	6 (10.7)	
MBI-EB†	7.0 (0–24.0)	9.0 (0–47.0)	0.160
MBI-PS†	24.0 (1.0–32.0)	25.5 (1.0–36.0)	0.350

: mean±SD (Independent Sample T-test), †: median (min-max) (Mann–Whitney U test), ‡: n(%) (Pearson Chi-Square Test), **MBI-EE: Maslach Emotional Exhaustion Score, **MBI-PA:** Maslach Personal Accomplishment Score, **BAI:** Beck Anxiety Inventory, **STAI-1:** The State Anxiety Inventory, **STAI-2:** Trait Anxiety Inventory*

Therefore, it is speculated that hypertension may increase the level of anxiety in children. Studies conducted with a similar hypothesis to ours, comparing the anxiety levels of patients with chronic diseases, showed that the anxiety levels of healthy children were significantly higher than in the study group (22-24). Conversely, various studies show that children with chronic diseases have higher anxiety scores than healthy children (25,26). The low STAI-2 scores found in our study compared to the control group may be due to the fact that children are able to adapt more quickly and easily than adults to changes in social life or health conditions. Acute changes in health conditions and first-time hospitalization may increase anxiety in children. Still, the fact that children do not have difficulty adapting to changes that follow a certain order over time may explain the results of our study. Thus, the STAI-1 inventory scores were higher in the control group. The reason for the high anxiety levels of this group may be that children with acute illness do not know where they will be examined or who they will encounter in terms of health personnel. They may also have uncertainty about whether an invasive procedure will be applied. Therefore, selecting healthy individuals without acute or chronic illnesses for the control group in future studies may facilitate a more objective interpretation of the psychological effects of chronic illnesses on children and their families. Also, the STAI-1, a measure of state anxiety, may be interpreted as a finding that is expected to be low in children monitored for hypertension during clinical check-ups. This observation aligns with expectations, considering that similar protocols are consistently employed and healthcare professionals remain unchanged across examinations. Conversely, elevated scores on the BAI, a self-assessment instrument for personal anxiety levels experienced by patients, suggest that hypertensive individuals may endure ongoing anxiety in their daily lives attributable to their chronic condition. Nonetheless, further comprehensive and objective research is requisite to substantiate these preliminary findings.

A meta-analysis examining the anxiety levels of children with chronic disease emphasized that the disease state spreading over a long time might create adaptation to the condition and regression of anxiety symptoms (27). The development of trust between children with chronic disease and healthcare professionals over time and the fact that the patients and their families are informed about the course of the disease may reduce anxiety. Another reason for the low anxiety levels of patients and their families could be the familiarity with hypertension, a common chronic disease found in 31% of adults in our country. A study conducted on the anxiety and depression levels of cancer patients under the age of 18 and their families found that 28.3% of the patients and 46.2% of the families had moderate to severe anxiety levels after cancer treatment (28). The low mortality rate of hypertension compared with the high mortality rate of diseases, such as malignancy, may be another reason for patients' low anxiety levels.

In our study, no significant difference was found between genders in inventory scores. The anxiety levels of children with chronic diseases were studied in Jordan, and it was reported that there was no significant difference between the inventory scores of the genders as in our study (23). Other studies found that girls are more anxious than boys (29,30). Our study group was made up of adolescents, an age where anxiety levels related to social media are already elevated, which might account for no differences observed between genders (31).

In our study we found that the STAI-1 scores increased with younger age. The STAI-1 assesses the subjective anxiety a person experiences in stressful situations. Young children may experience greater anxiety regarding potential invasive procedures in the hospital, leading to higher anxiety levels compared to older children.

On the other hand, the analysis of the study and control groups revealed a weak correlation between age and BAI scores, increasing with age. Similar to our study, a study conducted with Tibetan children found that moderate and severe anxiety levels were higher in late adolescents than in early adolescents (32). When the literature is examined, it has been determined that although there are various inventories used to measure anxiety levels in children with chronic diseases, it is not possible to compare according to age, disease type and gender due to the lack of specific methods that can be used widely (9). For this reason, more extensive and varied studies are needed to develop a standard methodology on the psychosocial status of chronically ill children.

Similar to our study results, the anxiety levels of obese hypertensive patients were examined, and no relationship between obesity and anxiety could be found (33). Another study conducted with 3021 patients between the ages of 14–24 in Germany found no relation between body mass index and mental disease or psychopathologies (34). The fact that psychological symptoms of obese patients were found to be lower in previous studies reveals the need for more studies in this field.

Our study found that the burnout inventory scores of the mothers of male patients were higher than those of the mothers of the females. With its patriarchal structure, our society may perceive the disease state as a critical defect in boys, thus affecting their parents' anxiety levels. Boys are more extroverted, while girls are more withdrawn. Anxiety

symptoms are more prominent in girls, while antisocial behaviors such as acrimony and running away from school are more prominent in boys. Combating these difficulties can make hypertensive boys' families more exhausted. Although there is a limited number of studies on this subject in the literature, a positive correlation was found between the depression scores of the children and their mothers in a study of type 1 diabetes patients and their families in terms of psychosocial aspects (35).

There was no significant relationship between the anxiety levels of the study group and target organ damage caused by hypertension, such as retinopathy, left ventricular hypertrophy, and nephropathy. The patients attending the center where the study was conducted have low socioeconomic status and limited parental education. These factors may contribute to reduced anxiety levels and pose challenges in comprehending the severity and progression of the disease. Consequently, future research should consider selecting patient and control groups from diverse socioeconomic backgrounds to enable the inclusion of this variable analyses

One of the hypotheses we established when starting our study was that the duration of follow-up and the number of medications used could affect anxiety levels in children. However, in the data obtained, it was determined that this did not affect the children's anxiety levels. In a study conducted with children with type 1 diabetes, another common chronic disease, neither the duration of diagnosis nor the insulin dose used was related to the children's anxiety levels (35). The fact that children adapt to changes in their lives more easily compared with adults may explain this situation, but more studies are needed to examine children with chronic diseases and their psychosocial aspects.

Limitations

Our study has some limitations. First, selecting the children as the control group for our study when seen at the pediatric outpatient clinic may have led to the children's high instances of anxiety scores. In studies like ours, choosing the control group among healthy children without acute or chronic diseases may result in different outcomes. Second, examining the socioeconomic levels of the individuals and families included in the study will contribute to the investigation of whether their anxiety and burnout levels are affected by their socioeconomic situation. Third, the sample size was set at 67 patients and 60 control group members, owing to the availability of data and the accessibility of participants, specifically 67 hypertensive patients and their respective families during the study period at our center. Nevertheless, investigations incorporating larger cohorts of patients, control groups, and their families may provide more comprehensive insights results. Despite all these limitations, we believe that our study will contribute to the scientific literature and inspire future studies, as it is one of the few studies evaluating the anxiety of children being monitored for hypertension and the exhaustion of their families.

Conclusion

Hypertension is a chronic disease of childhood, which may be expected to cause some psychiatric symptoms and diseases for parents. However, contrary to expectations, children can tolerate chronic disease more easily than adults. We speculate tracking the parents of children with chronic diseases, which are difficult to care for and can cause burnout and informing them in detail about the condition and its course can provide better care and support during the illness process. Further studies should be conducted to examine the psychosocial comorbidities of chronic diseases and support the mental health of children and their families. The follow-up and treatment of patients and their families during and after the illness is important, both physically and mentally.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Pediatrics Hematology Oncology Research and Training Hospital (03/07/2017, reference number: 2017-112).

Contribution of the authors

S.Ö.T. wrote the main manuscript text. All authors contributed data and reviewed the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Hepatosplenomegaly in children: A gateway to inherited metabolic disorders

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ABSTRACT

Objective: Hepatomegaly and/or splenomegaly (HSM) are common clinical findings with a broad differential diagnosis, including infectious, hematologic, malignant, and inherited metabolic diseases. Although inborn errors of metabolism (IEM) are rare, they constitute critical and often treatable causes of HSM. This study aimed to evaluate pediatric patients presenting with hepatomegaly and/or splenomegaly for underlying metabolic disorders and to identify diagnostic indicators that may facilitate early recognition and appropriate management of IEM.

Materials and Methods: This retrospective study evaluated 223 children presenting with hepatomegaly, splenomegaly, or hepatosplenomegaly between June 2023 and October 2025 at a pediatric metabolic clinic. Only those with genetically confirmed diagnoses of IEM were included in the final cohort. Clinical features and laboratory findings were evaluated.

Results: Twenty-seven patients (15.4%) received a confirmed IEM diagnosis. The most frequent disorders were glycogen storage diseases (n=13, 7.4%), followed by Gaucher disease (n=6, 3.4%), acid sphingomyelinase deficiency (n=3, 1.7%), and single cases of Niemann-Pick type C, Mucopolysaccharidosis type II, GM1 gangliosidosis, hereditary fructose intolerance, and galactosemia. Consanguinity was present in 84.6%, and characteristic systemic findings such as hypoglycemia, hyperlipidemia, cytopenias, cholestasis, neurological involvement, or coarse facies served as critical diagnostic clues.

Conclusion: Inborn errors of metabolism should be considered in children presenting with hepatomegaly and/or splenomegaly, particularly in the presence of accompanying systemic findings, especially in regions with high consanguinity rates. Recognition of diagnostic clues may facilitate earlier referral, reduce diagnostic delays, and enable timely initiation of disease specific treatments, including enzyme replacement therapy or dietary modification.

Keywords: Hepatomegaly, inborn errors of metabolism, splenomegaly

Introduction

Hepatosplenomegaly (HSM), defined as enlargement of the liver and spleen, is a clinical finding frequently encountered in both hospitalized patients and outpatient clinics. Clinically, hepatomegaly is detected by palpation and percussion of the liver edge below the right costal margin, while splenomegaly is identified by palpation of the spleen below the left costal margin. Physical examination findings may vary according to the patient's age, body habitus, and examiner experience. Therefore, ultrasonography is considered the preferred imaging modality for confirming organ enlargement, as it provides objective measurements and allows comparison with age- and height-adjusted normative reference values.

Hepatomegaly and splenomegaly may result from a wide range of etiologies, including infectious, neoplastic, toxic, and inflammatory conditions (1). Hepatosplenomegaly may be a presenting feature of several inborn errors of metabolism (IEM), despite their rarity. These disorders often affect various organ systems and can present across all ages, from the neonatal period to adulthood. The most commonly reported inborn errors of metabolism associated with hepatomegaly and/or splenomegaly include lysosomal storage disorders (such as Gaucher disease, acid sphingomyelinase deficiency (ASMD), Niemann Pick type C (NPC) mucopolysaccharidoses and cholesteryl ester storage disease) and disorders of carbohydrate metabolism, particularly glycogen storage diseases (1). Due to

the varied clinical presentation of these disorders, a thorough clinical evaluation supported by specific laboratory and genetic testing is crucial for an accurate diagnosis.

This study aimed to identify underlying IEM in children with hepatomegaly and/or splenomegaly referred to a tertiary pediatric metabolism clinic. Additionally, the study sought to determine the clinical and laboratory clues that should prompt clinicians to consider metabolic diseases when diagnosing hepatosplenomegaly. By characterising these diagnostic indicators, we hope to facilitate the earlier recognition of IEM and reduce diagnostic delays.

