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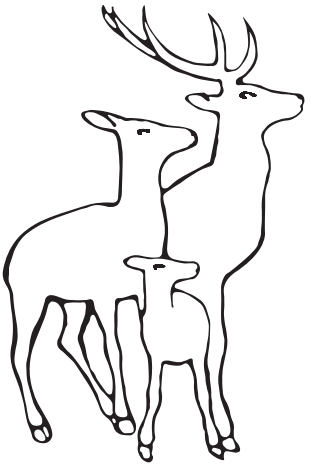

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CONTENTS

VOLUME: 68 ISSUE: 4 JULY-AUGUST 2026

REVIEW

ORIGINAL ARTICLES

CONTENTS

VOLUME: 68 ISSUE: 4 JULY-AUGUST 2026

CASE REPORTS

LETTERS TO THE EDITOR

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Review

Mortality characteristics in individuals with autism spectrum disorder across the lifespan: a narrative review

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ABSTRACT

This narrative review provides a comprehensive synthesis of mortality rates and associated risk factors among individuals with autism spectrum disorder (ASD) across the lifespan. Following a search across PubMed, Scopus, and Google Scholar, 31 peer-reviewed studies were identified for synthesis. The findings consistently demonstrate that individuals with ASD experience significantly higher mortality rates compared to neurotypical controls. Analysis shows a distinct developmental shift: in childhood and adolescence, external causes are predominant, with accidents—particularly drowning—accounting for a substantial portion of fatalities, estimated between 70% and 90% in some reports. In contrast, adult mortality is increasingly driven by natural causes. The evidence indicates a reduced life expectancy, with some studies reporting average ages of death as low as 36 years, depending on comorbid conditions. Furthermore, standardized mortality ratios appear notably higher in individuals with co-occurring intellectual disabilities and epilepsy, with some cohorts showing risks several times higher than the general population. A substantial proportion of ASD-related mortality is potentially preventable through targeted safety training, early metabolic screening, and ASD-friendly healthcare practices. Addressing communication barriers and sensory sensitivities in clinical settings is essential for early diagnosis and effective management of chronic conditions to reduce the mortality gap.

Key words: autism spectrum disorder, life expectancy, mortality, premature death.

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by problems with social communication and interaction, and restricted/repetitive behaviors or interests.[1] The prevalence of ASD is increasing. 3.2% of 8-year-old children are diagnosed with ASD, and it is three times more common in boys than girls.[2] Difficulties related to ASD are often observed throughout life, and a study in the USA indicated that 2.21% of adults have a diagnosis.[3] ASD is frequently accompanied by various psychiatric disorders such as attention deficit hyperactivity disorder (ADHD), anxiety disorders, and depression. Neurological disorders, including epilepsy, gastrointestinal problems, and metabolic disorders, can also frequently coexist.[4] The course of ASD symptoms varies from person to person. There are prognostic factors that indicate how this course will unfold.[5,6]

Unlike chronic diseases such as cystic fibrosis and muscular diseases, where mortality rates are better defined, studies on mortality rates in individuals diagnosed with ASD are quite limited.[7-9] The literature indicates that individuals diagnosed with ASD have a higher risk of mortality compared to neurotypical individuals in various studies.[10-12] However, despite ASD being a significant disease affecting a person's functionality and frequently co-occurring with other chronic

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diseases, the specific factors influencing the causes of early mortality in these individuals are still not fully understood. While intellectual disability and epilepsy have been identified as key contributing factors to increased mortality rates, the level of knowledge regarding common causes of death and effective prevention strategies in individuals diagnosed with ASD is still insufficient.[13,14]

The increased mortality rate in individuals diagnosed with ASD may be due to various factors, including comorbid physical illnesses, communication problems related to impaired social interaction that hinder access to healthcare, or chronic stress in parents. Unnatural causes of death, such as drowning, accidents, and suicide, are also more common in individuals diagnosed with ASD than in the general population.[15-17] Some studies indicate that the rates of unnatural deaths in these individuals are comparable to those of natural causes of death.[18] Since accidents and suicide are among the preventable causes of death, identifying age-specific risk factors in individuals diagnosed with ASD is crucial for developing primary prevention and autism-friendly health care policies.[19,20]

Studies in the literature generally present the mortality characteristics of children and adults diagnosed with ASD together, which makes it difficult to determine age-specific mortality characteristics in ASD. Drawing attention to this gap in the literature, this review aims to identify the most common causes of death in individuals of all ages diagnosed with ASD, to define the factors that increase and decrease the risk of death, and to determine how these factors differ according to the level of functionality. The literature compiled until July 1, 2025, has been divided into three groups: (1) studies focusing solely on children and adolescents, (2) studies including both child and adult populations, and (3) studies focusing exclusively on adults. This will make it possible to identify what clinicians and health policymakers can focus on in order to reduce mortality rates in individuals diagnosed with ASD.

Methods

This narrative review was conducted to synthesize current evidence regarding mortality characteristics in individuals with ASD. A comprehensive electronic search was performed across PubMed, Google Scholar, and Scopus databases between May 1, 2025, and July 1, 2025, to identify relevant peer-reviewed studies published from the inception of the databases up to the search date. The search strategy employed a combination of keywords including 'autism spectrum disorder', 'mortality', 'premature death', and 'life expectancy'.

To ensure a high standard of reporting, this review followed the SANRA (Scale for the Quality Assessment of Narrative Review Articles) guidelines.[21] The eligibility of studies was determined based on predefined criteria. To provide a holistic perspective, the inclusion criteria encompassed original research articles, clinical case reports, and key systematic reviews providing data on mortality in ASD. The selection was limited to studies published in the English language to ensure consistency in data interpretation. Studies such as editorials, book chapters, or conference abstracts were excluded.

The initial search yielded 186 records; after removing duplicates and screening, 50 articles were assessed in full. Ultimately, 31 studies meeting the criteria—including original research, illustrative case reports, and comprehensive reviews—were identified. For clinical interpretation, these were categorized into: childhood and adolescence (0–18 years), adulthood (>18 years), and lifespan perspectives (Fig. 1).

Results

The systematic synthesis of the literature yielded 31 studies that met the inclusion criteria, providing a comprehensive overview of mortality in individuals with ASD. These studies, which include original research, clinical case reports, and systematic reviews, highlight

a consistent pattern of increased mortality risk across the lifespan compared to the general population. The identified factors contributing to this risk are multifactorial, ranging from co-occurring medical conditions to external environmental hazards. A detailed summary of the characteristics, populations, and key findings of each included study is presented in Table I.

Mortality characteristics in children and adolescents with ASD

Ten studies, published between 2012 and 2024, specifically examined pediatric populations. The all-cause mortality risk in children with ASD is at least twofold compared to healthy peers, with a notable increase in the presence of comorbid intellectual disability (ID) and epilepsy.[12,22-26] While natural and external causes both contribute to higher mortality, suicide-related deaths are less prominent in this age group than in adults. Gender-based data indicate higher mortality rates in females.[12,22-26] Geographic and socioeconomic factors also influence outcomes; for instance, a South Korean cohort study (2002–2012) found higher mortality risks across all income levels, with children in the capital city showing lower risk compared to other metropolitan areas.[25]

External and unintentional causes of death—primarily accidents, drowning, and wandering—are more extensively reported in children than in other age groups.[27] One study identified the average age of accidental drowning victims as 7.7 years, with 73.9% of these fatalities occurring after wandering behaviors near the home.[28] In a Danish cohort, 22.8% of adolescent deaths were self-inflicted and 26.3% were accidental.[13] Regarding natural causes, epilepsy, and other neurological diseases, circulatory diseases,

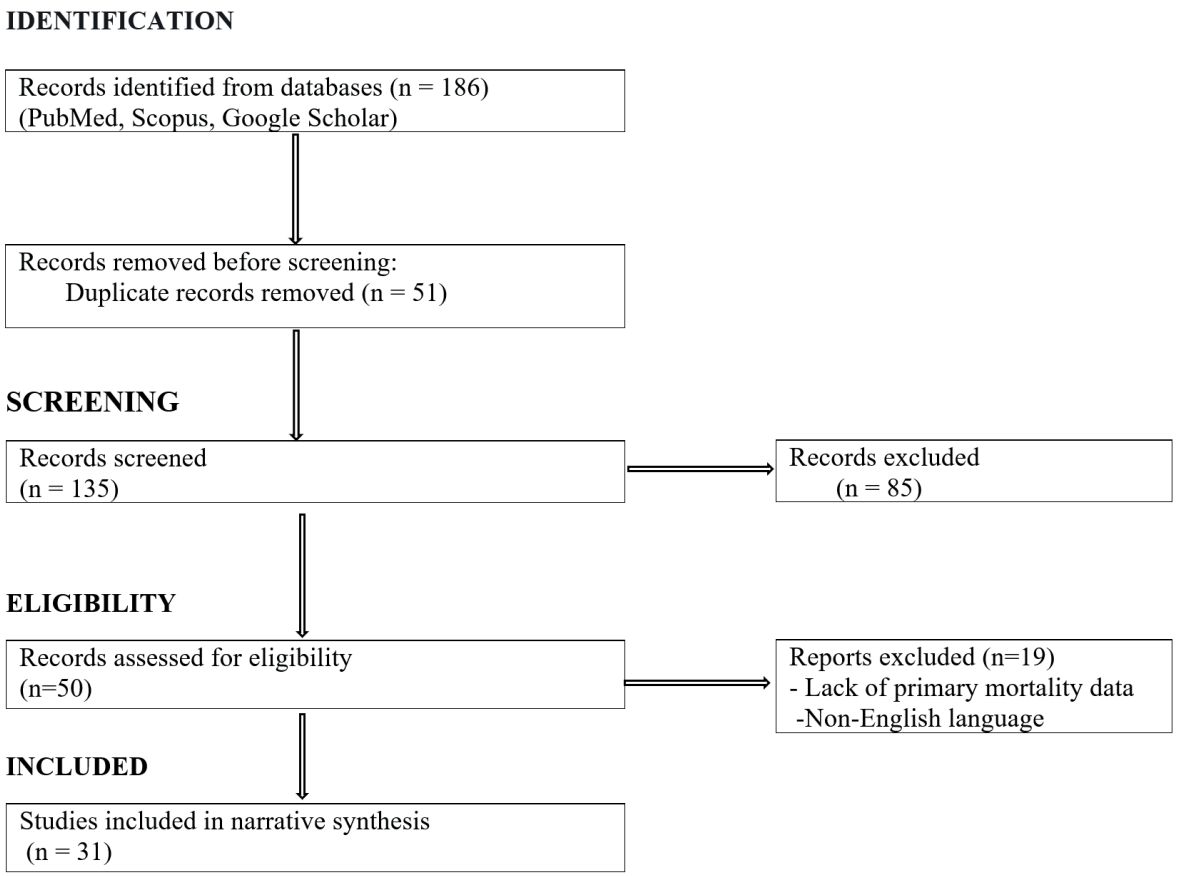

Fig. 1. Flow diagram of the study selection process.

Table I. Summary of included studies on mortality in individuals with ASD.

Author (year)	Population / country	Key findings & mortality causes
Childhood studies		
Kim et al.[23] (2021)	National cohort (South Korea)	ASD children had a significantly higher mortality risk than the general population; deaths often resulted from treatable or preventable medical conditions.
Woolfenden et al.[24] (2012)	Systematic review	Identified significant disparities in mortality rates; emphasized that most deaths in developmental disabilities are preventable with better healthcare access.
Yoo et al.[25] (2022)	Birth cohort (South Korea)	Early identification of hearing/physical problems correlates with future mortality risk.
Zylbersztejn et al.[26] (2018)	National cohort (UK)	ASD is associated with increased risk of death from treatable causes and accidents.
Guan and Li[28] (2017)	1,367 deaths (USA)	73.9% of drowning deaths occurred following elopement; average age 7.7 years
Smith et al.[29] (2021)	787,666 pupils (Scotland)	• Overall mortality risk in autistic children was higher but not statistically significant (SMR: 1.25). • Mortality was due to natural causes (e.g., diseases) rather than external causes. • Suicide and self-harm were higher but explained by comorbid psychiatric disorders.
Taylor et al.[30] (2022)	Case report (USA)	Sudden death due to ruptured AVM; highlights difficulties in verbalizing pain symptoms.
Adulthood studies		
Krantz et al.[11] (2023)	Medicare adults (USA)	Mortality gap narrows after age 65; cardiovascular and neurological diseases predominate.
Santomauro et al.[16] (2024)	Global meta-analysis	Suicide is a leading cause of death in high-functioning adults; higher risk in females.
DaWalt et al.[35] (2019)	Longitudinal cohort (USA)	• Found that better maternal health and family support are associated with increased longevity in autistic adults. • Highlights the role of social determinants in mortality risk.
Akobirshoev et al.[40] (2020)	Retrospective (USA)	In-hospital mortality is higher in ASD due to physical comorbidities
Lunsky et al.[41] (2022)	Population cohort (Canada)	• Autistic adults had significantly higher mortality than the general population. • Females and those with comorbid intellectual disability faced the highest risks. • Most deaths were from preventable/treatable causes.
Spanyol et al.[43] (2025)	COVID-19 cohort (Brazil)	ASD is an independent risk factor for in-hospital mortality; higher need for ventilation.
Lifespan studies		
Catalá-López et al.[10] (2016)	Systematic review & meta-analysis	ASD is associated with a significantly higher risk of all-cause mortality; accidents and nervous system diseases are major factors.
Schendel et al.[12] (2016)	1.9M cohort (Denmark)	Twofold increased mortality risk; higher in females and those with comorbid epilepsy/ID.
Bilder et al.[13] (2013)	305 individuals (USA)	Significantly higher risk for natural causes (epilepsy, respiratory) and unintentional injuries.
Forsyth et al.[14] (2023)	Systematic review	Confirmed significantly higher mortality risk in ASD; identified external causes (e.g., drowning, suicide) and preventable medical conditions as primary drivers.

ASD: autism spectrum disorder; ID: intellectual disability; SMR: standardized mortality ratio; USA: United States of America.

Table I. Continued.

Author (year)	Population / country	Key findings & mortality causes
Guan and Li[15] (2017)	Retrospective cohort (USA)	• Injury mortality was 3 times higher in ASD than the general population. • Suffocation, asphyxiation, and drowning were the leading causes. • Deaths often occurred during transitions or in wandering episodes.
Shavelle et al.[17] (2001)	13,111 cohort (USA)	Seizures and respiratory infections are primary causes; SMR significantly higher for females.
Kim et al.[18] (2025)	Retrospective cross-sectional (South Korea)	Age-standardized mortality rate was 5 times higher than the general population. Deaths were split nearly 1:1 between diseases (50.7%) and injury (49.3%). Average age at death was approximately 50 years lower than the general population.
Jokiranta-Olkoniemi et al.[22] (2021)	Nationwide cohort (Finland)	• Confirmed increased risk for premature mortality due to natural causes. • Suicide and self-harm rates were higher but explained by comorbid psychiatric disorders. • Calls for efficient recognition and treatment of comorbid conditions.
Rybczynski[27] (2024)	Review	High risk of mortality linked to wandering (elopement) and suicidal ideation.
Hirvikoski et al.[31] (2016)	27,122 cohort (Sweden)	Life expectancy reduced by 18 years. High suicide risk in those without ID.
Huang et al.[32] (2024)	National cohort (Taiwan)	• Higher overall mortality risk for ASD. • Females with comorbid ID showed the highest risk. • Highlights need for identifying psychiatric/physical comorbidities.
Hwang et al.[33] (2019)	National sample (USA)	• Mortality rate was 2.06 times higher than the general population. • Significant risk factors included epilepsy, intellectual disability, and chronic physical conditions. • Top causes: Nervous system disorders and injury/poisoning.
Mouridsen et al.[34] (2008)	30-year follow-up	Higher mortality in those with profound intellectual disabilities.
Shavelle and Strauss[36] (1998)	Comparative study (USA)	Overall mortality ratio was 213%. Notably, the risk for females (490%) was significantly higher than for males (167%). Mortality ratio decreased as age increased.
Kirby et al.[37] (2019)	20-year follow-up (USA)	High mortality from diseases of the nervous system and accidental poisonings.
Davis et al.[38] (2024)	Retrospective cohort (USA)	• Investigated the link between healthcare barriers and mortality. • Found that delayed medical care significantly increases the risk of premature death. • Stressed the importance of provider training in ASD.
Chen et al.[39] (2024)	Population cohort (Taiwan)	• Antidepressant use was associated with a decreased risk of all-cause mortality, particularly from accidents or natural causes. • Emphasizes the importance of early detection of comorbid disorders (e.g., depression, anxiety).
Bishop et al.[42] (2017)	Individuals with ASD (extracted from electronic health records) (USA)	Demonstrated that co-occurring epilepsy and lower intellectual ability are significant predictors of premature mortality in ASD.

ASD: autism spectrum disorder; ID: intellectual disability; SMR: standardized mortality ratio; USA: United States of America.

respiratory illnesses, and cancer are the most frequent.[22,24,29,30] Additionally, hearing-related problems identified in infancy are associated with higher mortality.[23]

Mortality characteristics in lifespan studies (children and adults)

Studies encompassing both children and adults confirm that individuals with ASD die several decades earlier than controls, with peak mortality occurring in the 20–30 and 40–60 age ranges.[10,13,14,17,18,31-35] ID and low functional levels in childhood are significant predictors of future mortality.[13,31-36] Mortality ratios for natural causes remain dominated by epilepsy, followed by cardiovascular diseases and cancer.[13,14,17,18,31,33]

Unnatural causes in this group include suffocation, asphyxiation, and drowning. A U.S. study (1999–2014) reported that the average age at death for individuals with ASD was 36.2 years, compared to 72.0 years in the general population, with 27.9% of deaths being injury-related.[15] Suicide rates are significantly higher in individuals without ID, particularly under the age of thirty, with females showing higher suicide mortality than neurotypical peers.[14,16,27,31,33,37] Furthermore, during the COVID-19 pandemic, individuals with ASD experienced significantly higher infection-related mortality.[38] Regarding pharmacological interventions, antidepressant use in adults (≥18 years) was associated with decreased mortality, a relationship not demonstrated in those under 18.[39]

Mortality characteristics in adults with ASD

Research focusing exclusively on adults (≥18 years) indicates that mortality occurs approximately twenty years earlier than in age-matched controls, although this gap appears to diminish in individuals aged 65 and above.[11,40-42] In contrast to pediatric data, some adult studies report higher mortality rates in males.[11,41] Cardiovascular, urinary, and digestive system diseases are prevalent in this population, while cancer incidence is reportedly lower in some adult ASD cohorts compared to controls.[42]

In terms of gender-specific outcomes in adulthood, distinct mortality patterns were observed between the sexes. Natural causes, including cancer, cardiovascular, and neurological diseases, were found to be more predominant in females, whereas unnatural causes, such as accidents and injuries, occurred more frequently in males.[40,41] Furthermore, the clinical severity of respiratory complications was highlighted during the COVID-19 pandemic; adult patients with ASD required significantly higher rates of both invasive and non-invasive mechanical ventilation during hospitalizations compared to those without ASD.[43]

Discussion

The findings of this narrative review indicate that mortality in individuals with ASD is driven by a complex architecture of behavioral, clinical, and systemic factors that extend far beyond simple biological vulnerability. To move beyond a mere statistical summary, this discussion is structured around four critical thematic pillars that emerged as the most significant drivers of premature death in the literature.

First, we examine the prominence of external mortality, a choice necessitated by the alarming rate of preventable accidents like drowning, which directly intersect with autistic sensory and wandering behaviors. Second, we address communication as a diagnostic barrier, highlighting how verbalization challenges lead to "diagnostic overshadowing" and fatal delays in treating physical illnesses. Third, we explore metabolic and systemic risks, focusing on the long-term impact of pharmacological interventions and healthcare access disparities that increasingly dominate adult mortality profiles.

The prominence of preventable external mortality

A prominent observation in the reviewed studies is the disproportionate impact of accidental deaths, particularly drowning and wandering, in children and adolescents. The high incidence of mortality following "elopement" behaviors—frequently described as being triggered by sensory seeking or a desire to escape overstimulating environments—points toward a critical safety gap highlighted in several cohorts.[27,29,44] The literature suggests that these incidents are closely linked to the core symptoms of ASD rather than being purely random accidents. Consequently, it has been suggested that swimming education and water safety training could be integrated into standard intervention plans for children with ASD.[15] Furthermore, incorporating traffic rules and risk-awareness training into specialized educational curricula may address the significant mortality associated with motor vehicle accidents.[44]

Clinical and diagnostic challenges: the role of communication

A recurring theme in the literature regarding increased mortality is the potential for delayed or inaccurate diagnosis of physical illnesses. Clinical reports indicate that the challenges individuals with ASD face in effectively verbalizing internal symptoms, such as pain, may lead to the progression of treatable conditions to fatal outcomes.[30] This communication barrier is also noted as a possible factor in why hearing-related problems in infancy correlate with higher mortality risks, potentially acting as an early indicator of broader communicative challenges.[23] It is hypothesized in the literature that "diagnostic overshadowing"—where physical symptoms are incorrectly attributed to ASD-related behaviors—contributes significantly to late-stage diagnoses of cancer and circulatory diseases.

Metabolic risks and healthcare barriers

The observation that adult mortality is increasingly driven by natural causes, such as cardiovascular and respiratory diseases, necessitates a focus on the long-term impact of pharmacological and systemic factors.[13,18,31] There is a strong emphasis in the literature that the chronic use of psychotropic medications, particularly antipsychotics, may induce significant metabolic side effects, thereby elevating cardiovascular risk over time.[41] These biological risks are further exacerbated by systemic barriers, including sensory sensitivities and "hospital phobia," which often converge with diagnostic overshadowing to create a "compounded neglect" in clinical settings.[42] This synergy of factors leads to reduced healthcare utilization, poor medication compliance, and the misinterpretation of acute physical distress as behavioral outbursts.[30,41] The impact of these disparities was particularly evident during the COVID-19 pandemic; the significantly higher requirement for both invasive and non-invasive mechanical ventilation among adults with ASD suggests that these individuals often present with advanced stages of illness due to delays in seeking or receiving initial care.[43]

Gender-specific mortality pathways

The reviewed literature presents conflicting findings regarding gender-based mortality, with some cohorts reporting higher risks for females and others for males. This inconsistency underscores the need for a more detailed analysis of gender-specific vulnerabilities. For example, certain studies indicate that females with ASD experience higher rates of premature mortality compared to neurotypical peers, often surpassing the relative risk observed in males.[31,34] This increased risk has been attributed to more significant diagnostic delays or the masking of symptoms, which can lead to later clinical presentations of comorbid physical and psychiatric conditions.[31,33] Additionally, research

suggests that social support mechanisms and protective factors differ by gender, influencing long-term health outcomes and suicide risk.[16,32] Although the influence of hormonal factors is still under investigation, it is hypothesized that biological differences may contribute to distinct risk profiles for metabolic and cardiovascular conditions throughout the lifespan. These nuanced gender differences emphasize the importance of clinical assessments that consider the unique phenotypic presentations of ASD in both males and females to reduce preventable mortality.

Limitations

While this narrative review provides a comprehensive synthesis of the literature, several limitations must be acknowledged. First, the study's narrative nature precludes a formal quality assessment or meta-analysis, resulting in a synthesized overview where the strength of evidence remains heterogeneous across different cohorts. Furthermore, the search was restricted to English-language publications, which may introduce a geographical bias and limit the generalizability of the findings to low- and middle-income regions where mortality characteristics may differ. The included 31 studies also exhibit significant methodological variation in terms of sample sizes, follow-up durations, and diagnostic criteria, such as the transition from DSM-IV to DSM-5, making direct comparisons between age groups and regions challenging. Additionally, many studies did not fully control for critical confounding variables, including the severity of autism symptoms, socioeconomic status, or specific medication dosages. Finally, the accuracy of the reported trends may be influenced by historical shifts in diagnostic awareness and death certification practices, potentially leading to an overestimation of mortality in more recent cohorts.

Conclusion

This narrative review provides a comprehensive synthesis of the literature regarding mortality across the lifespan in individuals with ASD. The evidence consistently demonstrates that mortality rates in the ASD population are significantly higher than in neurotypical controls, with specific risk profiles evolving alongside developmental stages. While epilepsy and intellectual disability emerge as primary risk factors across all ages, the causes of premature death shift from external accidents in childhood—such as drowning and elopement—to chronic systemic diseases and suicide in adulthood.

The findings underscore that a substantial proportion of these deaths are potentially preventable. For children and adolescents, there is an urgent need for research-based preventive measures, including specialized safety training and wandering prevention strategies. For adults, particularly those without intellectual disability, the high suicide rate necessitates timely identification of comorbid psychiatric conditions and the enhancement of social support systems.

Furthermore, the disproportionate impact of natural causes of death across all age groups highlights the necessity for structural policy changes. Implementing "ASD-friendly" healthcare practices, reducing sensory and communication barriers in clinical settings, and improving proactive access to medical services are critical steps to reduce the mortality gap. It is hoped that the findings of this synthesis will serve as a foundation for future research aimed at developing targeted interventions and more inclusive healthcare policies for individuals with ASD.

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Author contribution

The authors confirm contribution to the paper as follows: Review conception and design: BK, DÜ, CA, KN; literature review: BK; draft

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Original Article

Relationship between obesity, digital game addiction, and sleep quality in secondary school students: a cross-sectional study

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ABSTRACT

Objective. The aim of this study was to determine the prevalence of obesity and to examine the associations between digital game addiction, sleep quality, and body mass index (BMI) among secondary school students.

Materials and Methods. This cross-sectional study included 902 students in grades 6–8 in Konya, a central province of Türkiye. Data were collected using a sociodemographic questionnaire, the Digital Game Addiction Scale (DGAS), and the Pittsburgh Sleep Quality Index (PSQI). Anthropometric measurements were performed, and BMI percentiles were calculated according to national reference charts.

Results. The prevalence rates of overweight and obesity were 13.2% and 3.8%, respectively. High-risk digital game addiction patterns (risky, addicted, or highly addicted) were identified in 50.8% of the cohort, and 72.2% of participants were classified as having poor sleep quality (PSQI > 5). No statistically significant associations were observed between BMI measures and either DGAS or PSQI scores ($p > 0.05$). In multivariable linear regression analysis, higher DGAS scores were significantly associated with poorer sleep quality (higher PSQI scores) (B = 0.049, 95% confidence interval: 0.037–0.062, $p < 0.001$; adjusted $R^2 = 0.138$).

Conclusion. Digital game addiction was not directly associated with weight status in this adolescent population, but it was significantly associated with poorer sleep quality. These findings highlight the potential role of problematic gaming behaviors in adolescent sleep health. Targeted school-based interventions addressing digital gaming behaviors may help improve sleep outcomes in early adolescence.

Key words: digital game addiction, sleep quality, obesity, adolescent, secondary school.

Obesity, defined by the World Health Organization as abnormal or excessive fat accumulation that presents a risk to health, has become a major public health concern worldwide and is commonly assessed using body mass index (BMI), calculated as weight in kilograms divided by height in meters squared (kg/m^2). The prevalence of obesity has risen markedly in recent decades, particularly among children and adolescents.[1] In Türkiye, recent studies have reported high rates of overweight and obesity among school-aged populations, indicating that childhood obesity represents a significant and growing national health concern.[2,3] Global projections for 2020–2035 suggest that this trend will continue, with obesity expected to reach 20% in boys and 18% in girls.[4]

A key contributor to the rising prevalence of childhood obesity is the shift toward sedentary lifestyles, largely driven by increased reliance

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on digital technologies. Digital gaming has become a ubiquitous activity across all age groups and may displace physical activity while contributing to prolonged sedentary behavior among adolescents.[5] Although digital gaming has become a widespread form of entertainment among young people, excessive or uncontrolled use may lead to negative behavioral and functional outcomes, including impaired social and physical functioning and problematic use or addiction.[6] According to the results of a comprehensive meta-analysis, the prevalence of digital game addiction in the general population is 6.04%.[7] However, recent studies have reported high rates of problematic digital gaming behaviors among adolescents, reaching 41.5% in a study by Ayaz-Alkaya et al. published in 2025.[8]

Sleep is a fundamental physiological process essential for metabolic, cognitive, and psychological health. In adolescents, insufficient or poor-quality sleep has been associated with metabolic disturbances, impaired cognitive performance, and behavioral problems.[9] Excessive screen exposure may negatively affect sleep through both behavioral and biological mechanisms, including delayed sleep onset, increased cognitive arousal, and suppression of melatonin secretion due to blue light exposure, thereby disrupting circadian rhythms. Collectively, these mechanisms highlight the potential adverse effects of screen exposure on sleep duration, quality, and circadian regulation in adolescents.[10,11]

Adolescence represents a critical developmental period during which patterns of digital media use, sleep, and health-related behaviors are established.[12] Although previous studies have examined the relationships between digital gaming, sleep, and obesity, these factors have often been investigated separately, and evidence assessing all three variables concurrently, particularly in adolescent populations, appears to be limited. In this context, by evaluating these interrelated factors simultaneously in a Turkish adolescent population and incorporating multiple lifestyle-related variables, this study adopts a more comprehensive behavioral health perspective.

Therefore, this study aimed to examine the interrelationships between obesity, digital game addiction, and sleep quality among secondary school students.

Materials and Methods

Study design and ethical approval

This descriptive cross-sectional study was conducted between February and May 2023 among secondary school students in the central districts of Konya, Türkiye. The study adhered to the ethical principles of the Declaration of Helsinki. Ethical approval was obtained from the Non-Pharmaceutical and Non-Medical Device Research Ethics Committee of KTO Karatay University Faculty of Medicine (Date: December 29, 2022, Decision No: 2022-001). Participation was strictly voluntary. Written informed consent was obtained from parents or legal guardians, and verbal/written assent was obtained from all participating students prior to data collection.

Sample size and sampling method

The study was conducted in six secondary schools located in the central districts of Konya (across three districts), with two schools selected from each district by the Konya Provincial Directorate of National Education. Analyses were conducted at the individual level.

The minimum sample size was calculated using OpenEpi v3.01 based on a study population of 101,500 students, assuming a hypothesized frequency of 50% to yield the maximum required sample size, a 5% margin of error, a 99% confidence level, and a design effect of 1. This resulted in a minimum required sample size of 660 participants. To account for potential data loss due to incomplete or erroneous responses, 1,000 participants were initially recruited. After excluding 98 questionnaires due to missing data or lack of parental consent,

the final analysis included 902 participants. The inclusion criteria were: (i) attendance at school on the day of data collection, (ii) absence of known mental or physical disabilities, and (iii) sufficient literacy to complete the questionnaire independently.

Anthropometric measurements and BMI

Participants' body weight and height were measured according to standard anthropometric procedures. Weight was measured to the nearest 100 g using a calibrated portable digital scale, with participants wearing light indoor clothing and no shoes. Height was measured to the nearest 0.1 cm using a portable stadiometer while participants stood upright. BMI was calculated as weight divided by height squared (kg/m^2). BMI percentiles were determined according to age- and sex-specific national growth charts for Turkish children and adolescents.[13] Underweight was defined as the <5th percentile, normal weight as the 5th–85th percentile, overweight as the 85th–95th percentile, and obesity as ≥95th percentile. For the logistic regression analysis, participants were categorized as being below the 85th percentile or at or above the 85th percentile.

Data collection tools

Sociodemographic and lifestyle questionnaire

A structured questionnaire was used to collect sociodemographic and lifestyle data. Age, sex, parental education level, and socioeconomic status were assessed using predefined multiple-choice questions. Parental height and weight were reported by students based on information obtained from their parents. Parental BMI was calculated as weight (kg)/height squared (m^2). Parents were classified according to the World Health Organization adult BMI criteria as underweight/normal weight (BMI <25 kg/m^2) and overweight/obese (BMI ≥25 kg/m^2).[14]

Lifestyle-related variables included digital device ownership (smartphone, tablet, and computer), daily screen time, daily digital game time, weekly physical activity, dietary habits (breakfast frequency, consumption of three main meals per day, fast food consumption, and snacking behaviors, including snacking between meals, while playing digital games, and in front of a TV/computer), and sleep characteristics (sleep duration and sleep problems). These variables were assessed using structured multiple-choice or yes/no questions, as appropriate.

Digital Game Addiction Scale for Children

This 24-item scale, developed by Hazar et al. (2017) and validated for the Turkish population, assesses four subdimensions: (i) excessive focus on and conflict related to digital gaming, (ii) tolerance development during gameplay and the value attributed to gaming, (iii) postponement of individual and social duties/responsibilities, and (iv) psychological and physiological withdrawal symptoms and immersion in gaming. Each item is rated on a 5-point Likert scale, with total scores ranging from 24 to 120. Scores were categorized according to the original validation study as follows: Normal (1–24), low risk (25–48), risky (49–72), addicted (73–96), and highly addicted (97–120). DGAS scores were analyzed as continuous variables in regression analyses, while categorical classifications were used only for descriptive purposes. In the original validation study, Cronbach's alpha was 0.90.[15] In the present study, internal consistency was also high (Cronbach's alpha = 0.91)

Pittsburgh Sleep Quality Index

Sleep quality was assessed using the PSQI, developed by Buysse et al.[16] (1989) and validated for Turkish populations by Ağargün et al.[17] (1996). Although originally developed for adults, the PSQI has been widely used and validated in adolescent populations.[18] The PSQI evaluates sleep quality over the past month and includes seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. Each component is scored from 0 to 3, with

total scores ranging from 0 to 21. A global score >5 indicates poor sleep quality. The internal consistency of the PSQI in this study was acceptable (Cronbach's alpha = 0.70).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0. Data distributions were assessed using Kolmogorov–Smirnov and Shapiro–Wilk tests. Normally distributed variables were expressed as the mean ± standard deviation, while non-normally distributed variables were presented as the median and interquartile range (IQR, 25th–75th percentiles). Categorical variables were compared using the chi-square test. For continuous variables, the Mann–Whitney U test was used for two-group comparisons. Multivariable logistic regression analysis was performed to identify factors associated with being in the higher BMI group (≥85th percentile). Multivariable linear regression analysis was conducted to examine factors associated with the PSQI score. Variables identified from the literature as clinically relevant to obesity and sleep quality, as well as variables showing significance in univariate analyses, were considered for inclusion in the multivariable models. Statistical significance was set at $p < 0.05$.

Results

Sociodemographic characteristics and weight status

The study included 902 participants (51.3% female, n = 463; 48.7% male, n = 439) aged 12–15 years (mean age: 12.86 ± 0.02 years). According to BMI percentile categories, 7.2% of the students were underweight, 75.8% were of normal weight, 13.2% were overweight, and 3.8% were obese. The mean physical activity level was 4.81 ± 0.17 hours/week. Most participants (85.8%) reported ownership of a computer, smartphone, or tablet. Daily screen time of ≥3 hours was reported by 54.5% of the students, and 36.6% reported a daily digital gaming time of ≥3 hours. While 20.2% of the participants reported subjective sleep problems, the PSQI global scores revealed that 72.2% had poor sleep quality (Table I).

Factors associated with overweight and obesity

Significant differences in BMI percentile categories were observed according to sex ($p < 0.001$), paternal BMI category ($p = 0.001$), snacking in front of a screen ($p = 0.022$), and the presence of sleep problems ($p = 0.012$). No statistically significant differences were found according to parental education level, screen time, or physical activity ($p > 0.05$) (Table II).

Digital game addiction levels

According to the categorical classification of the DGAS, 2.9% (n = 26) of participants were classified as normal, 46.2% (n = 417) as low risk, 40.1% (n = 362) as risky, 8.5% (n = 77) as addicted, and 2.2% (n = 20) as highly addicted. Overall, 50.8% of participants were classified as being at risk or above. DGAS scores differed according to sex, daily screen time of ≥3 hours, and daily digital gaming time of ≥3 hours ($p < 0.001$ for all). Scores were higher among participants who reported snacking while playing digital games, snacking in front of a screen, frequent fast-food consumption (≥2 days/week), and lower breakfast frequency (≤4 days/week) ($p < 0.05$ for all).

DGAS scores were higher among students who reported sleep problems and among those with poor sleep quality ($p < 0.001$) (Table III).

Multivariable analyses

In the multivariable logistic regression analysis, a BMI at or above the 85th percentile was associated with male sex (odds ratio [OR] = 2.296, 95% confidence interval [CI]: 1.483–3.555, $p < 0.001$), paternal overweight/obesity (OR = 2.014, 95% CI: 1.003–4.044, $p = 0.049$), and physical activity of ≥3 hours/week (OR = 0.623, 95% CI: 0.412–0.943, $p = 0.025$). No statistically

Table I. Sociodemographic, lifestyle, and sleep characteristics of participants (n = 902).

Variable	n (%) or mean ± SD
Age (years)	12.86 ± 0.02
Sex	
Female	463 (51.3)
Male	439 (48.7)
Family monthly income	
Low	44 (4.9)
Middle	465 (51.5)
High	393 (43.6)
Mother's education level	
Primary school	425 (47.1)
High school or above	477 (52.9)
Father's education level	
Primary school	317 (35.2)
High school or above	585 (64.8)
BMI percentile categories	
Underweight	65 (7.2)
Normal weight	684 (75.8)
Overweight	119 (13.2)
Obese	34 (3.8)
Physical activity (hours/week)	4.81 ± 0.17
Ownership of computer/smartphone/ tablet	
Yes	774 (85.8)
No	127 (14.2)
Daily screen time	
<3 hours	410 (45.5)
≥3 hours	492 (54.5)
Daily digital game time	
<3 hours	573 (63.4)
≥3 hours	329 (36.6)
Sleep duration	
≤8 hours	457 (50.7)
>8 hours	445 (49.3)
Sleep problems	
No	353 (39.1)
Sometimes	367 (40.7)
Often	182 (20.2)
PSQI	
Good	251 (27.8)
Poor	651 (72.2)

Data are presented as mean ± standard deviation (SD) for continuous variables and n (%) for categorical variables. BMI, body mass index; PSQI, Pittsburgh Sleep Quality Index.

significant associations were observed for age, maternal BMI category, family income, screen time, dietary variables, or digital gaming-related variables ($p > 0.05$). Daily sleep duration showed a borderline association ($p = 0.050$) (Table IV).

In the multivariable linear regression analysis, the model was statistically significant ($F = 16.981$, $p < 0.001$) and explained 13.8% of the variance in the PSQI score (adjusted $R^2 = 0.138$). PSQI score was associated with the DGAS score (B = 0.049, 95% CI: 0.037–0.062, $p < 0.001$), age ≥13 years (B = 0.448, 95% CI: 0.175–0.721, $p = 0.001$), daily screen time of ≥3 hours (B = 0.644, 95% CI: 0.213–1.074, $p = 0.003$), sex (B = −0.969, 95% CI: −1.392 to −0.546, $p < 0.001$), and breakfast frequency of >4 days/week (B = −0.923, 95% CI: −1.342 to −0.504, $p < 0.001$). No associations were found with physical activity, fast food consumption, snacking while playing digital games, or BMI (kg/m^2) ($p > 0.05$) (Table V).

Discussion

This study examined the relationships between obesity-related indicators, digital game addiction, and sleep quality among secondary school students. The findings demonstrated that digital game addiction was independently associated with poorer sleep quality, whereas no significant relationships were observed between BMI and either digital game addiction or sleep quality after adjustment for confounders. To contextualize these findings, the following discussion addresses anthropometric outcomes, digital gaming behaviors, and sleep-related indicators in turn, before considering their interrelationships.

The prevalence of overweight (13.2%) and obesity (3.8%) observed in the present study was lower than the prevalence reported in several previous studies conducted among Turkish adolescents. Studies from different regions of Türkiye have reported higher rates, including 20.3% for overweight and 13.2% for obesity in İstanbul and a combined

Table II. Sociodemographic characteristics and lifestyle habits according to BMI percentile categories.

Variable	Underweight n (%)	Normal weight n (%)	Overweight n (%)	Obese n (%)	p
Sex					**<0.001**
Female	34 (52.3)	378 (55.3)	46 (38.7)	5 (14.7)	
Male	31 (47.7)	306 (44.7)	73 (61.3)	29 (85.3)	
Age (years)					0.218
<13 years	19 (29.2)	237 (34.6)	40 (33.6)	17 (50.0)	
≥13 years	46 (70.8)	447 (65.4)	79 (66.4)	17 (50.0)	
Mother's education level					0.545
Primary school	53 (81.5)	524 (76.6)	91 (76.5)	29 (85.3)	
High school or above	12 (18.5)	160 (23.4)	28 (23.5)	5 (14.7)	
Father's education level					0.534
Primary school	44 (67.7)	464 (67.8)	79 (66.4)	27 (79.4)	
High school or above	21 (32.3)	220 (32.2)	40 (33.6)	7 (20.6)	
Maternal BMI category					0.125*
Underweight/Normal weight	65 (100.0)	669 (97.8)	114 (95.8)	32 (94.1)	
Overweight/Obese	0 (0.0)	15 (2.2)	5 (4.2)	2 (5.9)	
Paternal BMI category					**0.001***
Underweight/Normal weight	64 (98.5)	650 (95.0)	107 (89.9)	27 (79.4)	
Overweight/Obese	1 (1.5)	34 (5.0)	12 (10.1)	7 (20.6)	
Physical activity (hours/week)					0.106
<3 hours	29 (44.6)	373 (54.5)	65 (54.6)	24 (70.6)	
≥3 hours	36 (55.4)	311 (45.5)	54 (45.4)	10 (29.4)	
Daily screen time					0.396
<3 hours	45 (69.2)	463 (67.7)	73 (61.3)	20 (58.8)	
≥3 hours	20 (30.8)	221 (32.3)	46 (38.7)	14 (41.2)	
Daily digital game time					0.353
<3 hours	29 (44.6)	258 (37.7)	47 (37.5)	9 (26.5)	
≥3 hours	36 (55.4)	426 (62.3)	72 (60.5)	25 (73.5)	
Snacking while playing digital games					0.571
Yes	34 (52.3)	303 (44.3)	56 (47.1)	17 (50.0)	
No	31 (47.7)	381 (55.7)	63 (52.9)	17 (50.0)	
Fast food consumption (days/week)					0.709
<2 days	30 (46.2)	296 (43.3)	53 (44.5)	18 (52.9)	
≥2 days	35 (53.8)	388 (56.7)	66 (55.5)	16 (47.1)	
Breakfast frequency (days/week)					0.290
≤4 days	15 (23.1)	252 (36.8)	36 (30.3)	13 (38.2)	
>4 days	50 (76.9)	432 (63.2)	83 (69.7)	21 (61.8)	

Data are presented as n (%). $p < 0.05$ was considered statistically significant (bold).
* Fisher's Exact Test was used; all other p-values were calculated using Pearson's chi-square test.
BMI, body mass index.

Table II. Continued.

Variable	Underweight n (%)	Normal weight n (%)	Overweight n (%)	Obese n (%)	p
Three main meals per day (days/week)					0.201
≤4 days	27 (41.5)	371 (54.2)	60 (50.4)	20 (58.8)	
>4 days	38 (58.5)	313 (45.8)	59 (49.6)	14 (41.2)	
Snacking between meals					0.282
Yes	33 (50.8)	298 (43.6)	45 (37.8)	12 (35.3)	
No	32 (49.2)	386 (56.4)	74 (62.2)	22 (64.7)	
Snacking in front of TV/computer					**0.022**
Yes	23 (35.4)	184 (26.9)	23 (19.3)	4 (11.8)	
No	42 (64.6)	500 (73.1)	96 (80.7)	30 (88.2)	
Sleep problems					**0.012**
Yes	23 (35.4)	126 (18.4)	25 (21.0)	8 (23.5)	
No	42 (64.6)	558 (81.6)	94 (79.0)	26 (76.5)	
Daily sleep duration					0.109
≤8 hours	29 (44.6)	338 (49.4)	68 (57.1)	22 (64.7)	
>8 hours	36 (55.4)	346 (50.6)	51 (42.9)	12 (35.3)	

Data are presented as n (%). $p < 0.05$ was considered statistically significant (bold).
* Fisher's Exact Test was used; all other p-values were calculated using Pearson's chi-square test.
BMI, body mass index.

prevalence of 22.7% in Şanlıurfa.[2,3] These differences may be attributed to regional and demographic variations as well as differences in socioeconomic status, dietary habits, physical activity levels, and study populations. Within the present sample, further evaluation of factors associated with anthropometric outcomes revealed that paternal overweight or obesity was associated with higher odds of increased BMI in adolescents. This finding is consistent with previous studies that identified parental weight status as an important determinant of childhood obesity, likely reflecting shared genetic, environmental, and lifestyle factors within families. In contrast, some studies have emphasized maternal influences more strongly, suggesting that parental effects may vary across populations and cultural contexts.[19-21] Beyond familial factors, higher levels of physical activity were associated with lower odds of increased BMI in the multivariable analysis. Previous studies have generally reported an inverse relationship between physical activity and obesity-related indicators in children and adolescents; however findings differ across studies.[22,23] Considering the decline in physical activity during adolescence and the more pronounced changes in adiposity during this period, maintaining regular physical activity is particularly important for weight control in this age group.[24] Taken together, these findings suggest that both familial and lifestyle-related factors may be associated with anthropometric outcomes in this population.

Regarding digital gaming behaviors, the prevalence of problematic gaming observed in the present study indicates a substantial burden among adolescents. Previous studies from Germany (11.9%) and Taiwan (15.1%) have also reported notable levels of problematic gaming; however, direct comparisons are limited due to differences in assessment tools, definitions, and cutoff values across studies.[25,26] Notably, no significant association was observed between digital game addiction and BMI in univariate analyses, consistent with previous large-scale studies by Busch and Cameron.[27,28] However,

Table III. Comparison of sociodemographic and lifestyle characteristics according to digital game addiction scale scores.