Materials and Methods

This retrospective study initially evaluated children with hepatomegaly, splenomegaly, or hepatosplenomegaly between June 2023 and October 2025. A total of 223 patients referred to the Pediatric Metabolism Clinic at Adana City Training and Research Hospital were initially included. After excluding 48 patients who were lost to follow-up, 175 were included in the final analysis. No predefined age restriction was applied; the age of the included patients ranged from 1 to 15 years. Organomegaly was confirmed by clinical examination and ultrasonography. Liver and spleen size were evaluated interpreted according to published age-and height-adjusted normative reference values for Turkish children (2,3). Among these, only patients who subsequently received a confirmed diagnosis of IEM were included in the final analysis, while those with acute infectious diseases, hematologic malignancies, autoimmune or rheumatologic disorders, or incomplete clinical data were excluded. Detailed clinical history, including additional symptoms, family history, and parental consanguinity, was systematically obtained. All patients underwent standardized laboratory testing, including complete blood count, liver function tests, coagulation profile, lipid panel, and metabolic screening tests (plasma amino acids, acylcarnitine profile, and urine organic acids), performed in accordance with institutional protocols. Targeted tests, including lysosomal enzyme assays, urine carbohydrate chromatography, and other diagnosis-specific metabolic studies, were added when clinically indicated.

Genetic analyses were conducted for all patients with suspected inborn errors of metabolism. Depending on clinical suspicion, next-generation sequencing–based targeted gene panels or whole-exome sequencing were performed, followed by Sanger confirmation when appropriate. Clinical diagnoses were established through integration of clinical, laboratory, radiological, and genetic findings. Missing or incomplete data were excluded from the final analysis.

Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics (version 23.0; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean and standard deviation or median, whereas categorical variables were reported as counts and percentages.

Results

A total of 223 patients who were referred to the Pediatric Metabolism Clinic with hepatomegaly, splenomegaly, or hepatosplenomegaly were included in the study After excluding 48 patients lost to follow-up, 175 patients were included in the final analysis. Of these, 27 (15.4%) were diagnosed with an IEM. The most frequent diagnoses were GSD (13 patients, 7.4%; Type I = 4, Type III = 2, Type IXA = 2, Type IXB = 2, Type VI = 3), Gaucher disease (6 patients, 3.4%), ASMD deficiency (3 patients, 1.7%), Niemann-Pick type C disease (1 patient, 0.57%), MPS II (1 patient, 0.57%), GM1 gangliosidosis (1 patient, 0.57%), hereditary fructose intolerance (1 patients, 0.57%), and galactosemia (1 patient, 0.57%).

Among patients with a confirmed IEM, 84.6% had consanguineous parents. Five patients (18.5%) had a positive family history of IEM. All patients displayed additional clinical features relevant to their underlying conditions. In patients with GSD, hepatomegaly was consistently present in patients with GSD. Elevated liver enzyme levels were evident, with mean alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels of 70.2±26.7 U/L and 79.3±30.1 U/L, respectively. Hypertriglyceridemia was also observed, with mean triglyceride levels of 248.8±155.0 mg/dL. Additionally, hypoglycemia was observed in six patients, all of whom had a diagnosis of GSD type I or III (mean blood glucose: 44.2±4.8 mg/dL) while elevated creatine kinase levels were detected in two patients (1422 and 2300 U/L) diagnosed with GSD type III (Table I). Short stature and growth retardation were also observed in three patients. Of the six patients diagnosed with Gaucher disease, four presented with hepatosplenomegaly, and two with isolated splenomegaly. All patients exhibited thrombocytopenia (mean platelet count: 83.167±32.514/μL) and anemia (mean hemoglobin: 8.2±1.2 g/dL) while serum alanine aminotransferase (16.0±5.5 U/L) and aspartate aminotransferase (55.7±17.9 U/L) levels were within normal limits. Patients diagnosed with ASMD deficiency presented with hepatosplenomegaly accompanied by thrombocytopenia and anemia (The mean platelet count was 136±19.80/μL, and the mean hemoglobin level was 9.6±0.5 g/dL). Mean ALT and AST levels were 129.3±26.7 U/L and 222.3±46.4 U/L, respectively. All patients diagnosed with ASMD had decreased high-density lipoprotein (26.3±2.3 mg/dL) cholesterol levels. Elevated triglyceride levels were detected in two patients (437 and 396 mg/dL). NPC was identified in one patient and, in addition to hepatosplenomegaly, displayed neurological involvement, including hypotonia, seizures and supranuclear gaze limitation. In patients with GM1 gangliosidosis, coarse facial features, mental retardation, and a cherry-red spot on fundoscopic examination were observed. In those with MPS II (neuropathic phenotype), coarse facial features, developmental delay, dysostosis multiplex on radiologic imaging, and increased urinary glycosaminoglycans (20.3 mg/mmol creatinine) were noted. Another patient, diagnosed with hereditary fructose intolerance, showed isolated hepatomegaly together with hypoglycemia, metabolic acidosis, elevated lactate levels (4 mmol/L), and dietary fructose avoidance was observed. The patient with galactosemia exhibited hepatomegaly, cholestasis, elevated liver enzymes (ALT: 103 U/L; AST: 77 U/L), feeding difficulties and cataract. The accompanying clinical and laboratory features of these metabolic disorders are summarized in Table I.

Table I: Clinical findings accompanying hepatomegaly and/or splenomegaly in patients diagnosed with metabolic disorders, and the percentage distribution of diagnoses among all metabolic disorders

Disease	Frequency*	Hepatomegaly	Splenomegaly	Other Findings
Glycogen storage disease (I, III, IXA, IXB, VI)	13 (48.1)	+	-	Hypoglycemia (6), elevated liver enzyme, hypertriglyceridemia, elevated CK (2),
Gaucher disease	6 (22.2)	-	+	Thrombocytopenia, anemia
ASMD	3 (11.1)	+	+	Thrombocytopenia, anemia, mild elevated liver enzyme,
NPC	1 (3.7)	+	+	Seizures,developmental delay, supranuclear gaze limitation
MPS II	1 (3.7)	+	-	Coarse facial features, developmental delay, dysostosis multiplex and increased urinary glycosaminoglycans
GM1 Gangliosidosis	1 (3.7)	+	-	Coarse facial features, cherry red spot , developmental delay
Hereditary fructose intolerance	1 (3.7)	+	-	Hypoglycemia, metabolic acidosis elevated lactate levels
Galactosemia	1 (3.7)	+	-	Hypoglycemia, cholestasis, cataract

***:** *n(%),* ***ASMD:** *Acid Sphingomyelinase Deficiency,* ***CK:** *Creatine Kinase;* ***GSD:** *Glycogen Storage Disease;* ***HSM:** *Hepatosplenomegaly;* ***IEM:** *Inborn Errors of Metabolism;* ***MPS:** *Mucopolysaccharidosis;* ***NPC:** *Niemann–Pick Disease Type C. The symbol "+" indicates presence and "–" indicates absence of the respective clinical finding.*

Discussion

Hepatosplenomegaly in the pediatric population can result from both inherited and acquired causes. Common etiologies include infections, hematologic and oncologic disorders, liver and biliary diseases, as well as metabolic disorders (4,5). In children presenting with this condition, IEM represents rare but clinically critical diagnoses that must be considered. IEM can involve multiple organ systems and may present at various ages; therefore, early recognition and appropriate referral are essential not only for optimizing patient prognosis and providing accurate genetic counseling to families, but also for initiating timely treatment that can substantially reduce morbidity. These considerations highlight the importance of routinely including IEM in the differential diagnosis of HSM and adopting a multisystemic, metabolically oriented diagnostic approach.

Despite these considerations, the proportion of patients ultimately diagnosed with an IEM varies substantially between cohorts. Previous studies have reported that a significant proportion of patients assessed for potential metabolic disorders were ultimately diagnosed with an IEM. In Bulut et al.'s (6) study, 55.9% of patients received an IEM diagnosis. In contrast, this proportion was markedly lower in our cohort (15.4%). There may be several possible explanations for this situation. Firstly, in previous years, physicians may have referred patients to pediatric metabolic specialists after preliminary etiological investigations, and only those in whom a diagnosis could not be established may have been referred. In recent years, however, many patients with hepatomegaly or splenomegaly have been referred to pediatric metabolic units even in the absence of typical metabolic features. While this has increased the number of patients undergoing metabolic evaluation, it has naturally resulted in a lower proportion of confirmed metabolic diagnoses.

In our cohort, a high proportion of patients' parents were consanguineous. Additionally, all patients presented with accompanying clinical and laboratory findings, including growth retardation, coarse facial features, hypoglycemia, hyperlipidemia, thrombocytopenia, anemia, metabolic acidosis, and cholestasis depending on the specific underlying disorder. These factors collectively represent important diagnostic clues for identifying IEM. The most frequently diagnosed disorder in our study was GSD. In hepatic forms of GSDs, hypoglycemia and hepatomegaly constitute the predominant clinical manifestations, whereas types with primary muscle involvement are characterized by exertional muscle weakness and progressive myopathy (7-9). Moreover, in GSD IIIa both liver and muscle (skeletal and cardiac) involvement may occur while early hepatomegaly, fasting hypoglycemia, hyperlipidemia, and elevated liver enzymes dominate the picture in childhood, progressive myopathy, elevated CK, exercise intolerance, and eventual cardiomyopathy may develop over time (10). Laboratory assessments in both groups commonly reveal elevated liver transaminases, along with metabolic acidosis, hypertriglyceridemia, and hypercholesterolemia. In our cohort, affected patients exhibited hypoglycemia and hyperlipidemia, underscoring the diagnostic value of these findings for early recognition and timely referral. The individual with GSD type III additionally showed elevated CPK levels, consistent with the muscle involvement characteristic of this subtype.

Lysosomal storage disorders (LSDs) are IEM that are individually uncommon; however, as a group, they are relatively frequent, with an estimated overall incidence of approximately 1 in 5.000 live births (11). Hepatosplenomegaly (HSM) is a common feature observed across several LSDs, including Gaucher disease, ASMD, NPC, mucopolysaccharidoses (MPS I–VII), lysosomal acid lipase deficiency, GM1 gangliosidosis type I, galactosialidosis, and saposin C deficiency (1). In our study, patients presenting with HSM were diagnosed with Gaucher, ASMD, NPC disease, MPS II, and GM1 gangliosidosis. Many LSDs associated with organomegaly may show liver function tests within normal limits, and therefore normal biochemical results do not exclude these disorders (12). In our study, ALT and AST levels were normal in patients diagnosed with Gaucher disease, GM1 gangliosidosis, and MPS, and mild elevations were also noted in those with ASMD and NPC. In both Gaucher disease and ASMD, splenomegaly is frequently

accompanied by thrombocytopenia and other cytopenias. In our cohort, all six patients who presented with HSM and were diagnosed with Gaucher disease had thrombocytopenia and anemia. Similarly, both patients diagnosed with ASMD exhibited thrombocytopenia and anemia. Therefore, in these two disease groups, the presence of cytopenia alongside visceromegaly should be considered an important diagnostic clue (13). In addition, dyslipidemia, including decreased HDL cholesterol levels and hypertriglyceridemia, is reported in patients with ASMD (14). In our patients, low HDL cholesterol levels were detected in all cases, and elevated triglyceride levels were present in two. Enzyme replacement therapy (ERT) is currently used for the treatment of both Gaucher disease and ASMD. In Gaucher disease, ERT has been available for many years and provides highly favorable clinical outcomes. In contrast, prior to 2022, treatment for ASMD was limited to supportive care; currently, ERT demonstrates promising results, which is supported by numerous recent studies (15-19). Therefore, early recognition and diagnosis are critically important for patients with both Gaucher disease and ASMD. NPC is another lysosomal storage disorder that may present with hepatomegaly and is characterized by developmental delay, supranuclear gaze palsy, seizures and in later stages, psychosis, and cognitive decline (20,21). In our cohort, the patient diagnosed with NPC demonstrated supranuclear gaze limitation, developmental delay, and seizures. Thus, awareness that hepatomegaly in NPC is often accompanied by neurological manifestations is essential for timely recognition and accurate diagnosis. The other two lysosomal storage disorders associated with neurological findings in our cohort were GM1 gangliosidosis and MPS II with a neuropathic phenotype. GM1 gangliosidosis is characterized by psychomotor regression, hepatosplenomegaly, extensive Mongolian spots, coarse facial features, retinal cherry-red spot, and skeletal abnormalities (22). In the presented GM1 gangliosidosis case, coarse facial features, intellectual disability, and the presence of a cherry-red spot on fundoscopic examination were key findings that supported the differential diagnosis. Although isolated AST elevation has been reported in some neurodegenerative and lysosomal storage disorders, liver transaminase levels were within normal limits in our patient with GM1 gangliosidosis (23,24). In the MPS II case, coarse facial features, developmental delay, dysostosis multiplex evident on radiologic imaging, and increased urinary glycosaminoglycans were important for establishing the diagnosis.