Variables	Total score	DGAS subdimensions			
		Excessive focus & conflict	Tolerance / value attribution	Role postponement	Withdrawal / immersion
Age (years)					
<13 years	51 (40–62)	13 (11–18)	17 (14–21)	11 (8–14)	8 (6–10)
≥13 years	48 (37–59)	13 (9–17)	17 (13–21)	10 (7–14)	7 (6–9)
p	0.026	0.009	0.265	0.063	0.090
Sex					
Female	44 (34–55)	12 (9–15)	15 (11–19)	9 (7–12)	7 (5–9)
Male	53 (42–66)	14 (11–19)	19 (15–23)	11 (8–15)	8 (6–10)
p	<0.001	<0.001	<0.001	<0.001	<0.001
BMI percentile categories					
Underweight/Normal weight	49 (38–60)	13 (10–17)	17 (13–22)	10 (7–14)	7 (6–9)
Overweight/Obese	48 (40–61)	13 (10–17)	17 (13–21)	11 (8–14)	8 (6–10)
p	0.840	0.758	0.641	0.322	0.318
Daily screen time					
<3 hours	45 (36–55)	12 (9–16)	16 (12–20)	9 (7–12)	7 (5–9)
≥3 hours	56 (46–72)	15 (12–21)	20 (16–25)	12 (9–17)	9 (7–11)
p	<0.001	<0.001	<0.001	<0.001	<0.001
Daily digital game time					
<3 hours	46 (36–55)	12 (9–16)	16 (12–20)	10 (7–13)	7 (5–9)
≥3 hours	64 (49–76)	17 (13–22)	22 (17–27)	14 (10–17)	9 (8–11)
p	<0.001	<0.001	<0.001	<0.001	<0.001
Snacking while playing digital games					
Yes	53 (42–70)	14 (11–20)	19 (15–24)	11 (8–15)	8 (6–10)
No	47 (37–58)	12 (9–16)	16 (12–21)	10 (7–13)	7 (6–9)
p	<0.001	<0.001	<0.001	<0.001	<0.001
Fast food consumption (days/week)					
<2 days	47 (36–57)	12 (9–16)	16 (12–20)	10 (7–13)	7 (5–9)
≥2 days	50 (39–63)	13 (10–18)	18 (14–22)	11 (8–14)	8 (6–10)
p	<0.001	0.005	<0.001	0.007	0.014
Breakfast frequency (days/week)					
≤4 days	52 (40–64)	14 (10–18)	17 (14–21)	11 (8–15)	8 (6–10)
>4 days	48 (38–59)	13 (9–17)	17 (13–21)	10 (7–14)	7 (6–9)
p	0.009	0.009	0.651	0.001	0.008

Data are presented as median (25th–75th percentile). Group comparisons were performed using the Mann–Whitney U test. $p < 0.05$ was considered statistically significant. The DGAS consists of four subdimensions: (i) excessive focus on and conflict related to digital gaming, (ii) tolerance development during gameplay and value attributed to gaming, (iii) postponement of individual and social duties/responsibilities, and (iv) psychological and physiological withdrawal symptoms and immersion in gaming.

BMI, body mass index; DGAS, Digital Game Addiction Scale; PSQI, Pittsburgh Sleep Quality Index.

Table III. Continued.

Variables	Total score	DGAS subdimensions			
		Excessive focus & conflict	Tolerance / value attribution	Role postponement	Withdrawal / immersion
Three main meals per day (days/week)					
≤4 days	50 (39–63)	13 (10–18)	17 (13–22)	11 (8–14)	8 (6–10)
>4 days	48 (38–59)	13 (9–17)	17 (13–21)	10 (7–14)	7 (6–9)
p	0.040	0.107	0.502	0.008	0.031
Snacking between meals					
Yes	52 (39–65)	14 (10–18)	18 (14–23)	11 (8–14)	8 (6–10)
No	47 (37–58)	12 (9–16)	17 (13–20)	10 (7–13)	7 (6–9)
p	0.001	<0.001	0.001	0.013	0.096
Snacking in front of TV/ computer					
Yes	55 (45–70)	15 (12–21)	20 (16–26)	11 (9–16)	8 (6–11)
No	46 (36–56)	12 (9–16)	16 (12–20)	10 (7–13)	7 (5–9)
p	<0.001	<0.001	<0.001	<0.001	<0.001
Sleep problem					
Yes	54 (42–71)	15 (11–21)	19 (15–25)	12 (8–15)	8 (6–11)
No	48 (37–58)	13 (9–16)	17 (13–21)	10 (7–14)	7 (6–9)
p	<0.001	<0.001	<0.001	<0.001	0.001
Sleep quality (PSQI)					
Good	44 (34–55)	12 (9–14)	16 (12–20)	9 (7–12)	7 (5–9)
Poor	51 (40–64)	13 (10–18)	18 (14–22)	11 (8–14)	8 (6–10)
p	<0.001	<0.001	<0.001	<0.001	<0.001

Data are presented as median (25th–75th percentile). Group comparisons were performed using the Mann–Whitney U test. $p < 0.05$ was considered statistically significant. The DGAS consists of four subdimensions: (i) excessive focus on and conflict related to digital gaming, (ii) tolerance development during gameplay and value attributed to gaming, (iii) postponement of individual and social duties/responsibilities, and (iv) psychological and physiological withdrawal symptoms and immersion in gaming.
BMI, body mass index; DGAS, Digital Game Addiction Scale; PSQI, Pittsburgh Sleep Quality Index.

higher digital game addiction scores were associated with certain unhealthy dietary behaviors, including snacking during gaming or screen use, frequent fast-food consumption, and lower breakfast frequency, similar to findings reported by Aşut et al.[29]

Sleep-related outcomes represented another key domain examined in this study. The prevalence of poor sleep quality (72.2%) was higher than the rates reported in previous Turkish adolescent studies (53.0% and 65.7%).[30,31] This difference may be related to behavioral factors such as increased screen exposure and gaming habits, as well as physiological mechanisms including the suppression of melatonin secretion due to blue light exposure.[32] In the multivariable analysis, higher digital game addiction scores and longer daily screen time were associated with poorer sleep quality, consistent with previous findings linking digital media use to sleep disturbances in adolescents.[10,33]

Several additional factors may also have contributed to the relatively high prevalence of poor sleep quality observed in the present study.

Table IV. Factors associated with overweight / obesity: multivariable logistic regression analysis.

Variable	β	SE	Wald	p	OR (95% CI)
Sex (male vs female (ref.))	0.831	0.223	13.884	<0.001	2.296 (1.483–3.555)
Age (≥13 vs <13 years (ref.))	-0.097	0.140	0.477	0.490	0.908 (0.690–1.195)
Family monthly income (low vs high (ref.))	-0.064	0.208	0.093	0.760	0.938 (0.624–1.412)
Paternal BMI category (overweight/obese vs normal (ref.))	0.700	0.356	3.873	0.049	2.014 (1.003–4.044)
Maternal BMI category (overweight/obese vs normal (ref.))	-0.126	0.650	0.038	0.846	0.881 (0.246–3.152)
Physical activity (≥3 vs <3 hours/week (ref.))	-0.473	0.211	5.010	0.025	0.623 (0.412–0.943)
Sleep duration (≤8 vs >8 hours (ref.))	-0.405	0.207	3.826	0.050	0.667 (0.445–1.001)
Daily screen time (≥3 vs <3 hours (ref.))	0.226	0.223	1.029	0.310	1.253 (0.810–1.938)
Daily digital game time (≥3 vs <3 hours (ref.))	0.000	0.006	0.001	0.970	1.000 (0.987–1.012)
Fast food consumption (≥2 vs <2 days/week (ref.))	-0.005	0.211	0.001	0.980	0.995 (0.658–1.503)
Snacking between meals (yes vs no (ref.))	0.110	0.225	0.238	0.626	1.116 (0.718–1.735)
Snacking while playing digital games (yes vs no (ref.))	0.247	0.263	0.886	0.347	1.281 (0.765–2.143)

Reference categories are indicated in parentheses. $p < 0.05$ was considered statistically significant.
β, regression coefficient; BMI, body mass index; CI, confidence interval; OR, odds ratio; SE, standard error; Wald, Wald statistic.

Table V. Multivariable linear regression analysis of factors associated with PSQI score.

Variable	B	SE	β	t	p-value	95% CI
DGAS total score	0.049	0.006	0.265	7.648	<0.001	0.037–0.062
Age (≥13 vs <13 years (ref.))	0.448	0.139	0.102	3.215	0.001	0.175–0.721
Sex (male vs female (ref.))	-0.969	0.216	-0.148	-4.493	<0.001	-1.392– -0.546
Daily screen time (≥3 vs <3 hours (ref.))	0.644	0.219	0.098	2.936	0.003	0.213–1.074
Breakfast frequency (>4 vs ≤4 days (ref.))	-0.923	0.213	-0.135	-4.325	<0.001	-1.342– -0.504
Physical activity (<3 vs ≥3 hours/week (ref.))	-0.091	0.208	-0.014	-0.437	0.662	-0.498–0.317
Fast food consumption (≥2 vs <2 days (ref.))	0.153	0.208	0.023	0.733	0.463	-0.256–0.562
Snacking while playing digital games (yes vs no (ref.))	-0.207	0.238	-0.028	-0.870	0.385	-0.674–0.260
BMI (kg/m^2)	0.001	0.002	0.023	0.752	0.452	-0.002–0.004

Reference categories are indicated in parentheses. p < 0.05 was considered statistically significant (bold).
B, unstandardized coefficient; β, standardized coefficient; BMI, body mass index; CI, confidence interval; DGAS, Digital Game Addiction Scale; SE, standard error; t, t-statistic.

Self-reported sleep measures may not fully capture objective sleep parameters that can be assessed by actigraphy or polysomnography.[34] From a developmental perspective, this age group is characterized by a biologically driven circadian phase delay, in which sleep onset shifts later and may conflict with early school start times, potentially contributing to reduced sleep duration.[35,36] Pubertal hormonal changes may further amplify these sleep disturbances during this developmental period.[35] Finally, differences in the socioeconomic and lifestyle characteristics of the study population may have played a role in the observed findings.

A further consideration is the discrepancy between subjective sleep complaints and PSQI-defined poor sleep quality. This may reflect differences between the global self-perception of sleep and the multidimensional structure of the PSQI, which assesses domains such as sleep latency, duration, and daytime dysfunction. Adolescents may underreport sleep problems in general assessments, whereas structured instruments such as the PSQI may capture

broader sleep-related difficulties. Therefore, these findings should be interpreted within this methodological context.[18]

With respect to the relationship between anthropometric and sleep-related outcomes, BMI was not significantly associated with the PSQI score in the multivariable model used in this study. This finding is consistent with some adolescent studies but contrasts with others, suggesting that behavioral and developmental factors such as physical activity, dietary habits, and circadian changes may play a more prominent role than BMI during early adolescence.[37-39] Supporting this interpretation, several lifestyle factors identified in this study, including lower breakfast frequency, irregular meal patterns, increased snacking, and prolonged screen exposure, were associated with poorer sleep quality, highlighting the importance of behavioral factors in shaping sleep outcomes in adolescents.

Several limitations of the present study should be acknowledged. The cross-sectional design precludes causal inference, and self-reported measures of physical activity, digital game addiction, and screen time may be subject to recall bias and misclassification. Self-reported parental BMI and socioeconomic status may also introduce reporting bias. Furthermore, the absence of data on pubertal status and mental health factors may limit the interpretation of the findings, and the school-based sampling frame may restrict generalizability to the broader adolescent population. Despite these limitations, the study has notable strengths, including the use of validated instruments (PSQI and DGAS) and a relatively large school-based sample, which support the reliability and generalizability of the findings.

In conclusion, digital game addiction was associated with poorer sleep quality among secondary school students. In contrast, no significant associations were observed between BMI and either digital game addiction or sleep quality. These findings suggest that behavioral factors related to digital gaming may play a more prominent role in adolescent sleep health than anthropometric indicators during early adolescence. The high prevalence of both problematic gaming behaviors and poor sleep quality highlights the importance of addressing digital health behaviors in adolescent health assessments. Further longitudinal studies are needed to clarify the underlying mechanisms and causal pathways.

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Ethical approval

The study was approved by Non-Pharmaceutical and Non-Medical Device Research Ethics Committee of KTO Karatay University Faculty of Medicine (date: December 29, 2022, number: 2022-001). Written informed consent was obtained from parents or legal guardians, and verbal/written assent was obtained from all participating students prior to data collection.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: SP; data collection: MÖ; analysis and interpretation of results: MÖ, SK; draft manuscript preparation: MÖ, SK, SP. All authors reviewed the results and approved the final version of 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

Prevalence and determinants of suspected scoliosis in fifth-grade students: a population-based school screening study

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ABSTRACT

Background. The aim of this study was to conduct school-based scoliosis screening among fifth-grade students and to determine the rate of screening positivity for suspected scoliosis.

Methods. During the 2024–2025 academic year, scoliosis screening was conducted among 6,587 students attending all middle schools in Eskişehir province, Türkiye. Data were collected through scoliosis screening examinations performed by physiotherapists and a questionnaire administered to the students. The screening examinations included visual inspection, the forward bending test, and measurements using a scoliometer. Students with a trunk rotation ≥5° on scoliometer assessment and/or with physical signs such as visual asymmetry, scapular, shoulder, or pelvic imbalance, or apparent leg length discrepancy were referred for specialist evaluation. Chi-square test and logistic regression analysis were performed.

Results. The ages of the students ranged between 10-11 years (mean ± standard deviation: 10.26±0.44). According to the assessments performed by physiotherapists, visual asymmetry suggestive of scoliosis was observed on inspection in 240 students (3.6%). Scoliometer measurements showed trunk rotation angles of 5 degrees or greater in 355 students (5.4%). As a result of the screening examinations, 725 students (11.0%) were screening-positive for suspected scoliosis and were referred to higher-level healthcare facilities for further evaluation. Risk factors were more prevalent among female students. In multivariate analysis, screening positivity for suspected scoliosis was significantly associated with female sex, low body mass index, a family history of scoliosis in first-degree relatives, chest stabbing sensation or pain during breathing, and skin findings on the back (discoloration, large nevi, or localized hypertrichosis).

Conclusions. This study determined that the screening positivity rate for suspected scoliosis among fifth-grade students was 11.0%. Factors that may be associated with scoliosis were found to be more common in female students; however, the multifactorial nature of scoliosis suggests that screening positivity may be influenced by a complex interaction of biological, anthropometric, familial, and postural factors. The findings also highlight the importance of early recognition and risk-based approaches in school-aged populations, and underscore the public health relevance of awareness and screening practices integrated within existing school health services and primary care.

Key words: school, screening, scoliosis, spinal curvature.

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Scoliosis is a spinal disorder characterized by lateral curvature of the spine to the right or left in an S- or C-shaped pattern, accompanied by vertebral rotation.[1] It is the most common spinal deformity.[2] Although the etiology of scoliosis varies, it is generally classified as congenital, neuromuscular, syndromic, or idiopathic. Idiopathic scoliosis is the most prevalent type and is further categorized as infantile, juvenile, or adolescent idiopathic scoliosis according to the age of onset. Adolescent idiopathic scoliosis is the most frequently observed, as it develops during periods of rapid physical growth.[3-5] Adolescent idiopathic scoliosis develops insidiously in healthy children, with no clearly identifiable cause, and may progress over time. It is reported to affect approximately 2–3% of the adolescent population. Girls aged 10–12 years are at the highest risk for both the development and progression of scoliosis.[1,4,6,7] While scoliosis may be suspected on physical examination, a definitive diagnosis is established using radiological imaging. Radiographically, scoliosis is defined as a lateral spinal curvature of 10 degrees or greater.[3]

Scoliosis may lead to severe pain, functional limitations, progressive deformity, and serious complications involving the cardiopulmonary system. In addition, it can cause psychological, cosmetic, and social problems. Many postural disorders and spinal deformities observed in adulthood, including scoliosis, are known to originate in childhood and may progress during periods of ongoing skeletal growth. Therefore, early recognition is of critical importance.[8-10] With early diagnosis following appropriate clinical and radiological evaluation and timely intervention, disease progression can be closely monitored and slowed. Deformities detected at an early stage may be managed with exercise, physical therapy, and brace treatment, thereby preventing progression to a severity that would require surgical intervention. Early supportive interventions also help avoid invasive and costly surgical procedures,[8,11,12] ultimately improving quality of life in later years. Early diagnosis also provides social and psychological benefits for both the child and the family.[8]

Although school-based scoliosis screening programs remain a subject of debate in the literature, with some opposing views, many studies have reported that such programs facilitate early detection, reduce the need for surgery, and are cost-effective. Several studies, countries, and orthopedic associations recommend school screening for scoliosis, particularly in adolescents who are at high risk. Although screening age ranges vary between 7 and 18 years, scoliosis is most commonly detected between the ages of 13 and 15, and screening is generally considered most appropriate between 10 and 14 years of age.[4,8,11,13,14] School screenings can identify spinal curvatures that may not be noticed by families or teachers. In a national study, two-thirds of parents of children with a scoliosis angle between 10 and 19 degrees were reported to be unaware of the deformity.[15] Another national study found that parental awareness of scoliosis was low among parents of children aged 8–18 years, with most having never heard of the condition and lacking awareness of its risk factors.[16]

However, school-based scoliosis screening programs remain controversial, and concerns have been raised regarding potential disadvantages. Reported limitations include false-positive results leading to unnecessary referrals, increased healthcare costs, and exposure to additional radiographic examinations, despite potential benefits of early detection shown in recent meta-analyses.[17] Furthermore, issues related to potential stigmatization and the psychological impact of scoliosis on adolescents have been documented in the literature, including adverse effects on body image and psychosocial well-being that may influence treatment adherence and quality of life.[18,19] Anxiety in children and families following a positive screening result may represent an unintended consequence of such programs.

It should also be noted that scoliosis assessment is generally included in routine adolescent well-child visits in many healthcare systems as part of standard preventive care.[20] However, awareness of scoliosis among parents and adolescents is often limited, and attendance at regular preventive health visits during early adolescence may be inconsistent, leading to missed opportunities for early identification.[16] In this context, school-based screening may serve as an alternative or complementary strategy, particularly in settings where access to routine follow-up is suboptimal. Careful consideration of both the benefits and limitations of school-based screening is therefore necessary to inform evidence-based policy and clinical practice.

The aim of this study was to conduct scoliosis screening among fifth-grade students attending schools and to determine the screening positivity rate for suspected scoliosis.

Materials and Methods

Study design and study group

This study was part of a province-based population screening program conducted in Eskişehir Province, located in the Central Anatolia Region of Türkiye. The study was conducted within the scope of the "Early Detection and Screening Program for Scoliosis," which was implemented under a protocol signed between the Eskişehir Provincial Directorate of National Education and the Eskişehir Provincial Directorate of Health. The program aimed to identify students with suspected scoliosis through screening, ensure appropriate referral for early treatment, and prevent long-term complications. Within this framework, it was planned to reach all fifth-grade students (n=10634) enrolled in middle schools affiliated with the Eskişehir Provincial Directorate of National Education during the 2024–2025 academic year. No sampling method was applied.

Scoliosis screening was performed in all middle schools across the province (n=131) among 6587 students (61.9% of the target population) whose parents provided informed consent and who voluntarily agreed to participate. Screening could not be performed in 2145 students (20.2%) due to parental refusal. In addition, students were not screened due to chronic absenteeism in 117 cases (1.1%), absence on the screening day in 445 cases (4.2%), failure to return the consent form in 1121 cases (10.5%), refusal to participate in 6 cases (0.05%), a self-reported prior diagnosis of scoliosis in 44 cases (0.4%), and the presence of an orthopedic or intellectual disability preventing participation in 3 cases (0.02%). Moreover, a total of 166 (1.6%) students were excluded from the analysis because they reported ages other than 10 or 11, which is the expected age range for 5th grade. They were removed to prevent potential distortion in the interpretation of the results, as they may have been at different stages of growth and maturation. A flowchart illustrating the inclusion and exclusion of participants is presented in Fig. 1.

Data collection

Data were collected through scoliosis screening examinations performed by physiotherapists and a questionnaire administered to the students.

The first section of the questionnaire was completed by the students themselves in the classroom under supervision. This section included questions on sociodemographic characteristics (age, sex, weight, and height) and symptoms potentially associated with scoliosis, such as a family history of scoliosis in first-degree relatives; a sensation of stabbing or pain in the chest during breathing; pain while lying supine or when turning to the right or left; back pain during coughing or sneezing; and marked pain when carrying a school bag on one shoulder (right or left).

The second section of the questionnaire was completed by the healthcare personnel. The second part of the questionnaire included findings from the screening physical

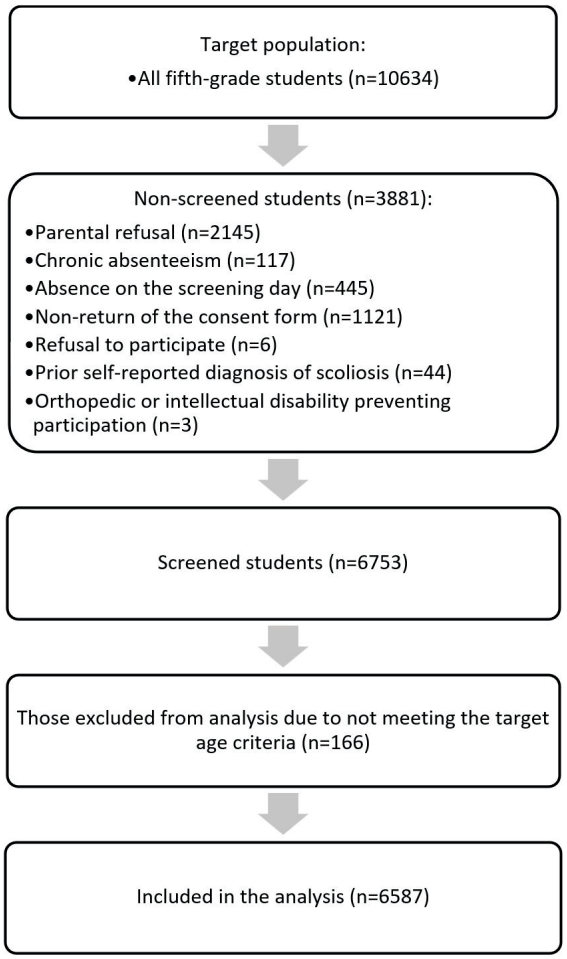

Fig. 1. Flowchart of participant inclusion and exclusion.

examination, which consisted of visual inspection, the forward bending test, and scoliometer measurement. Findings recorded included visual asymmetry suggestive of scoliosis, back skin findings (e.g., discoloration, large nevi, localized hypertrichosis), shoulder and pelvic imbalance, scapular asymmetry during the forward bending test, apparent leg length discrepancy in the standing position, and the angle of trunk rotation. In addition, female students were asked about menarche status.

The screening examinations were conducted by four physiotherapists. Prior to the screening, training on scoliosis assessment was provided to ensure that all examinations were performed in a standardized manner. Each physiotherapist was accompanied by one assistant healthcare staff (nurses, midwives, health officers, etc.). The assistant healthcare personnel did not perform the screening examinations; they were present only to support the physiotherapists during the examinations and to assist with completing questionnaires and maintaining records. Examinations were conducted in designated private areas prepared by the schools in accordance with privacy principles. Male students were examined with the upper body fully uncovered, while female students were examined wearing undershirts. Visual inspection was performed with students standing upright, feet shoulder-width apart and parallel. The presence of visual asymmetry suggestive of scoliosis visible on inspection was assessed. Shoulder balance was evaluated by comparing shoulder height levels.[8] Pelvic balance was assessed by examining the alignment of the anterior superior iliac spines while the feet were placed side by side with the medial malleoli touching.

The forward bending test, first described by William Adams in 1865, is a clinical assessment method that allows the identification of suspected scoliosis through evaluation of posture. Its main advantages include being easily applicable by physiotherapists, brief in duration, painless, and noninvasive. During the administration of the test, the examiner stood behind the child and asked the child to bend forward to approximately 90 degrees at the hips with the feet together and the knees in full extension. With the arms hanging downward and the palms facing each other, the spine was inspected, and the presence of asymmetry along the horizontal plane as well as imbalance between the scapulae was assessed.[2,3] This was followed by measurement using a scoliometer, and students with a trunk rotation angle (ATR) of 5 degrees or greater were considered screening-positive for suspected scoliosis. In accordance with the recommendations of the Scoliosis Research Society (SRS) International

Task Force, an expert panel composed of orthopedic surgeons and spine specialists, an ATR threshold of 5°–7° measured by scoliometer is generally used as a referral criterion in school scoliosis screening programs.[13,21] Although some sources have used 7° or higher cutoffs, some studies support adopting an ATR threshold of ≥5° as a practical criterion—particularly when combined with clinical examination findings—as it improves sensitivity and facilitates earlier detection in school-based screening programs.[4,22,23] Accordingly, consistent with these recommendations, an ATR of 5 degrees was adopted as the cutoff value in the present study.

Referral criteria

All students with visual asymmetry suggestive of scoliosis on inspection or a scoliometer-measured trunk rotation angle of 5 degrees or higher were referred to relevant specialist physicians for further evaluation and treatment. In addition, students with positive findings on physical examination (scapular imbalance detected during the forward bending test, shoulder imbalance, pelvic imbalance, apparent leg length discrepancy) were referred to the relevant specialist physicians for further evaluation, even if the angle of trunk rotation was <5, provided that these findings could not be attributed to causes other than suspected scoliosis.

Statistical analysis

Body mass index (BMI) was calculated by dividing body weight (kg) by height squared (m^2). Because weight, height, and BMI values vary by age in children and percentile values are used to monitor growth and development, BMI values in this study were evaluated according to age- and sex-specific reference percentile values after calculation.[24]

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 15 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented as frequency, percentage, minimum, maximum, mean, and standard deviation. The chi-square test was used for the analysis of categorical variables. To identify independent predictors of screening positivity for suspected scoliosis, multivariable logistic regression analysis was performed. The dependent variable was screening positivity for suspected scoliosis (0=no, 1=yes). Variables that were found to be statistically significant in the univariate (chi-square) analysis were entered into the multivariable model using the enter method, and all selected variables were included simultaneously. Independent variables included age, BMI, family history of scoliosis in first-degree relatives, chest stabbing sensation or pain during breathing, pain while lying supine or turning right/left, marked pain when carrying a school bag on one shoulder, and skin findings on the back (discoloration, large nevi, or localized hypertrichosis). All independent variables were coded as binary (0/1). Male sex, BMI >95th percentile, and the absence of the respective clinical features ("No") were used as reference categories. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the strength of associations. Multicollinearity among independent variables was evaluated using variance inflation factor (VIF) values prior to multivariable logistic regression analysis, and no significant multicollinearity was detected. VIF values ranged between 1.010 and 1.139. Statistical significance was set at $p<0.05$.

Ethical approval

The study was approved by Eskişehir City Hospital Scientific Research Ethics Committee.

Results

The ages of the students who participated in the screening ranged from 10 to 11 years, with a mean age of 10.26±0.44 years. Of the students, 52.5% (n=3457) were female and 47.5% (n=3130)

were male. The majority of the study group, 91.7% (n=6040), consisted of students attending schools in urban areas, while 8.3% (n=547) were enrolled in schools in non-urban areas.

The BMI of 82.6% of the students (n=5440) was within the 5th–95th percentile range. A total of 382 students (5.8%) reported a history of scoliosis in a first-degree relative. Overall, 587 students (8.9%) reported a stabbing sensation or pain in the chest during breathing, 472 (7.2%) reported pain while lying supine or when turning to the right or left, 407 (6.2%) reported back pain during coughing or sneezing, and 1641 (24.9%) reported marked pain when carrying a school bag on one shoulder.

According to the assessments performed by physiotherapists, visual asymmetry suggestive of scoliosis was detected on visual inspection in 240 students (3.6%). Scoliometer measurements showed trunk rotation angles of 5 degrees or greater in 355 students (5.4%). Additionally, 51 students (0.8%) had a trunk rotation angle of 7 degrees or greater, and 6 students (0.1%) had a trunk rotation angle of 10 degrees or greater. Skin findings on the back, including discoloration, large nevi, or localized hypertrichosis, were identified in 288 students (4.4%). Shoulder imbalance was observed in 626 students (9.5%), pelvic imbalance in 196 students (3.0%), and scapular imbalance during the forward bending test in 477 students (7.2%). Apparent leg length discrepancy in the standing position was detected in 40 students (0.6%).

As a result of the screening examinations, 725 students (11.0%) were identified as screening-positive for suspected scoliosis and were referred to higher-level healthcare facilities for further evaluation. Of the students with positive screening results, 670 (92.4%) were attending schools in urban areas and 55 (7.6%) were from non-urban areas; 65.7% (n=476) were female and 34.3% (n=249) were male. According to the univariate analyses, screening positivity for suspected scoliosis was higher in females and in individuals with a family history of scoliosis in first-degree relatives. In addition, it was determined that screening positivity increased as BMI percentile ranges decreased. Screening positivity was also significantly higher among those reporting chest stabbing sensation or pain during breathing, pain while lying supine or turning right/left, marked pain when carrying a school bag on one shoulder, and skin findings on the back (discoloration, large nevi, or localized hypertrichosis). The distribution of students with and without screening positivity for suspected scoliosis according to selected characteristics and symptoms potentially associated with scoliosis is presented in Table I.

A total of 81.8% of the female students (n=2828) reported having reached menarche. No significant difference was found in screening positivity for suspected scoliosis according to the menarche status of female students. The distribution of female students with and without screening positivity for suspected scoliosis according to menarche status is presented in Table II.

In the logistic regression analysis, the Hosmer–Lemeshow test indicated good model fit ($p=0.254$). The Nagelkerke R^2 value showed that the model explained 3.4% of the variance. No multicollinearity was detected (VIF values ranged between 1.010 and 1.139). According to the logistic regression analysis, screening positivity for suspected scoliosis was 1.68 times higher in female students. Compared with those with a BMI >95th percentile, screening positivity was 2.59 times higher in students with a BMI <5th percentile and 1.86 times higher in those with a BMI between the 5th and 95th percentiles. Additionally, screening positivity was 1.74 times higher in students with a family history of scoliosis in first-degree relatives, 1.3 times higher in those reporting chest stabbing sensation or pain during breathing, and 1.5 times higher in those with skin findings on

Table I. Distribution of students with and without suspected scoliosis according to selected characteristics and symptoms potentially associated with scoliosis.

Characteristics		Screening result		Total n (%)**	p
		Suspected scoliosis n (%)*	Normal n (%)*		
Sex	Female	476 (13.8)	2981 (86.2)	3457 (52.5)	<0.001
	Male	249 (8.0)	2881 (92.0)	3130 (47.5)	
BMI	< 5th percentile	75 (15.4)	413 (84.6)	488 (7.4)	<0.001
	5th–95th percentile	611 (11.2)	4829 (88.8)	5440 (82.6)	
	> 95th percentile	39 (5.9)	620 (94.1)	659 (10.0)	
Family history of scoliosis in first-degree relatives	Yes	70 (18.3)	312 (81.7)	382 (5.8)	<0.001
	No	655 (10.6)	5550 (89.4)	6205 (94.2)	
Chest stabbing sensation or pain during breathing	Yes	88 (15.0)	499 (85.0)	587 (8.9)	0.001
	No	637 (10.6)	5363 (89.4)	6000 (91.1)	
Pain while lying supine or turning right/left	Yes	66 (14.0)	406 (86.0)	472 (7.2)	0.032
	No	659 (10.8)	5456 (89.2)	6115 (92.8)	
Back pain during coughing or sneezing	Yes	48 (11.8)	359 (88.2)	407 (6.2)	0.600
	No	677 (11.0)	5503 (89.0)	6180 (93.8)	
Marked pain when carrying a school bag on one shoulder	Yes	218 (13.3)	1423 (86.7)	1641 (24.9)	0.001
	No	507 (10.3)	4439 (89.7)	4946 (75.1)	
Skin findings on the back (discoloration, large nevi, or localized hypertrichosis)	Yes	53 (18.4)	235 (81.6)	288 (4.4)	<0.001
	No	672 (10.7)	5627 (89.3)	6299 (95.6)	
Total		725 (11.0)	5862 (89.0)	6587 (100)	

*Row percentages
**Column percentages

Table II. Distribution of female students with and without suspected scoliosis according to menarche status.

Characteristics		Screening Result		Total n (%)**	p
		Suspected scoliosis n (%)*	Normal n (%)*		
Menarche status	Yes	390 (13.8)	2438 (86.2)	2828 (81.8)	0.938
	No	86 (13.7)	543 (86.3)	629 (18.2)	
Total		476 (13.8)	2981 (86.2)	3457 (100)	

*Row percentages
**Column percentages

the back (discoloration, large nevi, or localized hypertrichosis). The results of the logistic regression analysis performed using variables found to be associated with screening positivity for suspected scoliosis in univariate analyses are presented in Table III.

When the distribution of factors associated with screening positivity for suspected scoliosis identified in univariate analyses was examined according to sex, all factors were found to be more frequent in girls, except for "pain while lying supine or turning right/left" (Table IV).

Table III. Results of the logistic regression analysis of variables associated with suspected scoliosis.

Variable	p	OR	95% CI
Sex (Reference: Male)			
Female	<0.001	1.689	1.432-1.993
BMI (Reference: >95th percentile)			
5th–95th percentile	<0.001	1.867	1.333-2.613
< 5th percentile	<0.001	2.590	1.718-3.902
Family history of scoliosis in first-degree relatives (Reference: No)			
Yes	<0.001	1.741	1.321-2.295
Chest stabbing sensation or pain during breathing (Reference: No)			
Yes	0.041	1.309	1.011-1.695
Pain while lying supine or turning right/left (Reference: No)			
Yes	0.424	1.127	0.840-1.512
Marked pain when carrying a school bag on one shoulder (Reference: No)			
Yes	0.165	1.139	0.948-1.368
Skin findings on the back (discoloration, large nevi, or localized hypertrichosis) (Reference: No)			
Yes	0.011	1.509	1.101-2.068
Constant B:-3.136 p<0.001 OR: 0.043			

Omnibus tests of model coefficients p<0.001
Hosmer and Lemeshow test p=0.254
Nagelkerke R^2: 0.034.
CI: confidence interval, OR: odds ratio.

Table IV. Distribution of factors associated with suspected scoliosis according to sex based on univariate analyses.

Characteristics		Sex		Total n (%)**	p
		Female n (%)*	Male n (%)*		
BMI	< 5th percentile	300 (61.5)	188 (38.5)	488 (7.4)	<0.001
	5th–95th percentile	2893 (53.2)	2547 (46.8)	5440 (82.6)	
	> 95th percentile	264 (40.1)	395 (59.9)	659 (10.0)	
Family history of scoliosis in first-degree relatives	Yes	230 (60.2)	152 (39.8)	382 (5.8)	0.002
	No	3227 (52.0)	2978 (48.0)	6205 (94.2)	
Chest stabbing sensation or pain during breathing	Yes	336 (57.2)	251 (42.8)	587 (8.9)	0.016
	No	3121 (52.0)	2879 (48.0)	6000 (81.1)	
Pain while lying supine or turning right/left	Yes	261 (55.3)	211 (44.7)	472 (7.2)	0.204
	No	3196 (52.3)	2919 (47.7)	6115 (92.8)	
Marked pain when carrying a school bag on one shoulder	Yes	1011 (61.6)	630 (38.4)	1641 (24.9)	<0.001
	No	2446 (49.5)	2500 (50.5)	4946 (75.1)	
Skin findings on the back (discoloration, large nevi, or localized hypertrichosis)	Yes	256 (88.9)	32 (11.1)	288 (4.4)	<0.001
	No	3201 (50.8)	3098 (49.2)	6299 (95.6)	
Total		2457 (52.5)	3130 (47.5)	6587 (100.0)	

*Row percentages
**Column percentages

Discussion

In this study, fifth-grade students attending all middle schools were screened to investigate the prevalence of suspected scoliosis. Because the methods used for scoliosis screening are not definitive diagnostic tools, they may lead to false-positive or false-negative results. For this reason, combining multiple screening methods rather than relying on a single assessment approach is recommended to reduce false-positive findings and avoid unnecessary referrals.[4,8] In line with this approach, multiple screening methods were used in the present study. Supporting this strategy, a meta-analysis evaluating the clinical effectiveness of school-based scoliosis screening reported higher referral rates and lower positive predictive values when screening was conducted using the forward bending test alone.[25] Therefore, the use of a multimodal screening approach in large, population-based school programs may improve the accuracy of identifying students with suspected scoliosis and enhance the overall clinical and economic efficiency of scoliosis screening initiatives.

In the present study, the referral rate was 11.0%, which is higher than the pooled referral rates reported in the literature. A meta-analysis and a systematic review of school-based scoliosis screening programs reported pooled referral rates for radiographic evaluation of 5.0% and 6.6%, respectively, based on screening methods such as the forward bending test, ATR, and Moiré topography.[10,25] Previous school-based screening studies from different countries have reported a wide range of suspected scoliosis prevalence and positivity rates, generally varying between approximately 0.1% and 8.6%, depending on the screening methods and age groups.[9,26-32] Similarly, national studies have demonstrated a wide range of prevalence estimates, varying from as low as 0.48% to as high as 7.6%, depending on the screening approach and population characteristics.[2,15,33,34] In the present study, students with a scoliometer measurement of ≥5° were considered to have suspected scoliosis and referred for further evaluation. In addition, students with a trunk rotation angle of <5° were also referred if they had positive clinical findings on physical examination, such as scapular, shoulder, or pelvic asymmetry or apparent leg length discrepancy, when these findings were suggestive of scoliosis and could not be attributed to other causes. In the literature, although a threshold of 5° is commonly used, some studies recommend a higher cutoff value of 7° [35], which may partly explain the higher referral rate observed in our study. Overall, variations across studies are likely attributable to differences in screening methods, diagnostic thresholds, age groups, and the sociocultural and environmental characteristics of the populations. These factors should be considered when interpreting and comparing findings across different settings.

In the present study, suspected scoliosis was found to be 1.68 times more common among female students, indicating a moderate association. The magnitude of this association is consistent with the biological basis of idiopathic scoliosis and supports the contribution of sex-related factors to disease susceptibility. Consistent with our findings, in the literature, numerous studies have reported that both the risk and prevalence of scoliosis are higher among females.[2,4,8,9,15,28,29,36] In a study conducted in Croatia, the positivity rate of scoliosis screening increased from 5.8% to 8.3% among female students over a 10-year period, while it decreased from 3.8% to 3.2% among male students.[32] Conversely, a study from India reported a higher prevalence of adolescent idiopathic scoliosis among males[37], suggesting that sex-related differences in scoliosis risk may vary across populations and may be influenced by methodological, demographic, and contextual factors.

In this study, students with lower BMI had a higher prevalence of suspected scoliosis, which decreased as BMI increased. According to a study, suspected scoliosis was found to be 1.86 times more common in students with a BMI between the 5th and 95th percentiles, and 2.59 times more common in those with a BMI <5th

percentile, compared to students with a BMI at or above the 95th percentile, representing the strongest association among the variables examined. Consistent with our findings, the literature generally indicates that low BMI is more closely associated with scoliosis. School-based screening studies conducted in various countries have reported a higher risk of scoliosis among underweight students or those with low BMI.[9,28,32,37,38] This association may be explained by the greater likelihood of nutritional deficiencies among students with low BMI, including inadequate intake of vitamin D and calcium, reduced bone mineral density, and consequently lower bone strength, all of which may predispose these individuals to spinal deformities. The comparatively larger effect size observed for low BMI may therefore indicate a more prominent role in risk stratification within school-based screening contexts.

Previous studies have demonstrated a hereditary component in idiopathic scoliosis and have identified associations between certain genetic mutations and the development of idiopathic scoliosis.[39-42] In line with the existing literature, the present study found that students who reported having a first-degree relative with scoliosis had a 1.74-fold higher prevalence of suspected scoliosis, indicating a moderate association. This finding supports the contribution of genetic susceptibility to scoliosis development and highlights the importance of family history as a key factor to be considered in school-based screening programs, as incorporating familial risk may improve early identification of children with suspected scoliosis. The observed effect size is consistent with the known hereditary contribution and supports the inclusion of family history as a key component in risk-informed assessment strategies.

In addition to demographic and familial factors, certain clinical findings were also associated with suspected scoliosis. Skin findings on the back (discoloration, large nevi, or localized hypertrichosis) were associated with a 1.50-fold increase in prevalence, indicating a moderate elevation and suggesting a potentially meaningful clinical signal during observational screening. In contrast, symptoms such as chest stabbing sensation during breathing were associated with a 1.30-fold increase in suspected scoliosis, reflecting a more modest association and a comparatively limited contribution to the identification of at-risk students.

Taken together, these findings highlight that the interpretation of effect sizes should be considered within context rather than according to rigid numerical thresholds. Even modest associations may have public health relevance when the exposure is common within the population. The variability in effect magnitude observed in this study may therefore help inform risk-informed assessment strategies, prioritizing factors with comparatively larger associations while maintaining awareness of the multifactorial etiology of scoliosis.

In girls, sex hormones whose expression and levels increase after menarche play a critical role in bone growth, maintenance, and maturation. Menarche is associated with a deceleration in growth velocity. Because the risk of scoliosis progression is highest during periods of rapid skeletal growth, the risk of curve progression in girls is greater before menarche and decreases thereafter. Delayed menarche leads to delayed skeletal maturation, which may increase the risk of scoliosis development and progression.[1,43] A study conducted in South Korea reported a higher risk of scoliosis among girls with late menarche[43], whereas a study from Bosnia and Herzegovina and Serbia found no significant difference in age at menarche between girls with and without scoliosis.[44] The present study did not identify a significant association between menarcheal status and suspected scoliosis. The peak height velocity in girls occurs approximately 6–12 months before menarche.[45] Some premenarcheal girls may have already passed their peak growth velocity and, consequently, the period of greatest risk for the development or progression of scoliosis. For this reason, no significant difference in suspected scoliosis according to menarcheal

status may have been identified in our study. The discrepancies among studies in the literature may be attributed to differences in study design, age distribution, and criteria used to define suspected scoliosis.

In the present study, when symptoms commonly observed in spinal deformities and potentially associated with scoliosis were assessed, symptoms such as chest stabbing sensation or pain during breathing, pain while lying supine or turning to either side, and back pain during coughing or sneezing were reported relatively infrequently. In contrast, it was noteworthy that approximately one quarter of the students reported experiencing marked pain when carrying a school bag on one shoulder. Similarly, a study conducted in Turkey reported that nearly one fifth of students carried their school bags on a single shoulder, about one fifth frequently experienced back pain, and more than half were disturbed by the weight of their school bags.[2] Scoliosis may also develop secondary to impaired spinal balance without any underlying anatomical vertebral abnormality, a condition defined as functional scoliosis. Poor postural habits are among the factors that may contribute to the development and progression of functional scoliosis.[29,36] Postural patterns such as unilateral shoulder elevation or depression, increased lumbar lordosis and thoracic kyphosis beyond normal limits, and disturbances in lumbar and pelvic alignment are considered examples of improper posture.[29] Carrying a school bag on one shoulder may lead to asymmetrical shoulder positioning and unequal load distribution, which could theoretically contribute to postural imbalance and spinal asymmetry over time. Although in our study, students who reported pain while carrying their school bag on one shoulder were not found to be significantly associated with suspected scoliosis, the findings nevertheless indicate that students should be educated about proper school bag use.

In the Turkish healthcare system, children and adolescents are routinely followed by family physicians within the framework of primary care services, and musculoskeletal development is assessed during periodic health evaluations. Although there is no nationwide school-based scoliosis screening program, the existing primary care follow-up structure provides an important opportunity for early recognition of spinal asymmetries. Rather than suggesting a national mass screening mandate, the findings of the present study may support the consideration of structured, risk-informed assessment approaches within existing school health practices and family physician follow-up visits. Incorporating simple, standardized observational methods—particularly for students with identified risk factors such as female sex, low BMI, or positive family history—may enhance early detection without imposing substantial additional burden on the healthcare system. Furthermore, given the variability in pubertal timing between girls and boys, future screening strategies may benefit from incorporating indicators of biological maturation rather than relying solely on chronological age. Such an approach may improve the timing and clinical relevance of scoliosis assessments within adolescent health services.

Strengths and limitations

One of the major strengths of this study is that it was implemented as a large-scale, school-based field screening program conducted under real-world conditions. A substantial proportion of the target population participated, increasing the precision of prevalence estimates within the screened group. Furthermore, conducting the study within the school setting enabled access to a broad segment of the fifth-grade student population, reflecting routine public health practice and increasing the practical relevance of the findings. While the participation rate did not encompass the entire target population, the sample size remains considerable and provides valuable epidemiological insight into the prevalence of suspected scoliosis within the screened group.

However, despite being designed as a population-based screening initiative, only 61.9% of the target fifth-grade population was screened. The remaining 38.1% were excluded due to parental refusal, absenteeism, or other reasons, resulting in a considerable non-participation rate. This may introduce selection bias, as families who consented to school-based health screening may systematically differ from non-participants in terms of health awareness, socioeconomic characteristics, and access to healthcare services. Consequently, the representativeness of the screened cohort may be limited, and the findings should be interpreted with caution when generalizing to the entire target population. In addition to this potential selection bias, the study also has certain limitations. Some of the students who screened positive and were referred to specialist physicians for further evaluation did not present to the hospital. Consequently, the proportion of students who received a definitive diagnosis of scoliosis among those identified as having suspected scoliosis through screening could not be determined, and the overall effectiveness and diagnostic yield of the screening program could not be fully evaluated. Sensitivity, specificity and predictive values could not be reported. The diagnostic performance of the screening protocol could not be evaluated.

An additional limitation relates to the examination protocol. While male students were examined with the upper body fully exposed, female students were evaluated while wearing undershirts due to privacy considerations. As visual assessment is fundamental in scoliosis screening and relies on detecting subtle surface asymmetries of the trunk, clothing may have partially obscured minor deformities. This difference in examination conditions may have reduced detection sensitivity among female students and introduced potential measurement bias. Moreover, unequal examination conditions between sexes may limit the validity of gender-based comparisons.

Another limitation concerns the assessment of anthropometric measurements. Height and weight data were based on students' self-reports rather than direct measurements. Self-reported anthropometric values, particularly in children, may be prone to reporting errors or misestimation, potentially leading to misclassification in BMI categories. This measurement error may have biased the observed associations involving BMI and should be considered when interpreting related findings.