Hereditary fructose intolerance (HFI) is another IEM that can lead to hepatomegaly. Clinical manifestations of HFI typically include hepatic dysfunction, hypoglycemia, lactic acidosis, proximal renal tubulopathy, hypophosphatemia, and growth delay (25). Symptoms occur after dietary exposure to fructose, and aversion to sugar-containing foods is frequently reported in affected patients (26). Symptoms occur after dietary exposure to fructose. In our patient, referral was prompted by hepatomegaly and elevated liver function tests. The presence of hypoglycemia, metabolic acidosis, elevated lactate levels, and avoidance of fructose-containing foods supported the diagnosis. Another patient in our cohort who presented with hepatomegaly was diagnosed with galactosemia. Clinical features often include cholestatic jaundice, hepatomegaly, vomiting, feeding intolerance, hypoglycemia, and, if untreated, progression to hepatic failure (27). Direct (conjugated) hyperbilirubinemia is an important clinical clue in many inherited metabolic disorders, including galactosemia. In our patient, the presence of hepatomegaly together with elevated liver enzymes, direct hyperbilirubinemia, and cataract prompted further metabolic evaluation, ultimately leading to the diagnosis of galactosemia. Early recognition is crucial, as prompt initiation of a galactose-restricted diet can prevent life-threatening complications and improve outcomes.

Limitations

The main limitations of this study include its retrospective and single-center design, potential selection bias due to referral to a tertiary care center, and the limited sample size of individual disease subgroups.

Conclusion

Hepatomegaly and/or splenomegaly are common clinical findings with a broad differential diagnosis, in which metabolic disorders represent an important etiology. Our cohort highlights that normal liver function tests do not exclude metabolic etiologies and that associated features such as cytopenias, neurological manifestations, hypoglycemia, metabolic acidosis, cholestasis, and feeding intolerance can provide essential diagnostic clues. Early recognition and timely metabolic evaluation are crucial. Targeted or dietary interventions can significantly improve clinical outcomes. Increased clinician awareness of these diverse presentations is therefore critical for achieving prompt diagnosis and optimizing patient management.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Adana City Training and Research Hospital (23.10.2025, reference number: 783).

Contribution of the authors

EB: drafted and wrote the manuscript, MYÇ: contributed to data collection and manuscript editing. BK: performed the statistical analysis and assisted with data interpretation. All authors read and approved the final version.

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The authors declare that there is no conflict of interest.

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Original Article

From stomach to liver: The impact of *Helicobacter pylori* gastritis on pediatric hepatic steatosis

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ABSTRACT

Objective: The purpose of our study was to examine the association between endoscopically diagnosed *Helicobacter pylori* (HP) gastritis and hepatosteatosis, and to investigate the correlation between the presence of HP and biochemical and anthropometric measurements in children.

Materials and Methods: Patients who were followed up in the Pediatric Gastroenterology outpatient clinic of Kayseri City Training and Research Hospital and underwent esophagogastroduodenoscopy performed by the attending gastroenterologist were evaluated. Patients aged between 2 and 18 years, with a histopathological diagnosis of gastritis, both HP positive and negative, were enrolled in the study.

Results: In patients with HP-positive gastritis, the incidence of hepatosteatosis was found to be statistically significantly higher compared to those with HP-negative gastritis ($\chi^2 = 22.704$; $p < 0.001$). A statistically significant weak positive correlation was found between the density of HP and the grade of hepatosteatosis (rho = 0.344; $p < 0.001$).

Conclusion: The HP-positive gastritis in children is associated with the development of hepatosteatosis, and the higher grade of hepatosteatosis in patients with HP-positive gastritis suggests that HP gastritis may impact the development of fatty liver.

Keywords: Children, gastritis, *Helicobacter pylori*, hepatosteatosis

Introduction

Helicobacter pylori (HP) is a gram-negative bacillus that infects more than half of the world's population. It plays a role in the development of important gastroduodenal diseases such as peptic ulcer, gastric mucosa-associated lymphoid tissue lymphoma, and gastric adenocarcinoma (1). Children are most commonly infected with HP during preschool (2). A systematic meta-analysis examining the global prevalence of HP infection in children and associated risk factors reported that HP infection is present in 32.3% of children worldwide, reflecting differences according to the diagnostic methodologies used (3). Moreover, recent evidence suggests that the effects of HP are not limited to the gastrointestinal tract but may also modulate both the development and clinical course of several extragastric diseases (4). Particularly in gastrointestinal diseases, significant associations have been reported between HP positivity and conditions such as gastroesophageal reflux disease, inflammatory bowel disease, non-alcoholic fatty liver disease, and cholelithiasis in adulthood (5). On the contrary, very few studies have examined this relationship in the childhood age group. It has been reported that HP infection should be considered in the investigation of the causes of chronic immune thrombocytopenic purpura in childhood (6). A recent meta-analysis reported that HP infection in children is associated with growth retardation and may be specifically linked to height-for-age scores (7).

Childhood fatty liver disease is increasingly prevalent worldwide. Fatty liver disease that begins at an early age can progress to steatohepatitis, fibrosis, cirrhosis, and even hepatocellular carcinoma in later years. Therefore, early detection of hepatosteatosis and identification of associated risk factors are crucial for preventing long-term metabolic complications and progressive liver damage (8).

Various mechanisms have been proposed in the literature to suggest that HP may be implicated in the development of hepatosteatosis. These mechanisms suggest that HP may reach the liver via the bile and trigger a local inflammatory response (9). Infection-induced proinflammatory cytokines such as C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α) may contribute to the development of insulin resistance (10). Furthermore, HP infection may facilitate hepatic steatosis by decreasing adiponectin levels, which is known to inhibit fatty acid accumulation in the liver (11). Indeed, a meta-analysis of 21 studies found a significant and positive association between HP infection and hepatosteatosis. However, none of the studies included in this meta-analysis evaluated the pediatric age group (12).

The limited data available to evaluate the relationship between HP infection and hepatosteatosis in children necessitated the conduct of this study. The primary aim was to compare the presence and degree of hepatosteatosis in children with HP-positive and HP-negative gastritis and to evaluate a possible relationship. Secondly, this research was conducted to examine the relationships between HP colonization density and the degree of hepatosteatosis and selected clinical, laboratory, and anthropometric variables. This approach aimed to contribute to a better understanding of the relationship between HP infection and hepatosteatosis in childhood.

Materials and Methods

This retrospective observational study included 272 patients who underwent esophagogastroduodenoscopy between April 2024 and May 2025 and were diagnosed with gastritis based on histopathological findings. Endoscopic procedures were performed by the responsible investigator, and ultrasonographic examinations were performed by radiologists; this information was obtained from medical records.

The presence of HP gastritis was determined by reviewing the patients' endoscopy and histopathology reports. The presence of HP in the antral biopsy samples was evaluated based on Giemsa staining and scoring. In determining the severity of HP-associated gastric inflammation, bacterial density was assessed semi-quantitatively according to the amount of microorganisms observed on the mucosal surface and was graded from mild to severe as +1, +2, and +3, which were expressed as a score reflecting HP colonization density. Patients with gastritis without HP constituted the HP-negative gastritis group.

In patients with hepatosteatosis, other secondary causes of hepatic steatosis, including endocrine disorders, metabolic abnormalities, viral hepatitis, drug-induced liver damage, and genetic/metabolic liver diseases were evaluated and excluded. The grade of hepatosteatosis was assessed using liver ultrasonography findings from the same patients. Patients were evaluated as having Grade 1 (mild), Grade 2 (moderate) and Grade 3 (severe) hepatosteatosis based on the increase of liver parenchymal echogenicity (13). Biochemical parameters and anthropometric measurements were also obtained from patient records.

Statistical analysis

Data were evaluated using the IBM Statistical Package for the Social Sciences, version 22.0 (SPSS Inc., Armonk, NY, IBM Corp., USA). Descriptive statistics are presented as number (n) and percentage (%) for categorical variables, and as mean and standard deviation and median and minimum–maximum values for continuous variables. The normality of continuous variables was evaluated by examining the skewness and kurtosis coefficients; values within the range of ±1.5 were considered as an indicator of approximately normal distribution. The chi-square test was used to compare categorical variables including the presence of HP-positive gastritis according to the presence of hepatosteatosis. Associations between the grade of hepatosteatosis and continuous variables were evaluated using Spearman correlation coefficient. Binary logistic regression analysis was applied to examine the variables associated with the presence of hepatosteatosis; the results were reported with odds ratio (ORs) and 95% confidence interval. Variables included in the logistic regression models were selected based on clinical relevance and prior evidence from the literature. In addition, variables showing an association with hepatosteatosis in univariate analyses were considered for inclusion in the multivariate models. Model fit was evaluated using Cox and Snell and Nagelkerke R^2 values. The statistical significance level was accepted as $p < 0.050$.

Results

The study included 272 patients. Of the patients, 173 were female (63.6%). The mean age of study group was 13±3.9 years. HP-positive gastritis were statistically higher in females than in males. Histopathological examinations showed the HP-positive gastritis in 47.5% of all patients (n= 29). Of these, 57 showed mild, 31 had moderate, and 41 had severe HP colonization density. Hepatosteatosis was detected in 13.6% of all patients (n=37); of these cases, hepatic steatosis was graded as mild in 19 patients, moderate in 14 patients, and severe in 4 patients. Among the patients with HP-positive gastritis, 31 patients had hepatic steatosis, corresponding to 24% of this group. Descriptive characteristics of the cohort are displayed in Table I.

When the relationships between the degree ofx hepatosteatosis and independent variables were examined, a moderately positive and statistically significant correlation was found between the degree of HP colonization density and the grade of hepatosteatosis (rho =0.344; p<0.001). A weak but statistically significant positive correlation was found between AST and hepatosteatosis grade (rho =0.205; p=0.001), whereas no significant correlation was observed between ALT levels and hepatosteatosis grade (rho= 0.119; p=0.077). A weak but statistically significant positive correlation was also found between the ESR and the grade of hepatosteatosis (rho=0.205; p<0.001). The relationship between BMI-SD and the grade of hepatosteatosis was found to be moderately positive (r =0.334; p<0.001). These findings suggest that the grade of hepatosteatosis varies with BMI-SD and HP colonization density (Table II). There was a weakly negative correlation between the HP-positive gastritis and CRP

Table I: Demographic and clinical characteristics of the study population

Variables	Descriptive Statistics
Gender*	
Female	173 (63.6)
Male	99 (36.4)
Age (years)†	13.0±3.9
Hemoglobin (g/dl)†	13.61±1.71
Albumin (g/dl)†	4.71±0.27
Platelet (×10³/μL)‡	315 (158–646)
White blood cell (×10³/μL)‡	7.18 (4.14–22.31)
AST (U/L)‡	18 (9–61)
ALT (U/L)‡	13(5–108)
CRP (mg/dl)‡	4.7 (3.9–5.6)
ESR (mm/h)‡	4 (1–42)
BMI (SD)‡	–0.31 (–3.54–3.23)
Endoscopic Findings of Esophagus*	
Normal	201 (73.9)
Hyperemia	71 (26.1)
Endoscopic Findings of Antrum*	
Normal	115 (42.3)
Hyperemia	135 (49.6)
Ulcer	13 (4.8)
Nodularity	9 (3.3)
Endoscopic Findings of Duodenum*	
Normal	220 (80.9)
Hyperemia	46 (16.9)
Ulcer	5 (1.8)
Cobblestone appearance	1 (0.4)
Histopathologic Findings of Esophagus*	
Normal	150 (55.1)
Esophagitis	118 (43.4)
Eosinophilic esophagitis	4 (1.5)
Histopathologic Findings of Antrum*	
Lymphoplasmacytic infiltration	119 (43.8)
Chronic inflammation	58 (21.3)
Active inflammation and epithelial erosion	50 (18.4)
Active inflammation	45 (16.5)
Histopathologic Findings of Duodenum*	
Normal	247 (90.8)
Duodenitis	23 (8.5)
Villous atrophy	2 (0.7)

***: n(%), †: mean±SD, ‡: median (min–max), **ALT:** Alanine aminotransferase, **AST:** Aspartate aminotransferase, **BMI:** Body mass index, **CRP:** C-reactive protein, **ESR:** Erythrocyte Sedimentation Rate*

(rho=–0.180 p=0.006), and ESR (rho= –0.138 p=0.045). There was no correlation between the presence of HP and BMI-SD.

On the other hand, the hepatosteatosis was statistically higher in patients with HP-positive gastritis compared to patients with HP-negative gastritis (Table III).

In the logistic regression analysis conducted to evaluate factors associated with the presence of hepatosteatosis, metabolic and laboratory variables were included in the first model. In this model, only BMI SDS was found to be statistically significantly associated with the presence of hepatosteatosis, with a one-unit increase in BMI-SD approximately doubling the probability of hepatosteatosis (OR=2.13; 95% CI: 1.48–3.07; p<0.001). No statistically significant relationship was found between AST, ALT, and

Table II: Correlations between hepatosteatosis grade and independent variables

Variables	rho	p*
Hp colonization density (score)	0.344	0.001
Age	0.000	0.994
Hemoglobin	0.060	0.323
Platelet	–0.005	0.940
White blood cell	0.087	0.154
AST	0.205	0.001
ALT	0.119	0.077
Albumin	–0.019	0.756
CRP	0.074	0.266
ESR	0.205	0.001
BMI-SD	0.334	0.001

***: Spearman rank correlation analysis. **ALT:** Alanine aminotransferase, **AST:** Aspartate aminotransferase, **BMI:** Body mass index, **CRP:** C-reactive protein, **ESR:** Erythrocyte Sedimentation Rate*

Table III: Comparison of groups based on the presence of hepatosteatosis

	Hepatosteatosis*		χ^2	p‡
	Absent	Present		
Gastritis				
HP-Negative	137 (58.3)	6 (16.2)	22.704	<0.001
HP-Positive	98 (41.7)	31 (83.8)		

***: n(%), ‡: Chi-square test*

ESR levels and the presence of hepatosteatosis. In the second model, when HP-positive gastritis was added, the association between BMI-SD and hepatosteatosis was maintained, while HP-positive gastritis was also found to be significantly associated with the presence of hepatosteatosis (OR = 9.81; 95% CI: 3.32–28.99; p < 0.001). It was observed that adding the HP variable to the model improved model fit and increased the Nagelkerke R^2 value (Table IV).

Discussion

This study indicates that hepatosteatosis may accompany HP-positive gastritis in childhood and emphasizes that HP may contribute to the pathogenesis of fatty liver. The objective of this research was to contribute to the literature by demonstrating the relationship between HP and HS in children.

HP is generally asymptomatic in childhood. Current pediatric data and meta-analysis results report that HP gastritis occurs at similar rates in girls and boys (3). In contrast, the rate of HP gastritis was higher in girls at 63.6%. The risk of developing gastric or duodenal ulcers due to HP reported in the pediatric data ranges from 0.4% to 12% (14). In our study, ulcers were observed in less than 5% of patients. The ESPGHAN guidelines for HP screening recommend testing only in children with suspected gastric or duodenal ulcers presenting with complaints such as epigastric pain, weight loss, and loss of appetite (15).

While the long-term development of ulcers or gastric cancer depends on the extent of the persistence of the infection, the risk of malignancy associated HP in childhood is considered to be quite low (16,17). HP initiates primary gastric adenocarcinoma by direct contact with the gastric epithelium

Table IV: Factors influencing the presence of hepatosteatosis

	B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
					Lower	Upper
Model 1						
AST	0.030	0.032	0.350	1.031	0.967	1.098
ALT	–0.009	0.027	0.742	0.991	0.939	1.046
ESR	–0.012	0.031	0.710	0.988	0.930	1.051
BMI-SD	0.757	0.186	0.001	2.132	1.479	3.073
Constant	–2.490	0.606	0.001	0.083	-	-
Model 2						
AST	0.046	0.035	0.193	1.047	0.977	1.122
ALT	–0.019	0.029	0.496	0.981	0.927	1.037
ESR	–0.003	0.039	0.944	0.997	0.925	1.076
BMI-SD	0.778	0.194	0.001	2.177	1.487	3.186
HP-positive gastritis	2.283	0.553	0.001	9.810	3.320	28.987
Constant	–3.034	0.726	0.001	0.048	-	-

ALT: *Alanine aminotransferase,* ***AST:*** *Aspartate aminotransferase,* ***BMI-SD:*** *Body mass index standard deviation score,* ***ESR:*** *Erythrocyte sedimentation rate,* ***HP:*** *Helicobacter pylori,* ***B:*** *Regression coefficient,* ***S.E:*** *Standard error,* ***Exp(B):*** *Odds ratio,* ***CI:*** *Confidence interval. Model fit was evaluated using Cox and Snell and Nagelkerke R^2 values. Model 1: Cox ve Snell R Square = 0.116; Nagelkerke R Square = 0.205, Model 2: Cox ve Snell R Square = 0.208; Nagelkerke R Square = 0.366*

and transmembrane translocation. Immune cell infiltration triggered by the microorganism induces proinflammatory cytokines, and chronic inflammation leads to the production of reactive oxygen species, cellular damage, and ultimately, carcinogenesis (18). Beyond well-known gastric effects of HP, the association between HP and various systemic diseases is increasingly being reported (19). Among all these, iron deficiency anemia is the most widely recognized; its prevalence occurs at a high rate in adolescents with HP-positive gastritis compared to adolescents with HP-negative gastritis (20). Furthermore, Type 1 Diabetes Mellitus, atherosclerosis, and pernicious anemia have also been found to be associated with HP (21,22). Studies based on pathogenetic mechanisms have reported that HP induces chronic systemic inflammation by stimulating T and B cells, macrophages, and other inflammatory mediators (23). Furthermore, HP treatment has been shown to reduce IgE, IL-4, and IL-13 levels and to increase IFN-γ and IL-10 levels, producing a potential anti-inflammatory effect (24).

Literature generally reports an increased correlation between HP infection and inflammatory parameters such as ESR and CRP (25,26). However, in our study, a weak and negative correlation was found between HP gastritis and CRP and ESR. This difference is thought to be related to the fact that HP infection in childhood mostly presents with a local and low-grade inflammatory response, and non-significant systemic acute phase response.

A weak symptom-disease severity correlation has been emphasized in the literature, HP colonization density and inflammation severity are considered to indicate the clinical presentation (16,27). Due to an insufficient number of patients regarding HP density, patients could not be evaluated according to the presence and severity of HP symptoms. In addition to the gastointestinal outcomes, HP may also be linked with under-recognized systemic implications, including hepatic inflammation, especially in pediatric patients where information is scarce. Fatty liver disease is a type of liver damage caused by metabolic stress. While numerous research from Asia have proposed that HP could be an individual contributor for fatty liver, others have not supported this relationship (28,29).

Previous studies have shown that the relationship between HP infection and hepatosteatosis may be associated with obesity and metabolic dysfunction (30). However, studies in the pediatric population report that HP infection may be associated with fatty liver disease independently of obesity and may be considered a potential risk factor (31). In our study, HP presence was related to hepatosteatosis, and increased HP positivity associated with a greater hepatosteatosis severity. Although an association was observed, its clinical implications appear modest and should be interpreted cautiously. The persistence of the association observed between HP-positive gastritis and hepatosteatosis after adjusting for BMI-SD in our study suggests that HP infection may contribute to hepatic steatosis through mechanisms beyond just fat accumulation, possibly via chronic low-grade inflammation and metabolic dysregulation, as previously suggested in pediatric and adult studies (9-11,19,28). This result suggests that HP may have a negative impact on liver health. However, the variable virulence of HP strains as well as host genetic predisposition also influence clinical outcomes (15). The virulence factors of HP strains and metabolic markers associated with hepatosteatosis were not evaluated. More comprehensive studies may reveal a link between hepatosteatosis and strain and host characteristics.

In the population we studied, no association was observed between BMI-SD and HP positivity. This supports the notion that hepatosteatosis was not largely mediated by obesity, indicating the plausibility of an HP-related link. Consistent with this, earlier research has also showed no association between overweight status or obesity and HP infection (32). Our study showed that BMI-SD was one of the strongest factors associated with the hepatosteatosis. However, it is noteworthy that HP-positive gastritis also occurs together with hepatosteatosis, and this relationship cannot be explained solely by BMI. The inclusion of HP positivity in the evaluation allowed for a more comprehensive consideration of the possible determinants of hepatosteatosis and suggested that HP infection may have an independent contribution to the hepatosteatosis process. This indicates

that HP gastritis may play a role in the development of hepatosteatosis through non-obesity mechanisms.

Emerging evidence suggests that HP infection may be associated with a growing number of extragastric pathologies. However, these pathologies do not typically manifest in childhood and may be influenced by various factors, such as age, gender, race, and geographic location. Therefore, large-scale, multicenter research is warranted to elucidate the role of extragastric manifestations, such as liver disease, in the pathogenesis of these conditions.

Strengths of this study include its focus on a childhood patient group, the grading of hepatosteatosis, the largely elimination of the influence of obesity, and the use of multifaceted clinical and histopathological data. Furthermore, demonstrating a relationship between HP colonization and the severity of hepatosteatosis increases the biological consistency supporting the possible metabolic effects of bacterial infection. The single-center, retrospective design of our research limited comprehensive evaluation of clinical symptoms and the identification of a causal association.

Limitations

The main limitations of this study include its retrospective design and the fact that hepatosteatosis was evaluated solely by ultrasonography. Due to the retrospective nature of the study, the inability to ensure imaging standardization, inter-observer agreement, and blinding conditions may have limited the reliability of hepatosteatosis grading.

Furthermore, this study does not allow for determining whether HP gastritis occurs before or after the development of hepatosteatosis. Accordingly, the findings only show a correlation between HP gastritis and hepatosteatosis, not a causal or temporal relationship.