Another important limitation of this study is that both sexes were screened at the same chronological age (10–11 years) without a comprehensive assessment of biological maturation. Although chronological age and menarche status were recorded, more objective indicators of pubertal development—such as Tanner staging or peak height velocity—were not evaluated. Given that idiopathic scoliosis is closely associated with periods of rapid growth and that peak height velocity occurs earlier in girls than in boys, some fifth-grade boys may not yet have reached their growth spurt. Therefore, sex-based comparisons may have been limited, and the observed associations with sex, age, and BMI may partly reflect differences in maturation timing rather than true independent risk relationships. These findings should therefore be interpreted with caution.

Although multiple univariate analyses were conducted to identify candidate variables, the primary inferences of the study were based on the multivariable logistic regression model. Nevertheless, since no formal adjustment for multiple comparisons was applied in the univariate stage, the possibility of type I error inflation cannot be completely ruled out and should be considered when interpreting the findings.

Conclusions and recommendations

In conclusion, this study determined that the screening positivity rate for suspected scoliosis among fifth-grade students was 11.0%. Screening positivity was higher in female

students and was associated with BMI, family history, selected clinical symptoms, and back skin findings, supporting a multifactorial pattern. These findings suggest that screening positivity may be influenced by a complex interaction of biological, anthropometric, familial, and postural factors. The relatively high screening positivity rate observed in this study compared with many reports in the literature highlights the importance of early detection and preventive strategies during the school years.

Accordingly, it is recommended that awareness-raising activities targeting students, teachers, and parents be implemented to improve knowledge about scoliosis, its risk factors, and early warning signs. Regular educational programs focusing on spinal health, correct posture, ergonomics, and appropriate schoolbag use should be integrated into school curricula. Within the current structure of the Turkish healthcare system, these educational initiatives could be aligned with existing school health services and primary care follow-up visits conducted by family physicians, thereby reinforcing musculoskeletal health monitoring without requiring the establishment of a separate nationwide screening mandate. In addition, population-based approaches that enable early identification of children at increased risk, supported by clearly defined referral and follow-up pathways, may help ensure timely clinical evaluation while minimizing unnecessary referrals. Developing standardized observational guidance for use in schools and primary care settings, clarifying referral thresholds, and strengthening coordination between schools and primary healthcare providers may enhance the feasibility, consistency, and sustainability of scoliosis-related preventive practices. Rather than advocating universal mass screening at a fixed chronological age, future strategies may benefit from risk-based and maturation-sensitive approaches that take biological growth variability into account. Further research is warranted to optimize screening strategies and to determine the most efficient and cost-effective models for early detection in school-aged populations within the framework of Türkiye's existing adolescent health services.

Ethical approval

The study was approved by Eskişehir City Hospital Scientific Research Ethics Committee (date: 22.01.2025, number: ESH/BAEK 2025/90).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: ŞEG, BIA, YB, BM; data collection: ŞEG, BIA, SAG; analysis and interpretation of results: SAG, BIA, ŞEG; draft manuscript preparation: SAG, ŞEG, BIA. All authors reviewed the results and approved the final version of 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

The face of pediatric and adult brain abscesses, differences and clinical characteristics: a single center 10-year experience

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ABSTRACT

Background. Brain abscesses (BA) are a medical emergency in all age groups and require early diagnosis and treatment. Childhood BA constitute 25% of all abscesses and may have a different clinical course than adults. This article aims to investigate patients followed up for adult and child BA over a 10-year period.

Materials and Methods. A retrospective analysis was performed on adult and pediatric patients diagnosed with BA. Demographic, clinical, predisposing factors, imaging, treatment modalities, and prognosis of the patients, and clinical differences were examined.

Results. Of a total of 46 patients; 54.3% of the patients were children and the mean age was 10.9±6.3 years for the pediatric group and 46.2±16.7 years for the adult group. Fever, vomiting, and seizures were significantly higher in children ($p<0.05$). When the differences between the groups were examined, headache was the most common finding in the adult group, while the most common finding in children was fever and vomiting. The classic triad of fever, headache, and focal neurological deficits was present in 12 (48%) of the children, compared to only 4 (19.1%) of the adults. Trauma history (21.7%), immunosuppression (19.5%), and local spread (mastoiditis, sinusitis, and otitis) (32.6%) were among the most common predisposing factors. Previous otorhinolaryngogenic infections were the most common cause in children (36%), while immunosuppression was the most common cause in adults (28.5%). The frontal lobe was most frequently involved among the patients (47.8%). BA was more commonly localized in the left hemisphere in both groups. Culture growth was detected in 23.9% of all operated patients, with a positivity rate of 20% in children and 28% in adults. The most common microorganism was *Staphylococcus aureus* (8.6%). The average hospitalization time was significantly longer in children than in adults (46 ± 18 days vs 34 ± 13 days; $p=0.024$). 26.1% of the patients recovered with sequelae, and the mortality rate was 8.6%.

Conclusion. Our findings suggest that a high index of suspicion should be maintained for BA in children, especially in the presence of fever, vomiting, and seizures. This study highlights significant clinical and etiological differences between pediatric and adult BA, underscoring the importance of age-specific diagnostic and management strategies. The differences observed in clinical presentation and underlying causes between the two groups warrant further investigation to improve outcomes.

Key words: adult, brain abscess, child.

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Although the prognosis of central nervous system infections and their complications has improved significantly with advanced imaging techniques and antibiotics, they continue to be a significant cause of mortality and morbidity nowadays.[1,2] Brain abscesses (BA) are life-threatening intracranial infections characterized by localized suppuration in the intracranial parenchyma. They occur when pustular material is surrounded by a capsule and organized following a focus of cerebri.[3,4] Its incidence is 8% of intracranial masses in developing countries and 1-2% in Western societies and can be seen in almost all ages.[4] The mortality rate of BA is higher in the fourth decade of life.

Although BA predominantly affects adults, children comprise approximately one quarter of cases.[5] Within the pediatric population, the peak incidence occurs between 4 and 7 years of age. It is particularly important because of the neurological sequelae it may cause in children.[6,7] The most common causes of BA are; spread of infections from anatomically adjacent areas (otitis media, dental infections, mastoiditis, sinusitis), hematogenous spread (secondary to cyanotic congenital heart disease, lung abscess or empyema), direct inoculation after trauma or surgery. Between 4.6% and 43.4% of cases, no etiology can be found, these called cryptogenic.[8,9]

BA may not present clinical findings in the early stages, but may also present with nonspecific findings or a variable clinical course ranging from mild to severe. The most important factors determining the patient's clinical picture are the patient's age, stage, localization of the abscess, immune status and presence of meningitis.[5,7,10] In the early stages of the abscess, the patient may be asymptomatic. The classical triad of BA; fever, headache, and focal neurological deficits, is seen in only 9-28% of children.[5,10]

The microorganisms responsible for BA are aerobic and anaerobic streptococci and staphylococci. Other agents are *Bacteroides* species, *Proteus* species, *Haemophilus influenzae*, *Escherichia coli*, *Citrobacter*, *Nocardia*, *Aspergillus*, *Corynebacterium* and *Mycobacterium tuberculosis*.[11-14] The literature has shown that cultures are negative in 10-56% of cases.[14]

Treatment typically involves a combination of antibiotics for 6-8 weeks and, in most cases, surgical drainage. Antimicrobial therapy alone is recommended for small lesions (<2.5 cm), multiple abscesses, and deep-seated lesions.[8,10,12,15,16] While several studies in the literature evaluate either pediatric or adult BA, there is a scarcity of comparative studies that investigate the distinct features of these two age groups. This retrospective study aims to address this gap by comparing pediatric and adult BA over a 10-year period, discussing risk factors, clinical courses, and outcomes in light of the available literature. This work seeks to provide valuable insights into the age-specific differences in BA, contributing to improved diagnostic and management strategies.

Materials and Methods

In this retrospective study, a total of 46 patients followed at the Pediatric Infection and Neurosurgery Clinics of Adana City Training and Research Hospital between 2012 and 2022 were investigated. All patients under the age of 18 were defined as the pediatric group (n=25), while patients aged 18 and older were included in the adult group (n=21).

BA was defined as a localized parenchymal lesion with perilesional brain edema and contrast enhancement on cranial imaging or the presence of purulent material in the cranial cavity on biopsy/surgery. Patients with subdural empyema, epidural abscesses, or secondary abscesses due to shunt infection were excluded from the study. Ten patients were excluded from the study: six with subdural empyema, three with epidural abscess, and one with a secondary abscess related to shunt infection.

Differences between pediatric and adult patients were evaluated with respect to demographic characteristics, presenting complaints,

underlying risk factors, and outcomes. The indications for treatment modality were defined as follows: Patients with abscesses smaller than 2.5 cm, multiple lesions, or lesions in deep/critical locations received exclusive medical treatment (long-term intravenous antibiotics). All other patients (lesions >2.5 cm, accessible lesions) were considered for surgical drainage (stereotactic aspiration or excision) in addition to medical treatment. The hospital records were reviewed to obtain information on patient demographics, clinical presentation, laboratory findings, imaging results, treatment methods, and clinical outcomes. Surgical samples were immediately sent for aerobic and anaerobic culture and Gram staining. The hospital laboratory's capacity for anaerobic culture was noted to be limited, which may have contributed to the overall low culture yield observed in the study.

Ethics approval

The study's ethics committee approval was obtained by the Adana City Training and Research Hospital Clinical Research Ethics Committee (January 12, 2023, meeting number 120, decision number 2371).

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences version 20 (IBM Corp., Armonk, NY, USA) software package. Descriptive statistics of numerical parametric variables were calculated as mean±standard deviation (SD); categorical variables were expressed as percentage (%). Chi-square test was used to compare categorical variables between groups, independent samples T-test was used to compare numerical variables between groups if assumptions were met, otherwise Mann-Whitney U test and analysis of variance (ANOVA) were used to compare more than one group. P value <0.05 was considered statistically significant.

Results

Of the 46 patients followed, 25 (54.3%) were children and 21 (45.7%) were adults. The mean age of the patients was 27± 20.6 years (median 18 years, min-max: 3 months - 74 years) (Table I). There was a male predominance in the study group, with 71.8% of the patients being male and a male-to-female ratio of 2.6:1.

The most common complaints of the patients were headache (73.9%), vomiting (73.9%) and fever (54.3%). The triad of fever, headache and neurological dysfunction was present in 34.7% of the patients. Other reported conditions included feeding intolerance (54.3%), seizure (26.1%), confusion (26.1%), hydrocephalus (15.2%) and hemiplegia (15.2%). Increased intracranial pressure (ICP) findings were present in 7 patients (15.2%). When the two groups were compared, headache was the most common finding in the adult group, while vomiting was the most common finding in children. Vomiting history was present in 22 (88%) of the pediatric patients, while it was present in 12 (57.1%) of the adults (p=0.038). Fever history was present in 20 (80%) of the pediatric patients, while it was present in 5 (23.8%) of the adults, and the difference was statistically significant (p=0.001). The classic triad of fever, headache and neurological dysfunction was present in 12 (48%) of the children, compared to 4 (19.1%) of the adults. Although the triad appeared more frequent in children than adults, this difference was not statistically significant (p=0.065). Hydrocephalus was documented more often in children (24%) than adults (4.7%), and this difference was not statistically significant (p=0.119). Shift appeared more frequent in adults (38%) than in children (16%), and this difference was not statistically significant (p=0.059) (Table I). At the time of diagnosis, seizures were present in 10 (40%) of the children, while a history of seizures was present in 2 (9.5%) of the adults, and the difference was significant (p=0.029). Loss of consciousness was present in 36% of the children and 14.2% of the adults (Table I).

Table I. Comparison of clinical, demographic, radiological, and prognostic characteristics of patients.

Characteristic	Pediatric group (n=25)	Adult group (n=21)	p-value
Demographic characteristics			
Age, yrs, mean±SD (min-max)	10.9±6.3 (3 months-18 years)	46.2±16.7 (18-74 years)	-
Male gender, n (%)	18 (72)	15 (71)	0.821
Clinical symptoms and signs, n (%)			
Fever	20 (80)	5 (24)	0.001
Vomiting	22 (88)	12 (57)	0.038
Feeding intolerance	15 (60)	10 (48)	0.264
Headache	17 (68)	17 (81)	1.000
Classic triad*	12 (48)	4 (19)	0.065
Seizure	10 (40)	2 (10)	0.029
Status epilepticus	5 (20)	1 (5)	0.212
Hydrocephalus	6 (24)	1 (5)	0.119
Shift	4 (16)	8 (38)	0.059
Hemiplegia	4 (16)	3 (14)	0.446
Altered state of consciousness	9 (36)	3 (14)	0.133
Radiological and laboratory findings			
Frontal localization of abscess, n (%)	10 (40)	12 (57)	0.541
Located in left cerebral hemisphere, n (%)	14 (56)	8 (38)	0.476
Abscess size, cm,	3.6	3.8	0.734
WBC, /mm^3, mean±SD	17.747±7.988	14.473±7.694	0.118
CRP, mg/dL, mean±SD	50.07±87.52	45.59±76.30	0.682
Outcomes			
Length of hospital stay, days, mean±SD	46±18	34±13	0.024
Sequelae development, n (%)	7 (28)	5 (23.8)	0.883
Mortality, n (%)	3 (12)	1 (4.8)	0.622

*Triad: Association of fever, headache and neurological dysfunction.
CRP: C-reactive protein, SD: standard deviation, WBC: white blood cell

Regarding the underlying causes, trauma history was present in 10 (21.7%), immunosuppression (acute lymphoblastic leukemia [ALL], chronic granulomatous disease (CGD) in 9 (19.5%), local spread (mastoiditis, sinusitis and otitis history) in 15 (32.6%), previous surgery in 4 (8.6%) and congenital heart disease in 2 (4.3%) patients. Previous otorhinolaryngogenic infections were the most common cause in pediatric cases (36%), while immunosuppression was the most common cause in adult cases (28.5%). In total, no underlying cause could be detected in 6 (13%) patients. The underlying cause was detected in 24 (96%) of pediatric patients and 16 (76.1%) of adults (p=0.040) (Fig. 1).

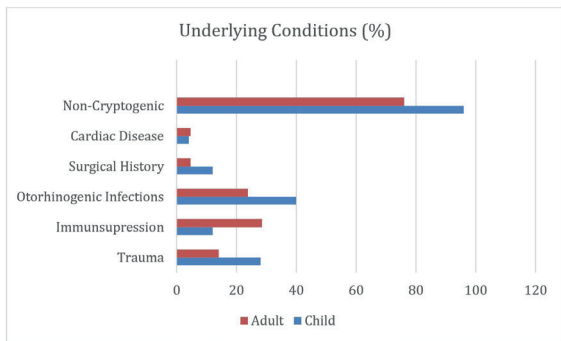

Fig. 1. Underlying conditions of brain abscess according to age groups.

Cranial computed tomography (CT) and magnetic resonance imaging (MRI) were the most commonly used imaging methods for diagnosis, with MRI being preferred more frequently in pediatric cases. The mean abscess size was similar in both groups (3.6 cm in children vs. 3.8 cm in adults), with no statistically significant difference (Table I). The frontal lobe was most frequently involved (n=22, 47.8%). BA was more commonly localized in the left hemisphere in both groups (47.8%), while abscesses were observed in both hemispheres in 23.9% of patients. There was no significant difference between the groups in terms of localization (Table I). Initial white blood cell (WBC) count and C-reactive protein (CRP) level were elevated in both children and adults, but no significant difference was observed between the groups (p=0.118, p=0.682 respectively).

Regarding surgical intervention, the timing of aspiration/drainage was generally performed within 24-48 hours of diagnosis for large or symptomatic lesions. No statistically significant difference in surgical timing was observed between the pediatric and adult groups ($p > 0.05$). Three of the patients (6.5%) received only medical treatment, while the others underwent surgical drainage in addition to medical treatment. The duration of medical treatment was 6-8 weeks. The most frequently initiated empirical treatment was ceftriaxone, vancomycin, and metronidazole (95%). Antibiotic therapy was adjusted according to the results of patients with positive cultures. Corticosteroid (dexamethasone) treatment was given to patients with shifts or significant cerebral edema (26.1%). Electrolyte imbalance developed in 10 of the patients (21.7%), 6 of whom were children, and one of these children also developed renal failure (2.1%). Culture growth was detected in 23.9% of all patients who underwent surgery, with a positivity rate of 20% in children and 28% in adults. The most common microorganism was *Staphylococcus aureus* (8.6%).

12 of the patients (26.1%) recovered with sequelae, 7 of whom were children. The most common sequelae were hemiparesis, epilepsy and hearing loss. The mean hospitalization day of the patients was 40.6 days. The hospitalization duration was longer in children than in adults (p=0.024) (Table I). Four of the patients (8.6%) died, the underlying diseases were immunosuppression (ALL), meningitis and intracranial hemorrhage in children and trauma in adults.

Discussion

BA continues to be an important cause of mortality and morbidity worldwide, especially in developing countries, despite advanced diagnostic methods and modern treatments. In this study, we found a male/female ratio of 2.6/1, which aligns with the general male dominance reported in the literature. While female dominance was noted in a pediatric BA series from Türkiye, another study reported male dominance, highlighting regional variations.[5,17] In our study, 25 cases were younger than 18 years. We observed that 69.4% of all cases were under 40 years of age. According to a meta analysis report, the average age was reported as 34 years.[18]

In children, especially at young ages, the presenting complaints are usually nonspecific. In studies, headache and fever were found to be the most common presenting complaints.[14] Although seizure is a less common finding, Lee et al. observed seizure in 48% of their patients in their study.[19] Again, Atiq et al. observed seizures in 45% of patients.[20] In our study, headache, neurologic dysfunction and fever were present in 34.7% of all cases and 48% of children. Fever and vomiting were the most common symptoms in children. Mental status changes and seizures were present in 26.1% of all cases, while seizures were more common in pediatric cases compared to adults and were statistically significant (p=0.029).

The underlying etiology is known in many cases. Cryptogenic abscesses have been reported in 4.6-43.4% of cases.[5] Identifiable causes were present in 86.9% of our cases. While previous

otorhinogenic infections were the most common cause in pediatric cases, immunosuppression was found to be the most common cause in adult cases. Several predisposing factors, including immunosuppression, underlying disease, and contiguous spread from adjacent structures, have been implicated in the development of BA. In developing countries, BA most commonly develops secondary to otitis media. Sharma et al. found neighboring infections such as sinusitis, otitis or meningitis in 42.5% of patients followed up for BA.[21] Nathoo et al., on the other hand, demonstrated abscess development after otorhinogenic infection in 38.5% and after trauma in 32.5%.[15] Otorhinogenic infections, which are the most important predisposing factor in the development of BA, are observed especially in the first decade of life.[21,22] In our study, the rate of otorhinogenic infection was 32.6%. This finding supports the literature on the role of adjacent infections, particularly in the pediatric age group. Immunodeficiency was present in 19.5% of our patients and these were mostly adult cases. This highlights a crucial etiological difference, with systemic factors being more dominant in adults. Cryptogenic cases were present in only 4.1% of pediatric cases and 23.8% of adult cases. The significantly lower rate of cryptogenic BA in children suggests a more readily identifiable underlying cause in the pediatric population, which can aid in timely diagnosis.

Of the patients' abscesses, 84.8% were single localized and 15.2% were multiple localized. Multiple localization was approximately similar in pediatric and adult cases (p=0.476). BA was mostly located in the left hemisphere in both pediatric and adult cases. There was no significant difference between the mean abscess sizes. A study showed that adult BA were mostly single localized in the temporal and temporoparietal region and only 2.6% cases were multiple localized.[16] In a study including 93 adult and pediatric patients, Dhar et al. reported that 77.4% of abscesses were 2.5 cm or more in size and mostly supratentorial.[23] In our patients, frontal lobe involvement was predominant in both groups. Evaluation of blood CRP level and WBC count can indicate whether the pathologic mass in the brain has an infectious character. Since, inflammatory parameters may be within normal ranges in 30-40% of patients; normal levels may not rule out BA. They do not contribute to the diagnosis of BA, however, they should be routinely included in the initial diagnostic process.[24,25] In our patients of all ages, baseline CRP and WBC values were elevated similar to the literature, but no significant difference was observed between age groups.

In the literature, it has been suggested that CT and MRI are the most preferred radiologic diagnostic modalities. MRI is significantly more specific (91%) and sensitive (92%) than CT, and should therefore be the first choice, but in cases where MRI is not available, cranial CT should be performed in the foreground.[26] In our study, cranial CT and MRI were the most commonly used imaging modalities, although MRI was preferred more frequently in pediatric cases. In the same study, it was stated that the empirical antibiotic treatment used may vary according to the patient's underlying cause of BA or antimicrobial resistance pattern. In community-acquired abscesses, the combination of 3rd generation cephalosporin and metronidazole, in immunosuppressed hosts, the addition of trimethoprim - sulfamethoxazole and voriconazole in addition to 3rd generation cephalosporin and metronidazole, and in abscesses developing after surgery, the combination of meropenem and vancomycin/linezolid were recommended.[26] They argued that the duration of treatment should be considered according to the balance between the absence of drug side effects and the risk of relapse. Although it has been suggested that the duration of antibiotic treatment should be at least 6-8 weeks, another study showed that patients who were given antibiotic treatment for 3-4 weeks and who underwent surgical abscess drainage and antimicrobial installation both had a good response to treatment and did not develop abscess again in a 26-month follow-up.[27] In our study, medical treatment was

given for at least 6-8 weeks and surgery was performed in 93.4% of the patients.

The rate of culture positivity obtained from drained abscess material has been reported as 33-80% in the literature.[5,22,26,28] Culture was positive in 23.9% of our cases, which is substantially lower than most published series. This low culture yield is a key limitation of our study. Our findings are in line with other reports showing a low yield in centers with limited resources or high pre-admission antibiotic use. We believe it may be attributed to several factors, including the high likelihood of antibiotic use prior to diagnosis, which can inhibit bacterial growth. Additionally, some microorganisms can be difficult to isolate, and potential issues with sample handling or the hospital's limited anaerobic culture capacity may have contributed to this low rate.[14]

The hospitalization day was longer in children than in adults (p=0.024). This finding is clinically important and may be due to the more non-specific initial presentation in children, which can lead to delayed diagnosis. The need for prolonged inpatient care for comprehensive follow-up and management of potential complications could also contribute to longer hospital stays. The observed difference warrants further investigation into age-specific care pathways.

Of the patients, 26.1% recovered with sequelae and the mortality rate was 8.6%. Our findings are consistent with the literature. In a cohort study examining a total of 6027 cases, the hospital mortality rate was 4.22% in the 0-14 years of age group, while it was 17.34% in individiuals over 60 years of age.[29] The presence of sequelae in over a quarter of our patients emphasizes the long-term impact of BA, particularly on the pediatric population who comprised the majority of cases with sequelae.[25]

Conclusion

This single-center retrospective study reveals significant differences between pediatric and adult BA cases. It should not be overlooked that the presenting complaints and underlying etiological causes differ between age groups, and this directly affects diagnostic and treatment approaches. Notably, symptoms such as fever, vomiting, and seizures are significantly more frequent in children (p<0.05), while the most common underlying cause is otorhinolaryngological infections in children and immunosuppression in adults. These findings underscore the importance of early diagnosis and age-specific treatment strategies.