Conclusion

This study highlights the relationship between HP gastritis and hepatosteatosis in childhood, demonstrating that the potential extragastric effects of HP infection should not be overlooked. The findings suggest that HP-positive gastritis may be associated with hepatosteatosis, even in children without metabolic risk factors. Therefore, hepatic health should also be monitored in patients with HP-positive gastritis who have gastric complaints. However, as the findings reflect an association rather than a causal relationship, prospective and longitudinal studies are needed to elucidate the potential effects of HP eradication on hepatosteatosis and to clarify the temporal aspects of this relationship.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Kayseri City Training and Research Hospital (15.04.2025, reference number: 407).

Contribution of the authors

Study conception and design: BDS, EZE; data collection: BDS, EZE; analysis and interpretation of results: BDS; draft manuscript preparation: BDS, EZE. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Turkish Journal of Pediatric Disease

Case Report

Recurrent isolated torsion of fallopian tube in premenarcheal 12-year-old girl

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ABSTRACT

Isolated torsion of the fallopian tube is an uncommon event. It is a difficult condition to evaluate clinically and surgery is often necessary to establish the diagnosis. In this case report, a 12 year old female isolated fallopian tube torsion (ITT) -a rare condition in the pediatric age group requiring laparoscopic surgery due to recurrance- is presented with acute pelvic pain, nausea, and vomiting. A diagnostic laparoscopy was performed which confirmed the diagnosis of isolated tubal torsion. Based on this experience as well as other similar reported cases, isolated torsion of the fallopian tube should beconsidered in the differential diagnosis of acute lower abdominal/pelvic pain in the female patient. Prompt surgical intervention may allow for preservation of the tube.

Keywords: Adolescent, fallopian tube, laparoscopy, torsion

Introduction

Isolated tubal torsion is a very rare cause of acute abdomen, and the majority of reported cases are in adult women of reproductive age (1). The incidence of isolated tubal torsion is thought to be 1 in 1.5 million women and considerably less common in the pediatric and adolescent population (2). Tubal torsion is a pathology whose cause has not been determined precisely. It is very rare in the pediatric age group and is difficult to evaluate clinically (2). The available literature regarding the pediatric age group consists almost entirely of case reports.

The clinical presentation is usually sudden onset of nonspecific abdominal pain accompanied by nausea and vomiting. There is ongoing debate in the literature regarding its treatment (3). In this case report, an isolated fallopian tube torsion (ITT) -a rare condition in the pediatric age group requiring laparoscopic surgery due to recurrance- is presented and discussed in light of the current literature.

Case Reports

A 12-year-old female patient was admitted to our emergency department with a one-month history of intermittent groin pain,which had acutely worsened over the past 24 hours. The patient's pain continued intermittently in the right lower quadrant. The patient, who had Covid-19 a month ago, has no additional disease. On her physical examination, there was no defense or rebound, but there was tenderness in the right adnexal area. The patient's vital signs were stable, and hemogram, biochemical tests, tumor markers, acute phase reactant and urinalysis, and standing direct abdominal X-ray were normal. Transabdominal and pelvic doppler ultrasonografi revealed that the uterus was of normal size, and there was folded tubular tissue adjacent to the right ovary, reaching 2 cm at its widest point (Hydrosalpinx?). The patient underwent a pelvic magnetic resonance (MRI) examination due to suspicion of an adnexal mass. MRI imaging demonstrated an intertwined configuration of tubular structures near the right ovary,which was considered suspicious for torsion or semitorsion (Figure 1).

The patient was given a preliminary diagnosis of ovarian torsion and tubal torsion, and a decision was made to perform diagnostic laparoscopy. After pneumoperitoneum was established, the uterus was observed to be normal. The left fallopian tube and ovary were normal in structure. The right ovary was larger than the left, but its blood supply was normal. The right fallopian tube was found to be torsed in an isolated manner, having twisted once around its own axis. It appeared

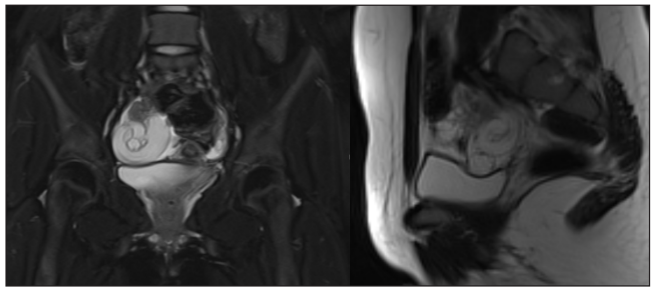

Figure 1: There is tortuous appearance and dilatation in the right fallopian tube on coronal and sagittal T2A images.

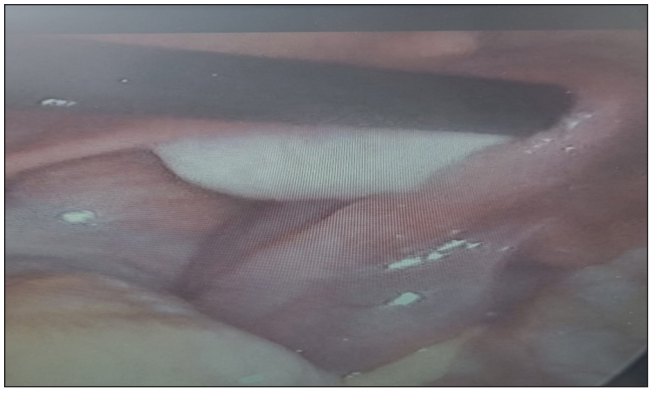

Figure 2: Return of blood flow to normal after detorsion

edematous,with relatively preserved vascularity. The tube was detorsioned laparoscopically, and after the detorsion procedure, the color change in the tube returned to normal (Figure 2). The right fallopian tube was fixed to the pelvic side wall. There was reactive fluid in the pelvis. A sample was taken for cytology. The patient who had no complications in the early postoperative period, was discharged with a recommendation for outpatient follow-up on the postoperative day 3. During follow-up,no clinical issues were observed. Cytological evaluation revealed histiocytes,and a few degenerated mesothelial cells. Control ultrasonography showed no significant findings apart from postoperative changes.

Three months after the first operation, the patient presented to our emergency department again with complaints of groin pain and vomiting that started suddenly approximately 4 hours ago and gradually became more severe. There was a history of Covid-19 exposure two weeks ago. There were signs of influenza infection at that time. However, the Covid-19 test result was negative. On her physical examination, there was significant tenderness, defense, and rebound in the right lower quadrant. Transabdominal and pelvic doppler USG revealed several thin-walled anechoic follicles in the right ovary, the largest of which was 17 mm in diameter. A tubular appearance measuring 29*12 mm was observed in the right adnexal area and was initially evaluated as residual hydrosalpinx. It was thought that the torsion might have recurred in the patient who had a previous surgery history and a decision for urgent exploration was made. The patient underwent laparoscopy with a preliminary diagnosis of acute abdomen. After pneumoperitoneum was established, the uterus was observed to be normal. The left fallopian tube and bilateral ovaries were normal. The right tube

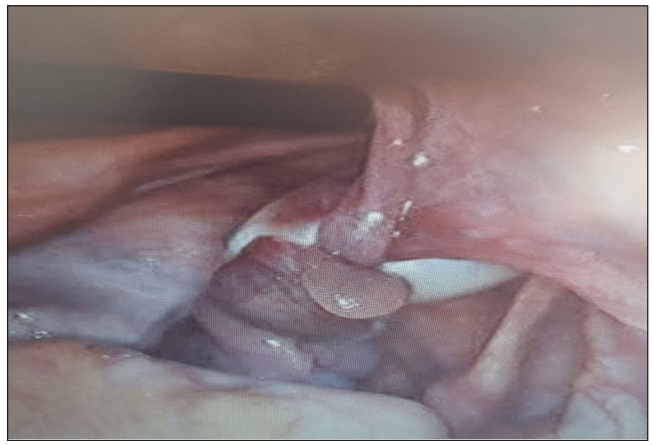

Figure 3: Isolated fallopian tube torsion

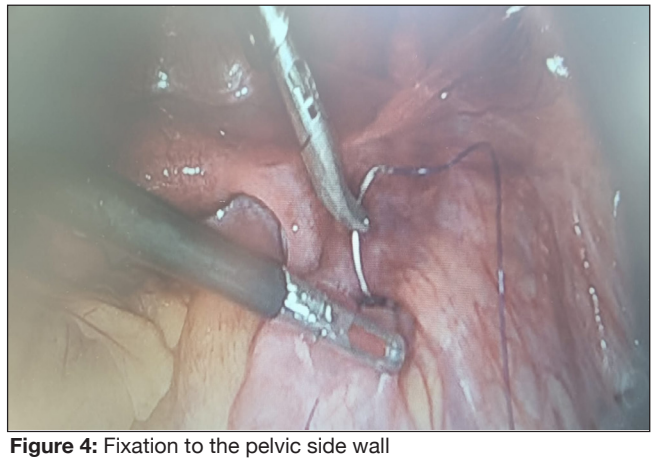

Figure 4: Fixation to the pelvic side wall

was torsioned around itself twice in an isolated manner, and appeared edematous and gangrenous (Figure 3). The tube was detorsioned laparoscopically, and after the detorsion procedure, the color change in the tube returned to normal. The right tube was fixed to the pelvic side wall at 3 points (Figure 4). There was reactive fluid in the pelvis. A sample was taken for cytology. The patient had no complications in the early postoperative period. On postoperative day 3, Pelvic Doppler ultrasonography revealed a detorsioned fallopian tube, Pelvic Doppler Ultrasonography evaluation demonstrated focal millimetric vascularization in the tubal wall.The patient was discharged after being advised to undergo outpatient clinic follow-up. The patient had no problems in her follow-ups, and her cytology result was “Degenerated mesothelial cells.” The patient is being followed up clinically without any problems in the 2nd year of her second surgery.

Discussion

The exact cause of isolated fallopian tubal torsion is unknown. It has been reported that it may be caused by certain pathologies, especially in adult patients. These pathologies include hydrosalpinx, previous intra-abdominal surgeries, adhesions due to tuberculosis or primary peritonitis, ectopic pregnancy, endometriosis, and some acquired or congenital anatomical anomalies related to the tubes and adnexa (3). However, no factor that may cause it before the reproductive period has been reported (3,4).

The incidence of isolated tubal torsion is reported to be approximately 1/1.5. The majority of reported cases are in adult women of reproductive age (4). Because the clinical findings of isolated fallopian tubal torsion are nonspecific, it is often difficult to distinguish it from other causes of acute abdomen. The first clinical symptom is sudden onset of severe abdominal pain in the lower quadrant of the abdomen. The pain typically intensifies within a few hours and continues intermittently. Although it may radiate to the flank and the pelvic region, it is usually localized to the side of the torsion. Pain may often be accompanied by nausea and vomiting (5). In such cases, ovarian torsion and distal ureteral stone should also be considered in the differential diagnosis. Likewise, there are no characteristic laboratory and imaging findings. However, the absence of fever and normal C-reactive protein levels in these patients should be kept in mind, especially when differentiating them from infective causes of acute abdomen (5,6).

Pelvic doppler ultrasonography may be helpful in preoperative diagnosis, but torsion should not be excluded based on pelvic doppler USG. Computed Tomography or Magnetic Resonance imaging may be helpful in diagnosis in complicated cases or incomplete or chronic torsion cases (6). As Isolated tubal torsion is predominantly involves on the right side (in nearly two-thirds of cases), it should be considered in the differential diagnosis of acute abdomen in female pediatric patients,especially when acute appendicitis is suspected (7). Because if the diagnosis and treatment of fallopian tubal torsion is delayed, organ loss and infertility may occur (8).

Although our patient's complaints were quite vague at her first presentation, she had sudden onset and severe progressive abdominal pain at her second presentation. Tenderness, guarding, and rebound were also evident on her physical examination. Since pelvic doppler usg did not yield definitive results when our patient first presented, MRI was performed to distinguish it from adnexal masses. On the second visit, the patient had a history of tubal torsion, so in order not to waste time, a pelvic USG was performed and an emergency laparoscopy decision was made. Laparoscopy revealed recurrence of tubal torsion. The dissolution of the fixation sutures (vicryl) was considered as the cause of the torsion. Therefore, in the second operation, fixations were made with prolene after detorsion.

The treatment of isolated fallopian tube torsion requires early surgical intervention to preserve the fallopian tube and future fertility (9). Laparoscopic detorsion of the tube is often the first choice for treatment in adolescent patients. In cases such as semi-torsion or early blood flow after detorsion, the fallopian tube can be preserved. If blood flow cannot be achieved in the fallopian tube, salpingectomy is performed (10). In our patient, detorsion and fixation was preferred in both operations because early tubal blood flow was achieved after detorsion.

Conclusion

In female pediatric patients, isolated tubal torsion is a rare and diagnostically challenging condition of uncertain etiology,often presenting with nonspecific clinical and laboratory findings.Delayed diagnosis and treatment may lead to tubal necrosis and potential infertility. It should be considered in patients presenting with acute abdominal symptoms, and early laparoscopic detorsion should be performed for treatment. To prevent recurrence, the fallopian tube should be fixed to the pelvic sidewall with nonabsorbable sutures.

Contribution of the authors

Study conception and design: FTG ; data collection: FTG, SY; analysis and interpretation of results: FTG, SY, ZAY,HNK; draft manuscript preparation: FTG, Zİ. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Review Article

RAS/MAPK Pathway and RASopathies

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ABSTRACT

The RAS/Mitogen-Activated Protein Kinase (MAPK) pathway is a core developmental signaling cascade that regulates proliferation, differentiation, survival, and tissue growth across multiple organ systems. Germline dysregulation of this pathway results in RASopathies. Although the causal variants affect different components of the pathway, they converge on abnormal downstream signaling. This explains why these disorders share a recognizable clinical core despite clear syndrome-specific differences. The most prevalent and well-known entity is Noonan syndrome, while other major subtypes include cardiofaciocutaneous syndrome, Costello syndrome, and Noonan syndrome with multiple lentigines.

RASopathies are characterized by distinctive craniofacial features and multisystem involvement. Congenital heart disease is a significant cause of morbidity. Neurodevelopmental difficulties are common across the spectrum and may be particularly pronounced in Cardiofaciocutaneous and Costello syndromes. Short stature, pectus anomalies, scoliosis, and other musculoskeletal findings are also recurrent features. Another important concern is the malignancy risk, which varies significantly by genotype.

Although these disorders share a common pathway, genotype-phenotype correlations are increasingly relevant in daily practice. Molecular findings now directly inform risk assessment and long-term follow-up. In parallel, early experience with pathway-directed therapies is beginning to influence the management of selected complications. MEK inhibitors have shown promising results in selected manifestations, particularly hypertrophic cardiomyopathy and refractory lymphatic complications.

In this review, we discuss the biological organization of the RAS/MAPK pathway and relate it to the clinical spectrum of RASopathies. We focus on shared and distinguishing phenotypic features, clinically relevant genotype-phenotype correlations, and the emerging role of targeted therapies.

Keywords: Genotype-Phenotype Correlation, Noonan syndrome, MAP Kinase Signaling System, RASopathies

Introduction

The RAS/MAPK pathway mediates the transmission of extracellular signals into intracellular responses that control key developmental processes. It regulates cell proliferation, differentiation, survival, and tissue growth across multiple organ systems. Precise regulation of this signaling is required for normal development and maintenance of tissue homeostasis (1–4).

The canonical pathway begins when cell surface receptors trigger RAS, initiating the RAF-MEK-ERK kinase cascade (Figure 1). ERK acts as the main downstream effector and phosphorylates multiple targets, which influences gene expression and cellular behavior (2,3,5). Cycling between active and inactive states, RAS proteins function as the pathway's molecular switches. This cycle is regulated by guanine nucleotide exchange factors and GTPase-activating proteins, which promote RAS activation and signal termination, respectively (1) (Figure 2). Efficient signaling relies on spatial organization at cellular membranes, where RAS and its regulators assemble with downstream effectors. This organization helps determine signaling specificity rather than simple pathway activation (1,3). Feedback mechanisms, phosphatases, and scaffold proteins further restrain signal strength and duration. Without these regulatory layers, identical stimuli could produce very different biological outcomes (2,3,6). Moreover, RAS/MAPK signaling is dynamic rather than static. Differences in the magnitude, duration, and timing of ERK activation can lead to distinct biological outcomes, even within the same cell type (2,5).

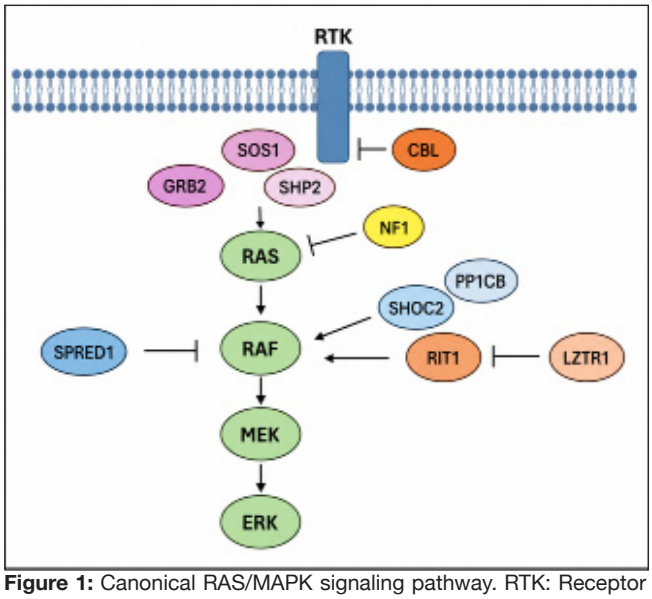

Figure 1: Canonical RAS/MAPK signaling pathway. RTK: Receptor Tyrosine Kinase

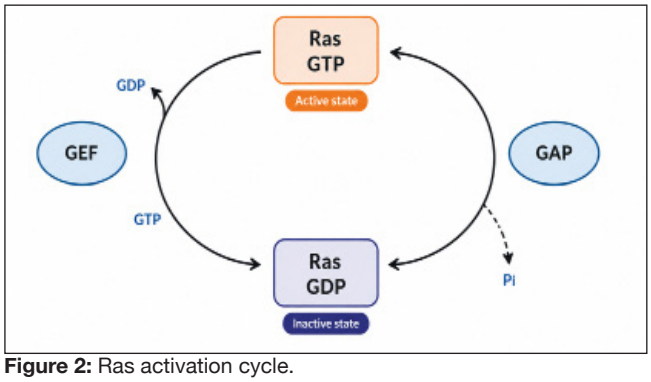

Figure 2: Ras activation cycle.

Accessory proteins contribute to the spatial and temporal organization of signaling components. Proteins such as scaffolds, adaptors, and other modulators, including SPRED1, SHOC2, and *CBL*, enable fine-tuning of RAS/MAPK signaling rather than simple on-off activation (Figure 1). They support graded and context-dependent responses during development and across different tissues (1,6). Disruption of the RAS/MAPK pathway changes normal developmental signaling and provides the molecular basis for a group of genetic disorders caused by germline pathway dysregulation (4,7).

RASopathies are a group of disorders that share overlapping features caused by germline pathogenic variants in genes that encode components or regulators of the RAS/MAPK pathway. These variants can affect different parts of the pathway, including upstream activators, core signaling proteins, or regulatory factors. These disorders are caused by dysregulated RAS/MAPK signaling, although the molecular consequences vary according to the affected gene and variant. Because the primary defect reflects dysregulated signaling rather than a single-gene effect, RASopathies are better viewed within a pathway-based framework (4,7,8). This perspective also provides a rationale for therapies that aim to modulate pathway activity (4).

RASopathies include Noonan syndrome (NS, MIM #163950), Cardiofaciocutaneous syndrome (CFCS, MIM #115150), Costello syndrome (CS, MIM #218040), Legius syndrome (LS, MIM #611431), Neurofibromatosis–Noonan syndrome (NF-NS, MIM #613113), Noonan syndrome with loose anagen hair (NS/LAH, MIM #607721), Noonan syndrome with multiple lentigines (NSML, previously LEOPARD syndrome, MIM #151100), Neurofibromatosis type 1 (*NF1*, MIM #162200), and several rarer related disorders (Table I). Clinically, these disorders are often discussed as core syndromic forms, neurocutaneous conditions, and less common related entities. This classification helps organize a phenotypically broad but mechanistically related group of conditions within the RAS/MAPK pathway spectrum (7,9). Although these disorders share overlapping clinical features, they arise from distinct molecular mechanisms affecting different parts of the pathway. Many disease-associated variants are missense changes that alter pathway output, often by increasing or prolonging signaling, particularly at the level of ERK activation. In contrast, loss-of-function mechanisms are central in specific conditions such as *NF1* and SPRED1-related disease. Variants in the same gene can lead to different clinical phenotypes depending on their type and functional impact within the pathway. This allelic heterogeneity explains both the overlap and the variable expressivity within individual syndromes, supporting a pathway-based classification rather than a strict one gene-one disease model (8,10,11).

In the following sections, we relate core RAS/MAPK biology to the clinical presentation of the major RASopathies, with particular emphasis on the syndromic forms most relevant to pediatric practice. We also review emerging pathway-directed treatments and consider their practical implications for long-term care.

Noonan Syndrome (NS)

As the most common RASopathy, Noonan syndrome (NS) is often considered the clinical prototype of this group (4,9). It is typically characterized by a recognizable facial appearance, short stature, and congenital heart disease, although expression is highly variable between individuals (10,12). Its estimated incidence is approximately 1 in 1 000-2 500 live births (8). Somatic oncogenic RAS pathway variants often drive strong and poorly controlled signaling. In contrast, germline variants associated with NS usually produce a milder but persistent disturbance of developmental signaling. This allows embryonic viability, but disrupts normal morphogenesis and tissue differentiation (7,10,13).