Our study has certain limitations, including its retrospective design and single-center setting. However, our findings demonstrate the existence of clinical differences that lead to a significantly longer hospital stay in children (p<0.05). This carries important clinical implications for treatment management and the planning of hospital resources. BA remains a serious clinical condition with high rates of morbidity and mortality.

In conclusion, the findings of this study support the necessity of age-specific approaches. Future multicenter and prospective studies would be beneficial to broadly validate our findings.

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Ethical approval

The study was approved by Adana City and Education Research Hospital Clinical Research Ethics Committee (date: January 12, 2023, number: 2371).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: TÇ, MC, ÜÇ; data collection: TÇ, ÜÇ, MKÇ, MC, AİÖ; analysis and interpretation of results: TÇ, MKÇ, ÜÇ; draft manuscript preparation: TÇ, MKÇ, ÜÇ, AİÖ. All authors reviewed the

results and approved the final version of 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

Psychosocial outcomes and related factors in adolescents using clean intermittent catheterization

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ABSTRACT

Background. Clean intermittent catheterization (CIC) is an established treatment for lower urinary tract dysfunction and has been used across age groups with voiding problems due to various etiologies. Although medically safe and straightforward, CIC may create social and emotional challenges for adolescents and their caregivers. During adolescence, when autonomy and peer acceptance become central, the need for continuous catheterization in daily life and, at times, dependence on another person can be difficult to cope with and may affect psychological well-being and peer relations. This study aimed to examine factors associated with potential psychopathology, self-perception, peer relationship characteristics, and quality of life in adolescents performing CIC.

Methods. This prospective cross-sectional study included 50 adolescents aged 12–18 years: 25 performing CIC and 25 age and sex-matched healthy controls. Participants with intellectual disability, low mental capacity preventing comprehension of study procedures, or uncorrected vision/hearing deficits were excluded. Psychiatric diagnoses were assessed using the Schedule for Affective Disorders and Schizophrenia for School-Aged Children—Present and Lifetime Version DSM-5 (K-SADS-PL). Self-perception, quality of life, behavioral difficulties, and peer relationships were evaluated using the Piers-Harris Children's Self-Concept Scale, Pediatric Quality of Life Inventory, Strengths and Difficulties Questionnaire, and Peer Relationship Scale. Parental attitudes and caregivers' psychological symptoms were assessed using the Parental Attitude Research Instrument and the General Health Questionnaire-28. Statistical analyses were performed using SPSS version 23.0. Group comparisons were conducted using the independent samples t-test or Mann–Whitney U test as appropriate; categorical variables were analyzed with the Chi-square or Fisher's exact test. Multiple linear regression analysis was performed to identify independent predictors. A two-tailed p value <0.05 was considered statistically significant.

Results. The groups were similar in age, sex and sociodemographic characteristics. Adolescents performing CIC showed higher social avoidance and poorer peer relationships. Eight adolescents (32%) in the CIC group met criteria for at least one psychiatric disorder according to DSM-5. Negative parental attitudes, maternal mental disorders, primary etiology requiring CIC, age at self-catheterization initiation, and catheterization performed by another individual were identified as significant predictors of lower self-esteem, reduced quality of life, and poorer peer relationships.

Conclusion. CIC may have meaningful psychological and psychosocial effects on adolescents, influenced by clinical variables and parental factors. Early identification of risk indicators and strengthening of protective factors are essential. A multidisciplinary approach incorporating psychiatric, familial, and psychosocial components should be included in the management and follow-up of adolescents performing CIC.

Key words: adolescents, clean intermittent catheterization, quality of life, psychopathology, self-perception.

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Clean intermittent catheterization (CIC) is the most important bladder rehabilitation method used for the prevention of urinary incontinence and the preservation of kidney function in conditions such as detrusor–sphincter dyssynergia, urinary diversion, and neurogenic bladder.[1] Current European Association of Urology (EAU) and European Society for Paediatric Urology (ESPU) guidelines recommend proactive management including early initiation of clean intermittent catheterization together with pharmacological treatment regulating bladder function in children with neurogenic bladder, often beginning in the first months of life.[2,3] Earlier initiation of CIC leads to the caregivers mastering the procedure and makes the process easier for children to accept and adapt to the CIC as they grow older.[4] When properly performed; CIC has been shown to improve quality of life by providing better symptom management, reducing the frequency of voids, which is especially beneficial at night, and improving sleep which lowers daytime fatigue.[5] Specific CIC-related difficulties among pediatric patients are reported as urethral pain, unavailability of the caregiver helping with the procedure, poor cooperation and collaboration, sphincter resistance to the insertion of the catheter, and poorer or inappropriate CIC routines during adolescence.[6-9]

In addition to its clinical implications, recent literature has highlighted the psychosocial burden associated with neurogenic bladder and catheterization-dependent pediatric populations. Children and adolescents requiring long-term bladder management may experience challenges related to social participation, emotional adjustment, and dependency on caregivers. Qualitative findings suggest that families report significant daily stressors associated with catheterization routines, privacy concerns, and the management of school-related situations. Moreover, psychosocial factors such as stigma, anxiety, and difficulties in treatment adherence have been increasingly recognized as important components of neurogenic lower urinary tract dysfunction management.[10,11]

Although recent studies have increasingly acknowledged psychosocial challenges associated with catheterization-dependent pediatric populations, much of the existing literature has primarily focused on medical outcomes such as the prevention of urinary complications, preservation of kidney function, and improvements in continence. Studies specifically addressing emotional well-being, psychiatric outcomes, and peer relationship characteristics in adolescents performing clean intermittent catheterization remain limited. In particular, comprehensive evaluations using structured psychiatric diagnostic interviews are scarce.[11]

Therefore, the present study aimed to compare psychopathology, self-perception, peer relationship characteristics, and quality of life between adolescents performing clean intermittent catheterization and healthy peers. In addition, we examined clinical and familial factors, including parental attitudes and parental psychological well-being, associated with these outcomes. By integrating structured psychiatric diagnostic assessment with multidimensional psychosocial measures, the study sought to identify independent predictors of psychological vulnerability in this population. We hypothesized that adolescents performing CIC would demonstrate higher levels of psychopathology and poorer psychosocial functioning compared to healthy peers.

Materials and Methods

Sample

This was a prospective cross-sectional study conducted at a single tertiary care center through collaboration between the Departments of Pediatric Urology and Child and Adolescent Psychiatry.The study sample comprised 25 adolescents performing CIC between the ages of 12 and 18 years who were followed in the pediatric urology department, and 25 age and sex-matched healthy adolescents recruited as

the control group. Patients who presented to the pediatric urology outpatient clinic between August 2019 and December 2020 were included in the study. Ethical approval for the study was obtained from the Ankara University Faculty of Medicine Human Research Ethics Committee (approval no: İ2-35-19). Written informed consent was obtained from parents or legal guardians, and verbal assent was obtained from all participating adolescents. The control group patients were randomly selected from patients who presented with urinary tract infection and did not have a chronic medical problem. The control group was selected to be comparable to the CIC group in terms of age, sex, and other sociodemographic characteristics based on information obtained from the Sociodemographic and Clinical Data Form. Inclusion criteria for the CIC group and control group were as follows: i) being between the ages of 12 and 18 years, ii) not being diagnosed with intellectual disability, iii) living with their family, and iv) being literate. In addition to these, the additional inclusion criteria for the control group was having no neurological or other serious medical conditions. In the CIC group, the diagnosis encompassed different forms of myelodysplasia, including occult spinal dysraphism, tethered cord, sacral malformation, and caudal regression syndrome. The patients included in the study had intact perineal sensibility and motor function in the lower limbs, but had severe bladder dysfunction requiring CIC. The main indication was bladder-emptying problems. Estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2) was calculated using the bedside Schwartz equation [eGFR = 0.413 × height (cm) / serum creatinine (mg/dL)]. Exclusion criteria for both groups were as follows: i) low mental capacity preventing understanding of the objective of the study and the presented questionnaire, and ii) presence of any uncorrected vision/hearing deficits in the adolescents or parents.

Instruments

Sociodemographic and clinical data form

This structured form was developed by the researchers to collect demographic and clinical background information about the adolescents, including age, sex, educational status, family characteristics, and clinical variables relevant to the study. The information obtained from this form was used to ensure comparability between the CIC and control groups in terms of age, sex, and other sociodemographic characteristics. The form functioned as a structured data collection tool and was not intended as a psychometric measurement instrument.

Schedule for affective disorders and schizophrenia for school-aged children:present and lifetime version DSM-5 (K-SADS-PL-DSM5):

It is a semi-structured interview used to diagnose various psychiatric disorders in children and adolescents.[12] It was applied to parents and adolescents by a specialist in child and adolescent psychiatry. The Turkish reliability and validity study of K-SADS-PL-DSM5 was conducted by Ünal et al.[13]

The Piers-Harris children's self-concept scale (Piers-Harris CSCS):

It was developed to provide a brief, self-report instrument for the assessment of self-concept in children and adolescents.[14] Higher scores indicate a more positive self-evaluation in the domain being measured. The Turkish validity and reliability study of the scale was conducted by Öner.[15]

Pediatric quality of life inventory (PedsQL™4.0):

PedsQL 4.0 was designed to measure the core physical, mental, and social health dimensions as delineated by the World Health Organization, as well as role (school) functioning.[16] Higher scores indicate better health-related quality of

life. The parent and adolescent versions of the PedsQL 4.0 were used in the present study. Turkish translation of the scale and reliability and validity studies were performed in 2007.[17]

Strengths and difficulties questionnaire (SDQ)

The SDQ was developed to determine adolescents' areas of strengths and problematic behaviours.[18] Lower scores on the social behavior subscale and higher scores on the other subscales indicate the existence of the problems addressed by that domain.[19] The validity and reliability of the Turkish version of the SDQ were established in 2008, with an acceptable internal consistency.[20] The parent and adolescent versions of the SDQ were used in our study.

Peer relationship scale (PRS)

The Peer Relationship Scale (PRS) was originally developed in the Turkish population by Kaner (2000), and its validity and reliability were established through comprehensive psychometric analyses, including factor analysis and internal consistency assessments.[21] Higher scores indicate positive relationships with friends, whereas low scores indicate negative relationships.

General health questionnaire-28 (GHQ)

The GHQ was developed by Goldberg to identify acute mental illnesses that are common in the community.[22] The Turkish validity and reliability study was performed by Kılıç.[23] The GHQ-28 contains 28 self-report items divided into four subscales: somatic symptoms, anxiety and insomnia, social dysfunction, and severe depression. Each subscale contains seven items asking participants to indicate how often they have recently experienced relevant symptoms on a four-point Likert scale. Based on established scoring procedures and Turkish validation studies, a GHQ-28 score of ≥5 was accepted as the cut-off indicating increased risk for psychological distress.

The parental attitude research instrument (PARI)

This scale is completed by parents and aims to rate parents' rearing attitudes toward their children.[24] Developed by Shaffer and Bell, this scale's validation and reliability in Turkish were tested by Le Compte et al. and Küçük et al.[25,26] Increased scores for factors other than "democratic treatment and granting equality" indicate negative parental attitudes.

Procedure

The adolescents and parents were separately interviewed by the researcher using a sociodemographic data form. The K-SADS-PL-DSM5 was used to assess current and past psychiatric diagnoses based on the synthesis of information collected from interviewing the adolescent and the parent. Adolescents completed the Piers-Harris CSCS, PedsQL 4.0 adolescent form, PRS and SDQ adolescent version while parents completed the GHQ, PedsQL 4.0 parent form, SDQ parent version, and PARI.

Statistical analysis

SPSS (Statistical Package for Social Sciences) 23.0 program was used for data analysis and p values <0.05 were considered statistically significant. The Shapiro-Wilk test was used to analyze the normality of variables. Group comparisons for continuous variables were performed using Independent Samples t-test or Mann–Whitney U test, depending on normality assumptions. Associations between categorical variables were examined using Chi-Square or Fisher Exact analysis. Pearson and Spearman correlation analyses were conducted as preliminary analyses to examine bivariate associations between variables and to assess the suitability of variables for inclusion in the regression models. Since the dependent variables (scale scores) were continuous, multiple linear regression analysis was conducted to examine the independent predictors of the outcome variables. Predictor variables were selected based on theoretical

relevance and correlation analyses. Given the relatively small sample size (n = 25), the number of predictors included in the final model was restricted to avoid overfitting.

To assess potential multicollinearity among predictors, Variance Inflation Factor (VIF) and tolerance values were calculated. VIF values below 5 were considered acceptable. No problematic multicollinearity was detected. Regression coefficients (β), standard errors, and p-values were reported. Statistical significance was set at $p < 0.05$ (two-tailed).

Results

Sociodemographic variables of patient and control group

The study sample consisted of 50 adolescents (CIC, n = 25, control, n = 25) between the ages of 12 and 18. Groups did not differ regarding sociodemographic characteristics. Also, the presence of close friends was not statistically significant between adolescent groups (p:0.069). However; there was significant difference between the groups in the frequency of social activities. The most remarkable finding was that; while adolescents in the control group preferred to be with their friends, adolescents in the CIC group stated that they preferred to be alone rather than with their friends ($p < 0.01$) (Table I).

Clinical variables of adolescents who perform CIC

Clinical and etiological characteristics of adolescents who perform CIC are presented in Table II. All participants in the CIC group were diagnosed within the myelodysplasia spectrum according to the predefined inclusion criteria. Although the underlying conditions included various forms such as occult spinal dysraphism (n = 9), tethered cord (n = 7), sacral malformation (n = 5), and caudal regression syndrome (n = 4), the group was clinically homogeneous in terms of neurological status, intellectual functioning, and absence of additional major systemic comorbidities. None of the adolescents had a history of dialysis requirement at the time of clinical assessment. Based on estimated glomerular filtration rate (eGFR) values, seven participants had eGFR ≥90 mL/min/1.73 m^2, ten had Stage 2 chronic kidney disease, 60–89 mL/min/1.73 m^2), and eight had Stage 3 chronic kidney disease (45–59 208 mL/min/1.73 m^2). All patients were receiving oxybutynin hydrochloride at standard therapeutic doses (0.1–0.2 mg/kg). No participant was using additional medications known to have significant psychiatric or psychosocial side-effect profiles that could confound the study outcomes.

The outcomes of scales/instruments for adolescents and mothers in both groups

According to the Piers-Harris CSCS results, the mean self-concept scores of the control group were higher, except for the "anxiety" and "behaviour" subfactors. Self and proxy report PedsQL™ scores were statistically significantly different between groups for "total" and "physical health" scores ($p < 0.05$). When the "psychosocial health" scale subscores were evaluated, "psychosocial health total" scores were found to be significantly lower for the CIC group in proxy reports while "social functioning" scores were determined to be significantly lower for the CIC group ($p < 0.05$) in both self and proxy reports (Table III).

The SDQ scores for "peer relationship problems" and "prosocial behaviour" were significantly different between groups according to the self reports. "Prosocial behaviour" scores statistically distinguished the groups according to the parent reports (Table III).

The scores on the PRS in the CIC group were significantly lower except for the "trust and identification" subfactor when had been compared with those of participants in the control group (Table III). As shown in Table III, no statistically significant difference was observed between groups in terms of GHQ-28 total mean scores. However, based on the

Table I. Sociodemographic variables of CIC and control group.

	Group n(%)		
	CIC (n:25)	Control (n:25)	p
Sex, n (%)			
Male	13 (52)	15 (60)	0.774
Female	12 (48)	10 (40)	
Age (mean ±SD)	13.3±2.15	13.8±1.84	0.873
Maternal age (mean ±SD)	37.87±7.11	39.16±6.22	0.740
Paternal age (mean ±SD)	40.57±6.13	40.68±5.06	0.575
Number of sibling (mean ±SD)	1.21±0.86	1.32±0.94	0.376
Marital status of parents, n (%)			
Married	20 (80)	21 (84)	1.000
Separated	5 (20)	4 (16)	
Parental medical and psychiatric disorders, n (%)			
No	18 (72)	21 (84)	0.306
Yes	7 (28)	4 (16)	
Maternal education, n (%)			
Illiterate	1 (4)	-	0.939
Primary school	8 (32)	7 (28)	
Secondary school	11 (44)	15 (60)	
High school	3 (12)	2 (8)	
University	2 (8)	3 (12)	
Paternal education, n (%)			
Illiterate	-	-	0.252
Primary school	4 (16)	1 (4)	
Secondary school	13 (56)	15 (60)	
High school	5 (20)	7 (28)	
University	3 (12)	2 (8)	
Maternal profession, n (%)			
Yes	12 (48)	10 (40)	0.529
No	12 (48)	14 (56)	
Health employee	1 (4)	1 (4)	
Paternal profession, n (%)			
Yes	24 (96)	25 (100)	1.000
No	-	-	
Health employee	1 (4)	-	
Income (monthly), n (%)			
<2000 TL	7 (28)	7 (28)	0.799
2000-5000 TL	14 (56)	13 (52)	
>5000 TL	4 (16)	5 (20)	

Data are presented as mean ± standard deviation for continuous variables and as number (percentage) for categorical variables. Continuous variables were compared using the independent samples t-test. Categorical variables were analyzed using the Chi-square test or Fisher's exact test as appropriate. SD: standard deviation. $p < 0.05$ was considered statistically significant.
CIC: clean intermittent catheterization, TL: Turkish liras.

Table I. Continued.

	Group n(%)		
	CIC (n:25)	Control (n:25)	p
Family type, n (%)			
Nuclear family	18 (72)	20 (80)	0.733
Extended family	7 (28)	5 (20)	
Consanguinity between parents, n (%)			
Yes	7 (28)	4 (16)	0.107
No	18 (72)	21 (84)	
Social activity, n (%)			
No	2 (8)	-	0.001
Once a month	15 (60)	4 (16)	
Once a week	6 (24)	12 (48)	
2 or more times a week	2 (8)	9 (36)	
Close friend, n (%)			
Yes	14 (56)	20 (80)	0.069
No	11 (44)	5 (20)	
Friendship preference, n (%)			
Prefers to be with friends	13 (52)	23 (92)	0.002
Prefers to be alone	12 (48)	2 (8)	

Data are presented as mean ± standard deviation for continuous variables and as number (percentage) for categorical variables. Continuous variables were compared using the independent samples t-test. Categorical variables were analyzed using the Chi-square test or Fisher's exact test as appropriate. SD: standard deviation. $p < 0.05$ was considered statistically significant.
CIC: clean intermittent catheterization, TL: Turkish liras.

validated cut-off score for psychological distress (≥5 points), a significantly higher proportion of parents in the CIC group met the risk threshold compared with the control group (52% vs 24%, $\chi^2 = 8.32$, $p = 0.004$). The scores on the PARI were statistically significantly different between groups for the 'overprotective motherhood', 'rejecting of the housewifery role' and 'rigid disciplining' subscales (Table III). Correlations among the scale total scores are presented in Table IV.

Analysis of variables possibly affecting the scores of scales/instruments for adolescents who perform CIC

Multiple linear regression analyses were conducted to identify independent predictors of psychosocial scale scores among adolescents performing CIC (Table V). For the Piers-Harris CSCS, higher total scores on the PARI were significantly associated with lower self-concept scores ($\beta = -0.425$, $p < 0.001$). Increasing age was also a significant negative predictor ($\beta = -0.236$, $p = 0.019$). In addition, higher GHQ-28 total scores were strongly associated with lower self-concept scores ($\beta = -0.462$, $p < 0.001$). Regarding the PedsQL™4.0, PARI total score emerged as a significant negative predictor of quality of life ($\beta = -0.276$, $p = 0.018$). Age was also significantly associated with lower quality of life scores ($\beta = -0.414$, $p < 0.001$). Furthermore, poorer general mental health, as indicated by higher GHQ-28 scores, was independently associated with lower quality of life ($\beta = -0.339$, $p = 0.005$). For the Strength and Difficulties Questionnaire (self-report), higher PARI total scores were significantly associated with higher total difficulty scores ($\beta = 0.297$, $p = 0.040$), indicating more emotional and behavioral difficulties. Age

(p = 0.197) and GHQ-28 total scores (p = 0.382) were not significant predictors in this model.

In the Peer Relationship Scale model, age was a significant negative predictor of peer relationship scores (β = −0.409, p = 0.003). Additionally, younger age at initiation of self-catheterization was independently associated with better peer relationship scores, as higher age at self-catheterization initiation predicted lower scores (β = −0.541, p = 0.002). PARI total score (p = 0.101) and GHQ-28 total score (p = 0.699) were not statistically significant predictors in this model.

Table II. Clinical variables of adolescents who perform CIC.

Primary etiology, n (%)		Self-catheterization age (mean ±SD)	8.71±1.48
Myelodysplasia	25 (100)		
Hospital visit frequency, n (%)		Urinary incontinence, n (%)	
Once a month or more often	2 (8)	Yes	11 (44)
1 time in 3 months	11 (44)	No	14 (56)
1 time in 6 months	12 (48)		
Once a year	-		
Age at first urology visit (mean ±SD)	4.98±2.45	Hospitalization in the last 1 year, n (%)	
		No	11 (44)
		1 Times	10 (40)
		2-3 times	4 (16)
		3 and more	-
Presenting complaint, n (%)		Urinary tract infection in the last 1 year, n (%)	
Urinary tract infection	14 (56)	No	13 (52)
Urinary Incontinence	9 (36)	1 time	9 (36)
Consultation	2 (8)	2-3 times	3 (12)
		3 and more	-
Catheterization type, n (%)		Catheterization status, n (%)	
Urethral Catheterization	25 (100)	His / Herself	20 (80)
Suprapubic catheterization	0 (0)	Parents	5 (20)
Initiation age of CIC (mean ±SD)	6.04±2.64	Reaction when she/he tells anyone, n (%)	
		Regiment	-
		Pity	4 (16)
		Supporting	6 (24)
		Neutral	15 (20)
Daily number of catheterization (mean ±SD)	4.24 ± 1.05	K-SADS-PL diagnosis, n (%)	
		No	17 (68)
		Spesific phobia	1 (4)
		Social phobia	1 (4)
		Generalized anxiety disorder	3 (15)
		Major depressive disorder	2 (8)
		ADHD	1 (4)
		Other	-

Data are presented as mean ± standard deviation or number (percentage), as appropriate. CIC: clean intermittent catheterization; ADHD: attention-deficit/hyperactivity disorder; SD: standard deviation. K-SADS-PL Schedule for affective disorders and schizophrenia for school-aged children:present and lifetime version DSM-5.

Table III. The outcomes of adolescents and mothers scales for both groups.