The genes most commonly associated with NS are summarized in Table I. Although they affect different nodes of the pathway, they converge on abnormal ERK signaling. Variants in *PTPN11* increase SHP2 activity and enhance RAS/MAPK pathway signaling (11). Building on this mechanism, gain-of-function variants in *SOS1* and *SOS2* promote RAS activation by increasing the amount of its active, GTP-bound form. Pathogenic variants in downstream signaling proteins such as *RAF1*, and less commonly *BRAF*, enhance signal propagation through the MEK–ERK cascade, whereas variants in RAS-family genes, including *KRAS*, *NRAS*, and *RIT1*, dysregulate upstream pathway activation through gene-specific mechanisms (7,13,14). Experimental data suggest that even modest increases in

Table I: Molecular mechanisms and key clinical domains of RASopathies

Disorder	Primary Pathway Node	Gene(s)	Molecular Mechanism	Typical Variant Effect	Key Clinical Domains	Therapeutic Implications
Noonan syndrome (NS)	Upstream signal transduction / pathway regulation	*PTPN11, SOS1, SOS2, RAF1, RIT1, KRAS, BRAF, LZTR1, NRAS, RRAS2, RASA2, SPRED2*	Abnormal upstream pathway activation or signal amplification	Predominantly gain-of-function or dysregulated activation	Craniofacial features, short stature, cardiac, and neurodevelopmental involvement	Potential responsiveness to pathway-modulating therapies; emerging interest in MEK inhibition and upstream signal modulation
Cardiofaciocutaneous syndrome (CFCS)	Core kinase cascade (RAF–MEK–ERK)	*BRAF, MAP2K1, MAP2K2, KRAS*	Constitutive activation of the RAF–MEK–ERK cascade	Gain-of-function	Severe neurodevelopmental impairment, epilepsy, characteristic ectodermal features, cardiac defects, growth failure	Strong rationale for downstream pathway inhibition; MEK inhibitors explored in severe or refractory cases
Costello syndrome (CS)	RAS activation	*HRAS*	Persistent HRAS activation due to impaired GTP hydrolysis	Gain-of-function	Failure to thrive, cardiomyopathy, characteristic ectodermal features, severe neurodevelopmental impairment, increased malignancy risk	Potential benefit from pathway modulation; careful balance required due to tumor predisposition
Neurofibromatosis type 1 (NF1)	Negative regulation of RAS	*NF1*	Loss of neurofibromin-mediated RAS-GAP activity resulting in increased RAS signaling	Loss-of-function	Cafe-au-lait macules, Lisch nodules, skeletal abnormalities, tumor predisposition	Established clinical use of MEK inhibitors for plexiform neurofibromas
Legius syndrome (LS)	Negative regulation of RAS	*SPRED1*	Impaired recruitment of neurofibromin to the membrane, leading to increased RAS/MAPK signaling	Loss-of-function	Café-au-lait macules, absence of tumor burden	Supportive management; emphasizes need for molecular distinction from NF1 to avoid unnecessary tumor surveillance
Noonan syndrome with multiple lentigines (NSML)	Signal modulation at SHP2 / RAF level	*PTPN11, RAF1, BRAF*	Altered phosphatase or kinase activity with paradoxical effects on downstream signaling	Dominant-negative or dysregulated signaling	Multiple lentigines, hypertrophic cardiomyopathy, growth delay, sensorineural hearing loss	Potential responsiveness to pathway modulation; cardiac phenotype guides surveillance and therapy
Noonan syndrome with loose anagen hair (NS/LAH)	Pathway scaffolding and signal flux control	*SHOC2, PPP1CB*	Aberrant pathway scaffolding causing increased and mislocalized MAPK signaling	Gain-of-function	Distinct hair anomalies, developmental delay, cardiac defects, growth failure	Highlights role of non-enzymatic regulators; supports upstream signal modulation strategies
CBL syndrome	Ubiquitin-mediated signal termination	*CBL*	Impaired ubiquitination and degradation of activated signaling complexes	Loss-of-function / dominant-negative	Developmental delay, immune dysregulation, predisposition to JMML-like myeloproliferation	Clinical focus on hematologic surveillance; pathway inhibition considered in selected proliferative phenotypes

ERK signaling can disturb developmental processes such as cell fate decisions and tissue patterning. This sensitivity may partly explain the multisystem involvement observed in NS (2,5,13).

The craniofacial phenotype of NS commonly includes hypertelorism, downslanting palpebral fissures, ptosis, low-set posteriorly rotated ears, and a broad or webbed neck. In infancy, these features may be subtle, becoming easier to recognize during early childhood. Growth retardation is common, with postnatal growth failure being more prominent than prenatal growth restriction. Many children present with feeding difficulties and failure to thrive in infancy, contributing to early growth impairment (12,15). Clinical diagnosis of NS is supported by diagnostic scoring systems that integrate facial features, cardiac defects, growth patterns, and family history (16) (Table II). With the widespread use of molecular testing, genetic confirmation has become central to diagnosis, particularly in individuals with atypical or mild phenotypes (12,17). Prenatal diagnosis is increasingly recognized

Table II: Van der Burgt diagnostic criteria in NS, adapted from Van der Burgt (16).

Major Findings	Minor Findings
Typical facial dysmorphology (ptosis, downslanting palpebral fissures, low-set, posteriorly rotated ears, etc.)	Suggestive face dysmorphology
PS, HCM, and/or ECG typical of NS	Other cardiac defects
Height below the 3rd centile	Height below 10th centile
Pectus deformity	Broad thorax
First-degree relative with definite NS	First-degree relative with suggestive NS
Intellectual disability, cryptorchidism, and lymphatic dysplasia	One of the intellectual disability, cryptorchidism, or lymphatic dysplasia

Patients are diagnosed with NS if they have either one major facial feature plus one additional major criterion or two minor criteria, or a minor facial feature plus two major criteria or three minor criteria. ***NS:*** *Noonan syndrome,* ***HCM:*** *Hypertrophic cardiomyopathy,* ***ECG:*** *Electrocardiogram*

Table III: Well-recognized genotype-phenotype correlations reported in Noonan syndrome

Gene	Approximate frequency in NS	Pathway effect	Characteristic clinical associations
PTPN11	40–50%	Increased SHP2 phosphatase activity leading to enhanced RAS/MAPK signaling	PS, short stature, variable developmental delay
SOS1	10–15%	Enhanced RAS activation through increased guanine nucleotide exchange activity	Prominent ectodermal findings (e.g., keratosis pilaris, sparse hair), typically normal or mild cognitive involvement
RAF1	5–10%	Increased downstream MAPK signaling due to impaired inhibitory phosphorylation	Strong association with HCM
RIT1	5%	Dysregulated RAS-like signaling affecting downstream pathway activation	HCM, lymphatic abnormalities, prenatal findings
KRAS	<5%	Increased RAS signaling due to impaired GTPase cycling	More severe developmental delay and complex phenotype
LZTR1	~5–10%	Impaired ubiquitination and regulation of RAS proteins	PS and typical Noonan features with variable developmental delay; both dominant and recessive inheritance described

NS: *Noonan syndrome,* ***PS:*** *Pulmonary valve stenosis,* ***HCM:*** *Hypertrophic cardiomyopathy. Frequencies are approximate and may vary across cohorts and sequencing strategies.*

through characteristic ultrasound findings, especially in the presence of lymphatic abnormalities or congenital heart disease, prompting targeted genetic evaluation (18). Well-recognized genotype-phenotype correlations reported in NS are summarized in (Table III).

Short stature is a common clinical feature. Bone age delay is frequent, and growth velocity may decline during childhood. Skeletal involvement also includes pectus deformities, scoliosis or kyphosis, limb abnormalities, and reduced bone mineral density (15,19).

Cardiac disease remains one of the most important determinants of morbidity in NS. While pulmonary valve stenosis (PS) and hypertrophic cardiomyopathy (HCM) are common, atrial septal defects and complex structural lesions can also be observed. Cardiac manifestations may present prenatally, at birth, or later in childhood. The disease severity ranges from mild lesions requiring observation to progressive conditions needing medical or surgical intervention (12,20). Specific genotype-phenotype correlations have been established for cardiac involvement: gain-of-function variants in *RAF1* show a strong association with HCM, reflecting enhanced MAPK signaling due to impaired inhibitory phosphorylation of the protein (21,22) (Table III). Pathogenic variants in *RIT1* are likewise frequently associated with severe and early-onset cardiac phenotypes, including HCM and PS (14,20). This genotype–cardiac association is clinically important, as MEK inhibition with trametinib has shown benefit in selected patients with severe disease (23,24).

Lymphatic abnormalities are an important but often underrecognized feature of NS. They may already be apparent prenatally, presenting as increased nuchal translucency, cystic hygroma, pleural effusions, or hydrops fetalis. After birth, peripheral lymphedema, chylothorax, or intestinal lymphangiectasia may occur. These complications may be transient or persistent and can significantly contribute to morbidity, particularly in infancy and early childhood (18,25).

Neurodevelopmental manifestations are core features of NS rather than secondary complications. Although overall intellectual functioning often falls within the low-normal range, affected children have a higher prevalence of neurodevelopmental disorders compared with the general population (26,27). Attention-deficit/hyperactivity disorder (ADHD) appears to be the most common condition, while oppositional defiant disorder and autism spectrum traits are also frequently reported (26). A systematic review and meta-analysis confirmed an increased prevalence of neurodevelopmental and psychiatric conditions in NS, including intellectual developmental disorder, ADHD, autism spectrum disorder, epilepsy, and anxiety or depressive symptoms (27).

Children with NS have an increased malignancy risk compared with the general pediatric population, reflecting germline RAS/MAPK dysregulation. Cohort studies estimate an approximately eightfold relative increase, although the absolute risk remains moderate (28). Reported tumors include juvenile myelomonocytic leukemia

(JMML), other myeloproliferative conditions, acute leukemias, rhabdomyosarcoma, neuroblastoma, and low-grade gliomas. Despite this increased risk, routine universal cancer surveillance is not recommended; instead, careful clinical monitoring is advised (28).

Classical growth hormone (GH) deficiency is not consistently present in NS, and growth impairment may partly reflect altered RAS/MAPK pathway signaling. GH, treatment generally improves growth velocity and height standard deviation score, although response may vary according to age at treatment initiation and genotype, particularly in individuals with *PTPN11*-related disease (12,29). Current evidence suggests that therapy is usually well tolerated, including in many patients with congenital heart disease, provided that cardiovascular and oncologic monitoring is maintained (12,28,29). Overall, GH remains a reasonable option for selected children with NS when used within a structured follow-up plan.

Cardiofaciocutaneous syndrome (CFCS)

Cardiofaciocutaneous syndrome (CFCS) stands out as a rare RASopathy defined by multisystem involvement, most notably significant developmental delay and ectodermal abnormalities (30,31). A nationwide epidemiologic survey suggested a prevalence of approximately 1 in 800 000 live births, although precise epidemiologic data remain limited (31-33). While *BRAF* variants are the most frequent cause, pathogenic changes in *MAP2K1*, *MAP2K2*, or *KRAS* also drive the pathway dysregulation that disrupts normal tissue maturation (30,34) (Table I). These alterations dysregulate ERK signaling during development and thereby affect proliferation, differentiation, and tissue maturation (34).

Cardiac findings commonly include PS, septal defects, and HCM, with variable severity requiring individualized follow-up (9,30). Craniofacial findings typically include a high forehead with bitemporal narrowing, hypertelorism, downslanting palpebral fissures, low-set ears, and a short nose with a depressed bridge (9,30,31). Diagnostic clues are often found in the skin and hair; hyperkeratosis and sparse, curly hair are hallmarks that support the clinical diagnosis across diverse populations. A multicenter dermatologic study reported common features such as hyperkeratosis, keratosis pilaris, sparse or curly hair, ulerythema ophryogenes, and palmoplantar keratoderma (35). Similar clinical patterns have been described in molecularly confirmed cohorts from different populations, supporting the consistency of the CFCS phenotype (33).

Feeding difficulties are highly prevalent in infancy and often contribute to failure to thrive. Severe reflux, vomiting, oral feeding difficulty, and the need for nutritional support are common in infancy. Musculoskeletal involvement is also common and includes pectus deformities, scoliosis or kyphosis, joint laxity, and other skeletal anomalies (30,33).

Neurologic involvement represents one of the most prominent clinical aspects of CFCS. In a multinational cohort of 138 individuals, intellectual disability was present in 82% and seizures in 55% of patients (36). Seizure onset most commonly occurred in early or middle childhood. Genotype-specific patterns have also been described: variants in *BRAF* and *MAP2K1* are generally associated with a higher frequency and greater severity of seizures compared with *MAP2K2* variants (36). Studies focusing on *BRAF*-related disease have reported particularly high rates of refractory and polymorphic seizure types (37). In addition to epilepsy, affected individuals frequently exhibit motor delay, hypotonia, and sleep disturbances, further emphasizing the significant neurologic burden associated with CFCS (33). CFCS may also include immune involvement. In an international cohort, a substantial subset of patients exhibited increased infection susceptibility and lymphopenia, highlighting the need for broader clinical awareness (38).

Costello Syndrome (CS)

Among the RASopathies, CS has a particularly recognizable clinical profile, primarily defined by its multisystem involvement and a significant predisposition to malignancy (39,40). CS is caused by heterozygous gain-of-function germline variants in *HRAS*, most commonly missense substitutions affecting codons 12 or 13. These mutations impair normal GTP hydrolysis in *HRAS* protein, resulting in persistent activation of RAS/MAPK cascade (39). Infants typically present with coarse facial features, macrocephaly, and severe feeding difficulties. However, the most striking diagnostic clues are often ectodermal; redundant skin, deep palmar and plantar creases, and cutaneous papillomas are hallmarks that help clinicians differentiate CS from other disorders in the RASopathy spectrum. CS also carries a well-recognized predisposition to both benign and malignant tumors, particularly rhabdomyosarcoma, neuroblastoma, and transitional cell carcinoma of the bladder (39,40).

Dermatologic findings are prominent in CS and may provide useful diagnostic clues. A prospective multicenter study reported frequent features, including curly or sparse hair, prominent eyebrows, acral excess skin with deep palmoplantar creases, papillomas or keratotic papules, acanthosis nigricans, and palmoplantar hyperkeratosis. These dermatologic findings may provide useful clues when distinguishing CS from other RASopathies (41).

Musculoskeletal abnormalities are also common in CS and include progressive spinal deformities, particularly kyphosis and scoliosis, which may develop during childhood and require longitudinal monitoring (42). Ophthalmologic abnormalities are frequently reported as well. These may include refractive errors, strabismus, nystagmus, and ptosis, while optic nerve and retinal abnormalities have also been described (43). Together, these observations support regular ophthalmologic assessment in individuals with CS (43,44).

One of the features that makes CS especially important in long-term follow-up is its marked tumor predisposition. A systematic review and meta-analysis demonstrated a markedly increased risk of malignancy compared with the general population. Tumors most often arise during childhood, although risk persists into adolescence and adulthood (45). Because of this elevated risk, children with CS require structured longitudinal follow-up and age-appropriate tumor surveillance. Current consensus guidelines

emphasize multidisciplinary follow-up and risk-adapted surveillance to facilitate early tumor detection (28).

CFCS and CS share substantial phenotypic overlap. Several features are more typically associated with CS, including deep palmar and plantar creases, joint hyperextension, and hyperpigmentation. These findings may also occur in CFCS, but are generally less prominent, reflecting the clinical overlap between the two disorders (46). In clinical practice, these distinctions may help differentiate the two disorders despite their shared pathway biology.

Noonan syndrome with multiple lentigines (NSML)

Noonan syndrome with multiple lentigines (NSML), historically referred to as LEOPARD syndrome, is a rare RASopathy characterized by multiple lentigines together with cardiac, facial, and growth abnormalities. The acronym "LEOPARD" reflects the key clinical features: lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonary stenosis, genital anomalies, growth retardation, and deafness. The estimated prevalence is approximately 1 in 100 000 individuals. Most cases are associated with pathogenic variants in *PTPN11*, although variants in *RAF1* and, rarely, *BRAF* have also been reported (Table I). Unlike classic NS, where variants typically increase pathway signaling, NSML-associated *PTPN11* variants often impair SHP2 catalytic activity yet still lead to dysregulated downstream signaling in a context-dependent manner (9,47).

Clinically, NSML shows a multisystem phenotype that overlaps with other RASopathies but has several distinguishing features. Lentigines usually become apparent in early childhood and increase in number over time (47). Cardiovascular involvement is common, with HCM representing the most frequent and clinically significant cardiac manifestation. It often develops during childhood and requires longitudinal follow-up (48). Conduction abnormalities and additional structural heart defects may also be observed. Sensorineural hearing loss has been reported in a subset of patients and may occasionally present early, particularly in individuals with *PTPN11*-associated disease (49).

Noonan syndrome with loose anagen hair (NS/LAH)

NS/LAH is a rare RASopathy that shares many clinical features with NS but is distinguished by characteristic hair abnormalities. The disorder is most commonly associated with pathogenic variants affecting the *SHOC2–MRAS–PPP1CB* signaling complex, which modulates RAS/MAPK pathway activation (Figure 1) (9). Individuals typically present with a Noonan-like facial gestalt, postnatal growth retardation, macrocephaly, and variable neurodevelopmental delay. A defining feature is the loose anagen hair phenotype, characterized by sparse, slow-growing, easily pluckable hair reflecting abnormal hair anchoring. Cardiac anomalies may also occur, although the spectrum is variable, and additional findings may become more evident over time (50,51). Recent reports also indicate that recurrent de novo missense variants in *PPP1CB* can produce a closely related phenotype overlapping with NS/LAH, further supporting the role of this signaling complex in disease pathogenesis (52).

Therapeutic Approaches in RASopathies

Management of RASopathies has traditionally focused on symptomatic and multidisciplinary care, addressing cardiac disease, growth problems, neurodevelopmental issues, and other complications (9,53). As understanding of RAS/MAPK pathway biology has improved, interest in therapies targeting this signaling cascade has increased (23).

MEK inhibitors such as trametinib have emerged as a potential targeted approach. Early clinical reports suggest improvement in manifestations related to signaling hyperactivation. Improvement of HCM has been reported in children with RASopathy-associated cardiac disease treated with MEK inhibitors (54). Similar strategies have also been explored in mosaic RASopathies; treatment with a MEK inhibitor in a pediatric patient with *KRAS*-associated epidermal nevus syndrome resulted in clinical benefit (55). In addition, MEK inhibition has been reported to reduce seizure burden in patients with drug-resistant epilepsy associated with CFCS and mosaic *KRAS*-related RASopathies (56). Targeted treatment approaches have also been described for specific complications. In NS, trametinib has been used for severe lymphatic manifestations with reported clinical improvement (24). In NSML, mTOR inhibition with everolimus has been reported as a therapeutic option for severe cardiac involvement in infancy (57).

Advances in targeted oncology have further informed treatment strategies in RAS pathway disorders. Selumetinib represents one of the clearest clinical examples of MAPK pathway inhibition in practice (58). It is approved for symptomatic, inoperable plexiform neurofibromas in children with *NF1*. It has demonstrated meaningful tumor shrinkage together with functional improvements such as reduced pain and improved pulmonary and motor function. MEK inhibitors have also been explored in other *NF1* manifestations, including low-grade gliomas and atypical neurofibromas, although evidence remains limited. Potential benefits for pain and neurocognitive outcomes have also been reported, supporting further investigation of selumetinib in RAS pathway-related conditions (59). Pathway-directed therapies have additionally been explored in RASopathies with skeletal involvement. In osteofibrous dysplasia, preclinical data and a reported case of persistent pseudarthrosis demonstrated improved bone healing following MEK inhibition (60). Although the available experience remains limited, these reports suggest that pathway-directed therapies may benefit selected patients by partially correcting the underlying signaling dysregulation.

Conclusion

RASopathies require careful and long-term clinical follow-up because of their overlapping features and multisystem involvement. Long-term follow-up is particularly important for monitoring potentially life-threatening manifestations such as cardiac disease, while supportive management addressing feeding difficulties and neurodevelopmental challenges plays a critical role in improving patient outcomes. Pathway-directed treatment remains investigational for most RASopathies. However, early reports suggest that selected complications may become amenable to targeted therapy. Most available data come from case reports and small series, and further studies will

be necessary to clarify long-term efficacy and safety in patients with RASopathies. As molecular understanding improves, pathway-directed treatments remain investigational for most RASopathies and have not yet become part of routine clinical care.

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Turkish Journal of Pediatric Disease

Letter to the Editor

Comment on "Hypertension in children with congenital adrenal hyperplasia: Prevalence and associated factors"

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Introduction

In the latest issue of the Turkish Journal of Pediatric Disease, İnözü et al (1) evaluated hypertension (HT) prevalence and determinants among Turkish patients with congenital adrenal hyperplasia (CAH). Based on the United States (US) reference values, which was released in 2017, İnözü et al. (1) detected HT in 10.5% of the CAH patients and the HT prevalence significantly varied depending on the CAH subtype ($p<0.001$) (2). The greatest prevalence was found among patients who had 11β-hydroxylase deficiency subtype (88.8%), followed by those who had 21-hydroxylase deficiency subtype (8.4%). However, no HT cases were noted in other CAH subtypes. Moreover, HT exhibited strong associations with age at last visit but moderate associations with body mass index and follow-up duration. Apart from several study limitations stated by İnözü et al. (1), we acknowledge the following methodological one. Thorough diagnosis and therapy of pediatric HT necessitate right estimation and judicious interpretation of the recorded BP readings demanding the reference to the corresponding BP charts. Since BP profile in a particular pediatric population is affected by numerous genetic, nutritional, environmental, socio-economic, and racial backgrounds, different pediatric populations-specific BP normative centiles have been derived for implementation in research and clinical settings (3-6). Hopefully, Türkiye formulated pediatric centiles for systolic and diastolic BP for both sexes in 2020 (7). The BP centiles employed in the İnözü et al's (1) study was endorsed by the American Heart Association and principally formulated for the Caucasian population (2). Interestingly, the constructed Turkish BP centiles were lower than the utilized US BP centiles (2,7). It appears questionable why İnözü et al. (1) referenced to the foreign BP centiles instead of the local ones in the study methodology (2,7). Consequently, this limitation might significantly corrode the correctness of the study findings. Irrespective of study limitations, cardiometabolic risk ought to be regularly assessed in CAH patients.

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Turkish Journal of Pediatric Disease

Letter to the Editor

Response to the Letter entitled "Comment on Hypertension in children with congenital adrenal hyperplasia: Prevalence and associated factors"

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Introduction

We thank the authors for their interest in our study and for their thoughtful comments regarding the use of blood pressure (BP) reference standards in pediatric populations.

We agree that population-specific BP reference values are important, as BP distributions may vary according to genetic, environmental, and socio-demographic factors. As highlighted by the authors, BP percentile charts specific to Turkish children have been developed and may provide valuable context for national clinical practice (1).

In our study, we used the 2017 American Academy of Pediatrics (AAP) Clinical Practice Guideline for the definition of hypertension (2). These criteria are widely adopted in international clinical and research settings and allow for direct comparison with previously published studies in children with congenital adrenal hyperplasia (CAH) and other pediatric endocrine disorders. In this context, the use of standardized international reference values was intended to enhance the comparability and external validity of our findings.

International guidelines, including those from the AAP and the European Society of Hypertension Task Force, acknowledge the potential use of population-specific BP reference values (2,3). However, the representativeness, methodological rigor, and external validation of such local reference data remain important considerations when selecting the most appropriate standard for research purposes.

We acknowledge that Turkish BP reference values have been reported to be lower than US-based percentiles (1), which may influence the estimated prevalence of hypertension. However, the primary objective of our study was not only to determine prevalence but also to investigate associations between hypertension and clinical factors such as CAH subtype, treatment exposure, and follow-up duration. These within-cohort associations are less likely to be substantially affected by the choice of reference standard, as relative comparisons remain consistent.

Nevertheless, we agree that future studies incorporating Turkish population-specific BP percentiles, and ideally comparing different reference standards within the same cohort, would provide additional insight into the epidemiology of hypertension in children with CAH.

We appreciate the authors' valuable contribution and their emphasis on the importance of appropriate BP assessment in pediatric populations.

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