	CIC (n:25)	Control (n:25)	p
The Piers-Harris children's self-concept scale			
Scale total score, mean ± SD	66±4.85	71.08±2.05	<0.001
Happiness and satisfaction	9 (7-12)	11 (10-12)	0.013
Anxiety	9 (8-11)	10 (9-11)	0.115
Popularity	8 (7-8)	9 (9-9.5)	<0.001
Behavior	11 (10-12)	12 (11-12.5)	0.07
Physical appearance and attributes	6 (6-7)	8 (7-8)	<0.001
Intellectual and school status	5 (5-6)	6 (6-7)	<0.001
Pediatric quality of life inventory (adolesence self-report)			
Scale total score-adolesence	74.76 (64.6-83.57)	80.54 (79.57-85.42)	0.021
Physical health total score	72.56 (65.03-81.73)	81.45 (78.72-97.5)	<0.001
Psychosocial health total score	76.7 (64.7-79.96)	78.75 (75.78-81.55)	0.103
Emotional functioning	80 (67.5-85)	80 (75-80)	0.968
Social functioning	75 (60-80)	80 (70-85)	0.007
School functioning	70 (67.5-77.5)	80 (75-85)	0.006
Pediatric quality of life inventory (parent proxy-report)			
Scale total score-adolesence	73.1 (68.34-80.11)	80.25 (78.67-80.65)	0.002
Physical health total score	72.35 (67.17-77.31)	79.8 (78.75-87.92)	<0.001
Psychosocial health total score	75.1 (68.24-79.8)	77.8 (77.5-80.25)	0.017
Emotional functioning	75 (67.5-85)	80 (80-80)	0.589
Social functioning	70 (67.5-77.5)	80 (75-85)	<0.001
School functioning	80 (75-85)	75 (75-82.5)	0.68
Strength and difficulties questionnaire (self)			
Scale total score, mean ± SD	10.44±2.97	9.28±3.33	0.218
Conduct problems	2 (1-2)	2 (1-2)	0.958
Hyperactivity-inattention	2 (1,5-3)	2 (2-3)	0.814
Emotional symptoms	3 (2-3,5)	3 (2-3)	0.183
Peer problems	3 (2,5-4)	2 (1,5-3)	0.001
Prosocial behaviour	5 (5-6,5)	8 (7-8)	<0.001
Strength and difficulties questionnaire (parent)			
Scale total score	11 (10-13)	10 (8-12)	0.248
Conduct problems	2 (1.5-2.5)	2 (2-3)	0.132
Hyperactivity-inattention	2 (2-3)	2 (1-3)	0.07
Emotional symptoms	3 (2-4)	3 (2-4)	0.509
Peer problems	4 (3-4)	3 (2-4)	0.145
Prosocial behaviour	6 (5-6)	8 (7-8)	<0.001

Normally distributed variables are presented as mean ± standard deviation and were compared using the independent samples t-test. Non-normally distributed variables are presented as median (Q1–Q3) and were compared using the Mann–Whitney U test. Statistical significance was defined as $p < 0.05$ (two-tailed). SD: standard deviation; CIC: clean intermittent catheterization.

Table III. Continued.

	CIC (n:25)	Control (n:25)	p
Peer relationship scale			
Scale total score	61 (54.5-67.5)	75 (73-77)	<0.001
Commitment	30 (26.5-32.5)	33 (32-35.5)	<0.001
Trust and identification	15 (13-16)	15 (14-17)	0.118
Self-disclosure	7 (6-10)	14 (13-14)	<0.001
Loyalty	10 (8-11)	13 (12-13.5)	<0.001
General health questionnaire-28			
Scale total score	5 (2-8)	4 (3-4.5)	0.186
Somatic symptoms	1 (1-2)	1 (1-2)	0.691
Anxiety and insomnia	2 (1-2)	1 (1-1)	0.026
Social dysfunction	1 (0-2)	1 (0.5-1.5)	0.436
Severe depression	0 (0-1)	0 (0-0)	0.289
The parental attitude research instrument (PARI)			
Overprotective mothership, mean ± SD	37.32±5.8	28.6±3.22	<0.001
Rejecting of housewifery role	28 (24-30.5)	25 (22-27)	0.007
Incompatibility, mean ± SD	14.12 ±2.24	14.08±2.28	0.95
Rigid disciplining, mean ± SD	31.12±4.64	26.8±2.85	<0.001
Democratic treatment and grantingequality, mean ± SD	24.24±3.63	25.8±2.9	0.09

Normally distributed variables are presented as mean ± standard deviation and were compared using the independent samples t-test. Non-normally distributed variables are presented as median (Q1–Q3) and were compared using the Mann–Whitney U test. Statistical significance was defined as $p < 0.05$ (two-tailed). SD: standard deviation; CIC: clean intermittent catheterization.

Table IV. Correlations between study variables (scale scores).

	Piers-Harris Self-concept	PedsQL (Self)	PedsQL (Parent)	SDQ (Self)	SDQ (Parent)	Peer relationship scale	GHQ-28	PARI
Piers-Harris Self-concept	—							
PedsQL (Self)	r: 0.677							
	p: <0.001							
PedsQL (Parent)	r: 0.633	r: 0.327						
	p: <0.001	p: 0.02						
SDQ (Self)	r: -0.417	r: -0.300	r: -0.095					
	p: 0.003	p: 0.034	p: 0.510					
SDQ (Parent)	r: -0.324	r: -0.288	r: -0.240	r: 0.289				
	p: 0.022	p: 0.043	p: 0.094	p: 0.042				
Peer Relationship Scale	r: 0.785	r: 0.630	r: 0.484	r: -0.303	r: -0.215			
	p: <0.001	p: <0.001	p: <0.001	p: 0.033	p: 0.134			
GHQ-28	r: -0.624	r: -0.501	r: -0.569	r: 0.244	r: 0.258	r: -0.411		
	p: <0.001	p: <0.001	p: <0.001	p: 0.088	p: 0.070	p: 0.003		
PARI	r: -0.538	r: -0.351	r: -0.209	r: 0.324	r: 0.088	r: -0.529	r: 0.262	—
	p: <0.001	p: 0.012	p: 0.145	p: 0.022	p: 0.543	p: <0.001	p: 0.066	

Pearson correlation coefficients between study scales total scores are presented.
PedsQL: Pediatric Quality of Life Inventory; SDQ: Strength and Difficulties Questionnaire; PRS: Peer Relationship Scale; GHQ-28: General Health Questionnaire-28; PARI: Parental Attitude Research Instrument.

Table V. Analysis outcomes of variables that affect scale scores of adolescents who perform CIC.

The Piers-Harris children's self-concept scale	B	Std. Error	Beta	t	p
(Constant)	97.930	5.555		17.628	<0.001
The parental attitude research instrument (PARI) total score	-0.151	0.035	-0.425	-4.333	<0.001
Age	-0.562	0.231	-0.236	-2.433	0.019
General health questionnaire-28 total score	-0.508	0.110	-0.462	-4.606	<0.001
Pediatric quality of life inventory					
(Constant)	168.587	20.761		8.120	<.001
The parental attitude research instrument (PARI) total score	-0.321	0.130	-0.276	-2.458	0.018
Age	-3.224	0.864	-0.414	-3.734	<0.001
General health questionnaire-28 total score	-1.214	0.412	-0.339	-2.948	0.005
Strength and Difficulties Questionnaire (Self)					
(Constant)	-4.346	5.633		-0.772	0.444
The parental attitude research instrument (PARI) total score	0.075	0.035	0.297	2.114	0.040
Age	0.307	0.234	0.182	1.310	0.197
General health questionnaire-28 total score	0.099	0.112	0.127	0.882	0.382
Peer Relationship Scale					
(Constant)	116.318	12.491		9.312	<0.001
The parental attitude research instrument (PARI) total score	-0.122	0.071	-0.201	-1.720	0.101
General health questionnaire-28 total Score	-0.100	0.256	-0.064	-0.393	0.699
Age	-1.642	0.494	-0.409	-3.324	0.003
Self-catheterization age	-1.660	0.474	-0.541	-3.502	0.002

Multiple linear regression analysis was performed to identify independent predictors of scale scores. Unstandardized regression coefficients (B), standard errors (SE), standardized coefficients (β), t values, and p values are presented. Statistical significance was defined as $p < 0.05$ (two-tailed).

Discussion

In this study, we comprehensively evaluated psychiatric and psychosocial functioning in adolescents performing clean intermittent catheterization (CIC) and examined potential familial correlates. The main findings were that adolescents in the CIC group demonstrated a higher burden of psychopathology and poorer psychosocial functioning compared with healthy peers, including lower self-perception and quality of life, alongside more pronounced difficulties in peer relationships and social participation. Notably, indicators of social withdrawal were prominent (e.g., preference for being alone, avoidance of social activities, and limited disclosure of CIC to peers), highlighting the potential role of stigma and secrecy in daily adolescent life. In addition, parental factors—particularly parental attitudes and parental psychological well-being—were associated with key adolescent outcomes, underscoring the importance of incorporating a family-focused perspective into CIC management. Collectively, these findings extend the existing literature, which has largely emphasized medical outcomes, by integrating structured psychiatric assessment with multidimensional psychosocial measures in a catheterization-dependent adolescent population. While psychosocial challenges associated with catheterization and chronic urological conditions have been previously explored in pediatric populations, much of the literature has emphasized medical outcomes and treatment adherence. Understanding how these challenges manifest within the developmental context of adolescence may therefore provide important insights into the unique psychosocial burden of performing CIC.

Previous studies describing catheterization-dependent pediatric populations have identified several psychosocial challenges associated with CIC, including reduced motivation, urinary incontinence despite treatment, embarrassment, difficulties organizing catheterization routines outside the home, fear of urethral injury, and inconvenience.[27] Furthermore, there is a close connection, both physically and emotionally, between the sexual organs and the urinary tract. Catheterisation can in many ways be perceived as a disturbing procedure, and some patients especially adolescents may experience the procedure as a traumatic event.[28] As a result of these potential obstacles, discontinuation rates of CIC in children range from 8% to 63%. Treatment adherence has been shown to be lower among adolescents.[8]

CIC requires great mental and physical capacity, as well as strict self-discipline.[29] In the adolescence period with its greater stress related to peer approval and body image, increased problems with accepting CIC may be anticipated.[30] There is also a group of children in need of CIC; apart from their severe bladder dysfunction, they look and act like all other healthy children. During their first years of life, their parents or caregivers perform CIC for these children. However, as these children grow up and become independent adolescents, it is not always easy to motivate them to continue CIC.[8]

One of the remarkable differences between the two groups was that; while adolescents in the control group preferred to be with their friends, adolescents in the CIC group stated that they preferred to be alone rather than with their friends. Consistent with this finding, parents in the CIC group also reported that their children occasionally had been avoided social activity. More than half of the adolescents (52%) did not tell their friends that they had been performing CIC. In addition, only a small group (24%) thought that if they shared this situation with their friends, they could receive a supportive response. These findings showing social avoidance behaviors were also supported by the evaluation of SDQ self reports and the PRS. Similar to our findings; Lopes et al. showed that children and adolescents with lower urinary tract dysfunction tend to develop an introspective behavior in relation to their peers, because they fear the discrimination that may result from the exposure of their dysfunction.[31] The presence of malformations or the need to undergo special medical procedures was associated with the fear of peer rejection or discrimination, which could characterize the impact of the presence of a chronic disease on socialization.[32] The "social stigma" and "invisibility" of the disorder can make the disclosure and the self-acceptance of the problem much harder.[33] Some adolescents who need CIC may be sensitive to peer opinions and remarks, therefore they may choose to be incontinent and wear diapers rather than be continent and perform CIC at school.[34] Even today, a stigma exists in society towards urinary problems in general, and this may cause reluctance to catheterize. Some patients have reported a feeling of shame when having to perform CIC. The importance given to secrecy and discretion results in some patients and especially in adolescents may avoid individuals to perform CIC in public toilets or at other people's homes.[35] It may be thought that this can be more common during adolescence and could be one of the main reasons for avoiding social activities. Patients also may view CIC as a task they are compelled to perform, rather than a technique that provides convenience and comfort in managing urinary troubles. This point of view is against the independent nature of adolescents, and it may lead the adolescent to completely withdraw from social environments.

In line with our findings, Lindehall et al. qualitatively explored psychosocial factors among teenagers and young adults with myelomeningocele who had long-term experience with CIC and highlighted themes related to disclosure, integrity/privacy concerns, and the impact of catheterization on friendships and close relationships.[9] Their participants commonly reported difficulties in deciding whether to inform peers and emphasized the fear of negative reactions, which is consistent

with the limited disclosure and low expectation of peer support observed in our cohort.[9] Notably, while Lindehall et al. focused on subjective experiences and interpersonal themes, our study extends this literature by combining structured psychiatric diagnostic assessment with quantitative measures of self-perception, peer relationships, and quality of life, thereby demonstrating that social and peer-related burdens may co-occur with clinically relevant psychopathology in a subset of adolescents performing CIC.[9]

Findings from other studies in adolescents and young adults similarly underline that adolescence is a particularly vulnerable period for maintaining adherence and coping with the daily demands of CIC.[8] In parallel with this literature, our results suggest that psychosocial challenges are not limited to practical barriers but also include developmental concerns such as autonomy, body image, and peer acceptance, which may contribute to social withdrawal and reduced well-being. Taken together, these findings support the need for multidisciplinary follow-up that addresses both urological management and age-specific psychosocial needs.[8,9]

The most important variables that predict low self-esteem, low quality of life and negative peer relationships in adolescents who perform CIC could be; negative parental attitudes, maternal mental disorders, age at self-catheterization initiation and catheterization by someone else. Similar to our findings, some of the studies based on children's self reports suggested that self-catheterization contributed to raising self-esteem in several instances.[27] However, some studies did not point to such a difference between self catheterization and catheterization by someone else.[36] Generally, the psychological consequences of stressors may be determined by their controllability. Therefore, it may be logical to think that children and adolescents gaining some mastery over their physical condition by being able to self-catheterize would have lower rates of psychological disturbance. Furthermore, improvements in self-esteem and the ability to engage in more independent social contacts would be expected if they were taking some responsibility for their own condition themselves.[36] Therefore, especially during adolescence which is characterized by the need to be independent, it may be important for clinicians to be vigilant and sensitive to these aforementioned issues in order to help adolescents to increase their quality of life and psychological well-being.

In line with our research, another important point we want to emphasize is that; studies of parental adaptation indicated that parents of children with disabilities were more likely than other parents to suffer from stress, anxiety, and depression, and experienced stress that was especially apparent in all interpersonal relationships but particularly prominent in the marital bond and relationships.[37] This impact may lead parents to develop negative attitudes toward controlling their children. In particular, overprotective parental attitudes which aimed at the well-being of the adolescent, could prevent the adolescent from gaining self-efficacy and reduce treatment compliance. Therefore, in adolescents performing CIC in addition to urological treatment, evaluating the psychiatric status of parents and their attitudes toward their children should be an important component of the follow-up. With this perspective, parents would be better equipped to help their children to overcome their anxiety and fears, and be more supportive in their children's ongoing care of the them.

The effect of performing CIC on quality of life has generally been investigated in adult populations and mostly focused on physiological measures of the application.[38,39] In our study, we aimed to reveal the difficulties experienced by adolescents due to CIC application, apart from the existing neurological barriers, by evaluating a group performing CIC. Contrary to studies showing that performing CIC did not have a negative effect on quality of life and self-perception, lower quality of life and self-perception scores were observed in the adolescent group who performed CIC compared to the healthy

group in our study.[5,40] Our explanation of our finding is that it may be related to the current study including only adolescents. Adolescence has been also characterized by heightened emotional reactions and believed to be a peak period for mental health problems.[41] The frequency of psychopathology (32%) detected in the CIC group also indicates the risk of this period especially for adolescents with chronic diseases.

Study limitations and strengths

There are several limitations to our study. First, the cross-sectional nature of the study did not allow us to conclude whether differences in quality of life, self-esteem and peer relationships were a result of performing CIC or whether they were just coincidental. Due to the same reason, we could not assess the possible changes in parental attitudes over time. Additionally, it was difficult to isolate the independent psychological impact of CIC from the broader effects of chronic disease burden, body image concerns, continence-related difficulties, social isolation, and underlying neurological conditions. The second limitation is that in order to complete psychometric evaluations, we excluded adolescents with intellectual disabilities. It is possible that this group has more cognitive, psychiatric and social problems. Another limitation of this study is the relatively small sample size, which may have limited the statistical power to detect small effect sizes. Although all eligible patients during the study period were included, the findings should be interpreted cautiously and considered exploratory in nature.

On the other hand, to our knowledge, this is the first study to assess the clinical variables related to these factors and the presence of possible psychopathology with a high-quality semi-structured psychiatric interview in this group.

Conclusion

In conclusion, these results suggest that performing CIC may have psychological and social impacts on adolescents. Furthermore, such effects may be affected by disease-specific clinical variables, parental attitudes, and parental mental state. Risk factors must be well identified to decrease these negative effects. Our findings may guide clinicians during adolescence, when treatment compliance may decrease. Efficient psychosocial evaluation and sensitivity to the emotional needs of adolescents are also equally essential, alongside educating adolescents and helping them gain competence in self-CIC. Our study emphasizes that psychiatric evaluations must not be disregarded in the follow-up of adolescents who perform CIC. Additionally, health care professionals who work with such patients must be aware of the warning signs of deeper psychiatric problems, pathological parental attitudes and the need for psychiatric consultation. Findings need to be confirmed in a larger sample with prospective studies.

Ethical approval

The study was approved by Human Research Ethical Committee of Ankara University (date: 18.07.2019, number: İ2-35-19).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: TMB, MB, MÇU, BB; data collection: TMB, GYE, MB, AA; analysis and interpretation of results: TMB, MÇU; draft manuscript preparation: TMB, MÇU, ÖY, BGK. All authors reviewed the results and approved the final version of 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

Growth and development in children with periodic fever, aphthous stomatitis, pharyngitis, lymphadenitis syndrome: a case-control study

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ABSTRACT

Background. Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome is the most common cause of recurrent fever in childhood. Although normal growth and development are included in the diagnostic criteria, this assumption has not been systematically evaluated in controlled studies. This study aimed to compare growth patterns and developmental screening outcomes between children with PFAPA and healthy controls.

Methods. A total of 138 children were enrolled, including 69 patients diagnosed with PFAPA according to the modified Marshall criteria and 69 age- and sex-matched healthy controls. The PFAPA group consisted of 26 females (37.7%) and 43 males (62.3%), while the control group included 26 females (37.7%) and 43 males (62.3%). The mean age was 52.1 ± 13.86 months in the PFAPA group and 50.28 ± 13.70 months in the control group. Growth was assessed using anthropometric parameters, including height, weight, body mass index (BMI), weight-for-height, and mid-upper arm circumference. The primary outcome was overall growth pattern, assessed by anthropometric measures, with particular attention to BMI. Developmental screening was performed using the Denver II Developmental Screening Test.

Results. Mean anthropometric measures, including height, weight, and BMI, were comparable between patients with PFAPA and controls. However, overweight/obesity was more prevalent in the PFAPA group than in controls (18.8% vs. 5.8%; odds ratio [OR] 3.77, 95% confidence interval [CI] 1.16–12.24, p=0.020). Patients with PFAPA who were overweight/obese had received a higher number of corticosteroid treatments (p=0.046). Developmental screening outcomes did not differ significantly between groups.

Conclusion. In this case-control study, children with PFAPA demonstrated overall growth patterns and developmental screening results similar to those of healthy peers, although a higher prevalence of overweight/obesity was observed. These findings support, but do not definitively establish, the assumption of preserved growth and development in PFAPA and underscore the need for further longitudinal studies.

Key words: PFAPA syndrome, growth, development, corticosteroids, obesity.

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Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is one of the most common autoinflammatory syndromes of childhood. It is characterized by regularly recurring febrile episodes accompanied by aphthous stomatitis, pharyngitis, and cervical lymphadenitis, with complete resolution of symptoms between attacks. PFAPA typically presents before the age of five years and is generally regarded as a benign, self-limited condition.[1]

Normal growth and development are included among the original diagnostic criteria for PFAPA syndrome and are frequently emphasized in the literature.[2,3] However, this assumption is largely based on clinical observation rather than systematic, objective evaluation. Children with PFAPA experience recurrent episodes of systemic inflammation during early childhood, which is a critical period for somatic growth and neurodevelopment. Chronic inflammatory conditions have been associated with disruption of the growth hormone–insulin-like growth factor-1 (GH–IGF-1) axis, increased metabolic demands, and growth-plate perturbations, which may plausibly influence growth trajectories.[4,5]

In addition, PFAPA attacks are commonly treated with intermittent systemic corticosteroids to rapidly terminate febrile episodes. Although these treatments usually involve short courses, repeated exposure over time may contribute to increased appetite and changes in body composition, raising concern about potential overweight/obesity in susceptible children.[6,7]

Despite these biologically plausible mechanisms, controlled studies systematically evaluating growth and developmental outcomes in children with PFAPA remain limited. Most available reports lack appropriate control groups, standardized anthropometric measurements, or formal developmental screening. Therefore, the primary aim of this study was to compare growth patterns and developmental screening outcomes in children aged 2-6 years diagnosed with PFAPA syndrome with those of age- and sex-matched healthy controls using standardized anthropometric measurements and a validated developmental screening tool. We hypothesized that overall growth and developmental outcomes in children with PFAPA would be similar to those of healthy peers, while the prevalence of overweight and obesity might be higher in the PFAPA group due to intermittent corticosteroid exposure.

Materials and Methods

A total of 138 children aged 2-6 years were included in this case–control study, comprising 69 patients diagnosed with PFAPA syndrome and 69 age- and sex-matched healthy controls. Patients with PFAPA were recruited from the pediatric rheumatology and general pediatrics outpatient clinics of our institution. Healthy controls were recruited from the general pediatrics outpatient clinic during the same study period. PFAPA diagnosis was established according to the modified Marshall criteria. Controls were matched to patients with PFAPA by age and sex. The same exclusion criteria were applied to both groups. Children with known chronic systemic diseases, congenital anomalies, or a prior diagnosis of or follow-up for growth or developmental delay were excluded from the study. Anthropometric measurements including height, body weight, body mass index (BMI), weight-for-height (WFH), and mid-upper arm circumference, were obtained using standardized techniques. Height, weight, and BMI z-scores and percentiles were calculated according to the World Health Organization (WHO) Child Growth Standards. Nutritional status was additionally evaluated using the Gómez and Waterlow classifications to assess acute and chronic malnutrition. Overweight was defined as a BMI-for-age percentile between the 85th and 95th percentiles, and obesity was defined as a BMI-for-age percentile at or above the 95th percentile, in accordance with WHO growth standards. Developmental assessment was performed using the Denver II Developmental Screening Test (DDST II) by

a trained child development specialist. The DDST II evaluates gross motor, fine motor, language, and personal–social domains. In accordance with standard clinical practice, DDST II results were interpreted using the overall test classification (normal, questionable, or abnormal), and domain-specific results were not reported separately. Demographic and socioeconomic data collected included age, sex, number of household members, parental education level, and family income. For patients with PFAPA, clinical characteristics such as age at disease onset, frequency and duration of febrile episodes, longest interval between episodes, and total number of attacks were recorded. PFAPA attacks were treated with intermittent systemic corticosteroids according to standard clinical practice. Data regarding the number of corticosteroid administrations were obtained from medical records. Detailed information on cumulative corticosteroid dose (mg/kg), dose per episode, or time since the last dose at the time of assessment was not consistently available and therefore could not be included in the analysis. Ethical approval was obtained from the institutional ethics committee (Approval date: 11/01/2023; decision number: 2022/12-17), and written informed consent was obtained from the parents or legal guardians of all participants. The study was conducted in accordance with the Declaration of Helsinki.

To detect a moderate effect size (Cohen's d = 0.50) with 90% statistical power and a type I error rate of 5%, a minimum of 64 participants per group (128 total) was required. Our final sample exceeded this minimum with 69 participants in each group. This calculation was based on the primary hypothesis that overall growth parameters would be comparable between children with PFAPA and healthy controls.

Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows, Version 30.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Continuous variables were presented as means ± standard deviations (SD) if normally distributed, or as medians (Q1–Q3; i.e., 25th–75th percentiles) if not normally distributed. For comparisons between two independent groups, Student's t-test was used for normally distributed variables, and the Mann-Whitney U test was used for non-normally distributed variables. The chi-square test and Fisher's exact test were employed for the comparison of categorical data. A p-value of <0.05 was considered statistically significant.

To assess correlations between variables, Spearman's rank correlation coefficient was used. The strength of correlations was interpreted as follows: $r \geq 0.91$: very strong, $0.71 \leq r < 0.91$: strong, $0.51 \leq r < 0.71$: moderate, $0.31 \leq r < 0.51$: weak, $r < 0.31$: negligible or no correlation.

Results

A total of 138 children, including 69 patients with PFAPA and 69 healthy controls, were included in the study. The descriptive characteristics of the children were compared between the two groups. Of the 69 patients with PFAPA, 43 (62.3%) were male and 26 (37.7%) were female. When the income status of the children's families was examined, families reporting that their income was equal to their expenses were statistically significantly more prevalent in the PFAPA group ($p = 0.002$). There was a statistically significant difference in the number of family members between the two groups ($p = 0.032$) (Table I). The mean age at onset of PFAPA symptoms was 25.29 ± 13.76 months, the mean age at diagnosis was 38.46 ± 13.78 months, and the mean interval between attacks was 27.2 ± 8.02 days (Table II).

The growth parameters of patients with PFAPA including weight, height, BMI, WFH, and mid-upper arm circumference, were similar to those of the control group when examined as categorical variables. In the PFAPA group, the weight was below the third percentile in 1 (1.4%) case. When compared with the control

Table I. Descriptive characteristics of PFAPA and control groups (n = 138).

		PFAPA (n=69) n (%)	Control (n=69) n (%)	p-value
Sex	Girl	26 (37.7)	26 (37.7)	1.000*
	Boy	43 (62.3)	43 (62.3)	
Income status	Income <Expenses	2 (2.9)	16 (23.2)	0.002*
	Income = Expenses	65 (94.2)	52 (75.4)	
	Income > Expenses	2 (2.9)	1 (1.4)	
	Illiterate	1 (1.4)	1 (1.4)	
Mother educational status	Primary school	7 (10.1)	13 (18.8)	
	Secondary school	15 (21.7)	10 (14.5)	0.191*
	High school	22 (31.9)	30 (43.5)	
	University	24 (34.8)	15 (21.7)	
	Illiterate	0 (0)	1 (1.4)	
Father educational status	Primary school	7 (10.1)	11 (15.9)	
	Secondary school	14 (20.3)	13 (18.8)	0.664*
	High school	31 (44.9)	26 (37.7)	
	University	17 (24.6)	18 (26.1)	
Age (months)		52.1 ± 13.86	50.28 ± 13.70	0.141**
Number of family members		3.8 ± 0.95	4.14 ± 0.96	0.032**

*Chi-square test; **Independent samples t- test

Table II. Clinical characteristics of patients with PFAPA (n=69).

Variable	Value mean ± SD or median (Q1-Q3)
Age of onset (months)	24 (13-36)
Age at diagnosis (months)	36.0 (28.5-49.0)
Periodicity (days)	30 (21-30)
Frequency of attacks (per year)	12 (12-15)
Duration of attacks (days)	4 (3-5)
Total number of attacks	20.0 (13.0-32.5)
Maximum interval between attacks (days)	30 (30-40)
Highest temperature (°C)	40.01 ± 0.68
Number of steroids taken	8 (2-12)

SD: Standard deviation.

group, there were no statistically significant differences between groups in weight standard deviation score (SDS) value or weight percentile value.

In the PFAPA group, short stature was detected in 2 (2.9%) cases. When compared with the control group, no statistically significant difference was detected between the groups in terms of the SD of height SDS or height percentile values.

Malnutrition was detected in 5 (7.2%) cases among patients with PFAPA, as determined by BMI, but no statistically significant difference was found between the PFAPA and control groups.

The groups did not show any statistically significant difference in terms of WFH SDS. In the PFAPA group, WFH was below the third percentile in 6 (8.7%) cases, and WFH SDS was below -2 SDS in a total of 10 (14.5%) cases. When compared with the control group, no statistically significant difference was found between the groups in terms of WFH SDS or percentile values (Table III).

When cases with overweight or obesity, defined as BMI above the 85th percentile were compared with the control group, 13 (18.8%) cases in the PFAPA group and 4 (5.8%) cases in the control group were identified. This difference was statistically significant (p = 0.02; odds ratio [OR] 3.77, 95% confidence interval [CI] 1.16–12.24) (Table IV).

No statistically significant difference was detected between the two groups in terms of DDST II results (Table V). Additionally, the neuromotor development parameters of the cases were evaluated according to the number of steroid administrations received (Table VI). The mean number of steroids administrations among patients with abnormal DDST II was 8.78 ± 5.35, and the mean number of steroids taken by patients with normal and suspicious DDST II was 7.86 ± 6.25. No statistically significant difference was found between the groups. The number of corticosteroid administrations

Table III. Comparison of continuous growth parameters of the cases between the two groups.

	PFAPA (n=69)	Control (n=69)	p-value
	mean ±SD or median (Q1-Q3)	mean ± SD or median (Q1-Q3)	
Weight (kg)	16.9 (15.0-20.0)	16.8 (14.9 -19.5)	0.523*
Weight SDS	0.01 (-0.80-0.80)	0.01 (-0.60-0.57)	0.998*
Weight percentile	30.21 (20.55-77.61)	50.40 (27.20-71.55)	0.997*
Height (cm)	105.91 ± 9.26	104.95 ± 9.12	0.577**
Height SDS	0.17 (-0.52–0.74)	0.17 (-0.45-0.77)	0.788*
Height percentile	57.93 (30.51-77.62)	56.7 (32.4-78.5)	0.905*
BMI (kg/m^2)	15.67 ± 1.83	15.48 ± 1.44	0.249**
BMI SDS	-0.05 (-0.86-0.69)	-0.10 (-0.77-0.49)	0.667*
BMI percentile	46.4 (18.0-75.5)	44.4 (21.6-66.0)	0.603*
WFH (%)	101.26 ± 12.02	100.25 ± 9.08	0.289**
WFH SDS	0.04 (-0.84-0.82)	-0.05 (-0.47-0.56)	0.958*
WFH percentile	51.6 (24.2-79.51)	48.0 (31.7-73.4)	0.919*
AAW (%)	101.43 ± 15.56	101.56 ± 14.37	0.480**
AAH (%)	100.41 ± 4.49	100.33 ± 3.71	0.452**
Mid-upper arm circumference (cm)	19.14 ± 1.11	17.88 ± 1.55	0.155**

AAH: age adjusted height; AAW: age adjusted weight; BMI: Body Mass Index; *Mann-Whitney U test; **Independent samples t-test; SD: Standard deviation; WFH: weight-for-height.

Table IV. Distribution of BMI categories in PFAPA and control groups.

BMI category	PFAPA (n=69) n (%)	Control (n=69) n (%)	p-value
Malnutrition	5 (7.2)	4 (5.8)	0.117
Normal weight	51 (74)	61 (88.4)	
Overweight	8 (11.6)	2 (2.9)	
Obesity	5 (7.2)	2 (2.9)	

Table V. Denver II Development Test outcomes.

Result	PFAPA (n=69) n (%)	Control (n=69) n (%)	p-value
Normal	51 (73.9)	57 (82.6)	0.189
Suspicious	9 (13.0)	3 (4.3)	
Abnormal	9 (13.0)	9 (13.0)	

Table VI. Steroid Usage by Development outcome (PFAPA group only).

Developmental Status	Median (Q1-Q3)	p-value
Normal/suspicious (n=60)	7.5 (2-12.5)	0.411*
Abnormal (n=9)	10 (3.5-13.5)	

*Mann-Whitney U test.

was significantly higher in children who were overweight or obese compared to those who were not (10.5 [2–18] vs. 6 [2–32], p = 0.046). A weak positive correlation was found between BMI and the number of steroids administrations (r = 0.34, p=0.046)

Discussion

According to current literature, PFAPA syndrome is generally considered to have minimal effects on growth and development in the pediatric population, and there is insufficient evidence to suggest a significant impact on long-term physical or neurodevelopmental outcomes. Although disease attacks may transiently affect appetite and general health status, these effects are episodic. The observation that children return to their baseline health status between attacks supports the expectation that overall growth remains preserved. Accordingly, normal growth and development have long been included among the diagnostic criteria for PFAPA syndrome.[1,2] However, despite this assumption, objective data derived from case–control studies addressing growth and development in PFAPA remain limited.[1,8]

In the present study, 69 children diagnosed with PFAPA were evaluated and compared with age- and sex-matched healthy controls. Although isolated cases of low weight, short stature, or malnutrition were observed among patients with PFAPA, no statistically significant differences were identified between the groups in most growth parameters, including weight, height, BMI, and WFH. However, the prevalence of overweight/obesity was significantly higher in the PFAPA group. These findings suggest that PFAPA does not involve a pathophysiological mechanism leading to sustained impairment of linear growth. PFAPA is characterized by intermittent inflammatory episodes presenting with fever, pharyngitis, aphthous stomatitis, and cervical lymphadenitis, driven by an autoinflammatory process rather than continuous systemic inflammation.[9]

In contrast to chronic inflammatory or autoinflammatory conditions associated with persistent disease activity, PFAPA follows a self-limiting course and does not exhibit an ongoing inflammatory burden between episodes. Moreover, spontaneous resolution with increasing age is commonly observed, further reducing the likelihood of long-term growth compromise.[8] Chronic inflammatory diseases are known to impair growth through mechanisms such as increased metabolic demand, reduced nutritional intake, and alterations in the GH–IGF axis. Indeed, Cimaz et al. reported reduced IGF-1 levels and growth failure in children with chronic inflammatory diseases characterized by sustained inflammation.[10] Such mechanisms, however, appear less applicable to PFAPA given its episodic and non-continuous inflammatory nature.

An important finding of this study was the higher prevalence of overweight and obesity among patients with PFAPA compared with controls, as well as the observed association between increased cumulative corticosteroid exposure and BMI. In PFAPA syndrome, systemic corticosteroids are typically administered intermittently and for short durations to abort febrile episodes.[11] This treatment approach is generally considered safe with respect to linear growth; however, repeated exposure over time may influence appetite regulation and body composition.[11,12] In the present cohort, overall growth parameters were preserved, supporting previous observations that PFAPA does not impair linear growth. Nevertheless, the increased frequency of overweight and obesity among patients with PFAPA underscores the importance of careful growth and metabolic monitoring, particularly in children receiving repeated corticosteroid treatments. Clinicians should balance the benefits of rapid symptom control with the potential metabolic effects of recurrent steroid exposure.

Regarding neurodevelopment, no significant differences were observed between patients with PFAPA and controls based on the DDST II. Although abnormal screening results were identified in a minority of patients with PFAPA, these findings were not associated with corticosteroid exposure. As the Denver II is a screening tool rather than a comprehensive neuropsychological assessment, these results suggest that, at the level of screening, neurodevelopmental outcomes in children with PFAPA are comparable to those of healthy peers.

This study has several limitations that should be acknowledged. First, although the overall sample size was adequate, the exploratory nature of the study and the relatively small number of overweight and obese cases limited the feasibility of multivariable analyses adjusting for potential confounders such as socioeconomic status and household characteristics. Additionally, the cross-sectional design limits the ability to establish causal relationships between variables. Therefore, residual confounding cannot be excluded, particularly with respect to obesity-related outcomes. Second, a clearly defined primary endpoint was not prespecified, and multiple anthropometric and developmental outcomes were assessed, introducing the possibility of multiple testing and chance findings. Third, developmental outcomes were evaluated using the DDST II, which is a screening instrument rather than a comprehensive neuropsychological assessment, and subtle or domain-specific differences may not have been fully captured. Fourth, the number of overweight and obese cases was relatively small, limiting statistical power and precision. Additionally, corticosteroid exposure was assessed using the number of administrations rather than cumulative dose or timing, which represents a coarse measure and limits causal interpretation.

Conclusion

In this case–control study, children with PFAPA syndrome demonstrated overall growth patterns and developmental screening outcomes comparable to those of healthy peers, despite the presence of isolated cases of growth or developmental delay. No association was observed between corticosteroid use and linear growth or developmental screening results. However, a higher prevalence of overweight and obesity was noted among patients with PFAPA, and these children had greater corticosteroid exposure. Although this observation should be interpreted with caution, it highlights the importance of monitoring growth and metabolic outcomes in children receiving repeated corticosteroid treatment for PFAPA. Further prospective studies with larger sample sizes and more detailed assessment of steroid exposure are needed to better clarify these relationships.

Ethical approval

The study was approved by Ethics Committee of Izmir Tepecik Training and Research Hospital, Ministry of Health (date: January 11, 2023, number: 2022/12-17).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: AK, YD, ÇB, BKD, MİA, HÖH; data collection: YD; analysis and interpretation of results: AK, ÇB, BKD; draft manuscript preparation: AK, ÇB, MİA, BKD. All authors reviewed the results and approved the final version of 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

Genotype–phenotype divergence in pediatric familial Mediterranean fever across two closely related populations: a Türkiye–Azerbaijan comparison

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ABSTRACT

Background. Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease and has a high prevalence in Türkiye. Despite shared ethnic ties, pediatric FMF in Azerbaijan remains poorly characterized. This study aimed to systematically compare the clinical, laboratory, and genetic characteristics of pediatric FMF patients from Türkiye and Azerbaijan to determine whether common ancestral origins result in uniform disease expression.

Methods. This retrospective bicentric study enrolled pediatric FMF patients aged 0–18 years who met the Eurofever/PRINTO criteria and had ≥12 months of follow-up at specialized centers in Türkiye and Azerbaijan. Demographics, clinical features, laboratory findings, Mediterranean FeVer (*MEFV*) genotypes, severity scores, and treatment data were compared.

Results. The cohort comprised 549 patients: 477 (86.9%) Turkish and 72 (13.1%) Azerbaijani. Azerbaijani patients had earlier symptom onset (30 [IQR 16-67] vs. 48 [IQR: 24–72] months, p=0.044) but a longer diagnostic delay (14 [IQR: 11.4–48.7] vs. 12 [IQR: 6–23] months, p<0.001). Turkish patients showed higher rates of chest pain (22.6% vs. 8.3%, p=0.005), arthralgia (52.6% vs. 32 %, p= 0.001), annual attack frequency (12 [IQR: 6–12] vs. 6 [IQR: 4–8], p<0.001), International Severity Score for Familial Mediterranean Fever (ISSF) scores (2 [IQR: 1–3] vs. 2 [IQR: 1–2], p=0.002), and C-reactive protein (CRP) levels (56 [IQR: 34–96] vs. 17.9 [IQR: 3.2–35.6] mg/L, p<0.001). Confirmatory exon 10 genotypes predominated in Turkish patients (66.7%) whereas unconfirmatory genotypes in Azerbaijani patients (59.7%). M694V was the most common variant in both groups. Within exon 10 homozygotes, Turkish patients had higher ISSF scores (median 3 [IQR: 2–4] vs. 2 [IQR: 1–3], p=0.037) and more arthritis (39% vs 6.3%, p=0.032). Colchicine response was comparable (90.6% vs. 93.1%), but anti–IL-1 use was higher in Turkish patients (11.5% vs. 2.9%, p=0.028).

Conclusion. This first systematic Türkiye–Azerbaijan comparison reveals distinct genotype–phenotype correlations in pediatric FMF, with Turkish patients showing a higher burden of confirmatory exon 10 genotypes and more severe disease, highlighting the need for center- and population-aware management strategies.

Key words: familial Mediterranean fever, genotype-phenotype correlation, phenotype.

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Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease (AID) worldwide, characterized by recurrent episodes of febrile serositis.[1] The disease is caused by gain-of-function mutations in the *MEFV* (Mediterranean FeVer) gene encoding the pyrin protein.[2] An overactive pyrin inflammasome leads to uncontrolled interleukin (IL)-1β secretion, resulting in FMF symptoms that range from mild, infrequent attacks to severe, debilitating disease with potential complications such as AA amyloidosis.[3] In pediatric populations, FMF poses unique diagnostic and therapeutic challenges, as early-onset disease is often associated with more severe clinical manifestations and a higher disease burden.[4]

FMF predominantly affects populations from the Mediterranean basin, particularly Turks, Armenians, Arabs, and non-Ashkenazi Jews.[1,5] Türkiye harbors one of the world's largest FMF populations, with an estimated carrier frequency of 1:5 to 1:3 in certain regions and a disease prevalence of approximately 1:1000.[6,7] The most comprehensive Turkish pediatric FMF cohort, comprising 3,454 patients demonstrated that exon 10 mutations correlate with earlier disease onset, more frequent attacks, and higher rates of severe clinical manifestations.[4]

Azerbaijan, sharing geographic proximity and ethnic ties with Türkiye, represents another high-prevalence region for FMF. However, systematic data on pediatric FMF characteristics in Azerbaijan remain limited.[8] While common ancestral origins suggest potential similarities in disease patterns, geographic separation, environmental influences, and differences in healthcare systems may have shaped distinct mutation distributions, clinical phenotypes, and treatment responses. A comprehensive evaluation of pediatric FMF in Azerbaijan is therefore needed to clarify whether the disease profile parallels that observed in Türkiye or exhibits region-specific characteristics. Given the limited comparative data between these closely related populations, we conducted a bicentric retrospective cohort study using data from specialized pediatric rheumatology centers in Azerbaijan and Türkiye. The study aimed to compare clinical characteristics, *MEFV* mutation distributions, disease severity, treatment responses, and genotype–phenotype associations between pediatric FMF patients in the two countries.

Materials and Methods

Study design, setting and population

This retrospective cohort study was conducted at two specialized pediatric rheumatology centers in Türkiye and Azerbaijan between November 2023 and June 2025. We included pediatric patients aged 0–18 years diagnosed with FMF according to the Eurofever/Pediatric Rheumatology International Trials Organisation (PRINTO) classification criteria for hereditary recurrent fevers.[9] All enrolled patients had been under regular surveillance for a minimum of 12 months, with routine clinical evaluations conducted at 3-month intervals. Patients with inadequate clinical documentation or insufficient follow-up records were excluded from the analysis.

To ensure diagnostic precision, true juvenile idiopathic arthritis (JIA) and IgA vasculitis were strictly differentiated from FMF-related arthritis using the ILAR and EULAR/PRINTO/PRES criteria (respectively), and patients with these concomitant conditions were excluded.[10,11]

Data collection and clinical definitions

Data were extracted from medical records using a standardized data collection form. Recorded parameters included demographic characteristics, family history of FMF, clinical characteristics of the attacks, laboratory findings, *MEFV* gene analysis, severity scores, and treatment modalities.

Genetic analyses were performed at both centers using either Sanger sequencing or next-generation sequencing, covering all coding exons of the *MEFV* gene. Identified variants

were interpreted according to the Infevers database (https://infevers.umai-montpellier.fr/web/), a curated international repository for autoinflammatory disease-associated variants.[12]

MEFV genotype distributions were compared between Turkish and Azerbaijani patients. Patients were classified into three groups according to the genetic mutation categories defined by the Eurofever/PRINTO classification criteria: (i) homozygous pathogenic variants, (ii) compound heterozygous pathogenic variants, and (iii) genotype-unconfirmed patients (carrying one pathogenic variant with one variant of uncertain significance [VUS], a single pathogenic variant, or two VUS variants).[9]

Colchicine was dosed according to age: 0.5 mg/day for children under 5 years, 0.5–1 mg/day for those aged 5–10 years, and 1.5 mg/day for children older than 10 years.[13] In colchicine-resistant cases, the maximum tolerated dose was administered under careful monitoring (maximum 1.5 mg/day for ages 5–10 years; maximum 2 mg/day for those older than 10 years). Colchicine resistance was defined as the occurrence of one or more attacks per month over a minimum period of six months and/or the presence of subclinical inflammation, despite treatment with the maximum tolerated dose of colchicine.[13] The same oral colchicine tablet formulation was used in both centers. In patients meeting the criteria for colchicine resistance, anti–IL-1 biological therapy (anakinra at 2 mg/kg/day or canakinumab at 2 mg/kg every 4 weeks) was initiated.[14,15]

Colchicine-related adverse effects monitored during follow-up included gastrointestinal symptoms (nausea, vomiting, diarrhea) and elevated liver function tests.

Amyloidosis was diagnosed by renal biopsy in patients presenting with elevated serum amyloid A levels, persistent proteinuria, and impaired renal clearance.[16]

Disease severity was assessed using the International Severity Score for Familial Mediterranean Fever (ISSF), a validated scoring tool evaluating attack frequency, duration, types of manifestations, inter-attack inflammation, and disease-related complications, with higher scores indicating greater disease severity.[17,18]

C-reactive protein (CRP) and serum amyloid A (SAA) levels were measured using immunoturbidimetric assays, with values greater than 5 mg/L for CRP and greater than 10 mg/L for SAA considered elevated at both centers.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics (version 22.0; IBM Corp., Armonk, NY, USA).

Normality of continuous variables was assessed using visual methods and the Kolmogorov–Smirnov and Shapiro–Wilk tests. As most variables were not normally distributed, data were expressed as medians (IQRs) and compared between groups using the Mann–Whitney U test.

Categorical variables were presented as frequencies and percentages and compared using the chi-square test or Fisher's exact test, as appropriate. Genotype distributions were analyzed according to Eurofever-recommended categories. All tests were two-tailed, and a p value <0.05 was considered statistically significant.

Ethical approval

The study protocol was approved by the Local Ethics Committees of both participating centers (Ethics Committee 1, date/no: 25.06.2025: 3429655 and Ethics Committee 2, date/no: 15.05.2025: 013/25). Since this study is retrospective, routinely archived patient data (November 2023–June 2025) were accessed and analyzed only after formal ethical approvals were granted. The research was conducted in accordance with the principles of the Declaration of Helsinki and complied with all applicable local laws and regulations.

Results

Demographic and clinical comparison

The study cohort comprised 549 pediatric FMF patients: 477 (86.9%) from Türkiye and 72 (13.1%) from Azerbaijan (Fig. 1.). The proportion of female patients was comparable between the groups, with females comprising 48% (n = 229) of Turkish patients and 38.9% (n = 28) of Azerbaijani patients (p = 0.131). The median age at diagnosis for the entire cohort was 63.5 months (IQR: 40-96), with a median age at symptom onset of 48 months (IQR: 24-72). The overall median diagnostic delay was recorded as 12 months (IQR: 7-24). Comparative analysis between the Azerbaijani and Turkish cohorts revealed that symptom onset occurred significantly earlier in the Azerbaijani group (30 months [IQR: 16–67] vs. 48 months [IQR: 24–72]; p=0.044). Although the median age at diagnosis was similar between the two groups (67.3 months [IQR: 37–117] vs. 63 months [IQR: 40–96]), the median diagnostic delay was significantly longer in the Azerbaijani cohort than in the Turkish cohort (14 months [IQR: 11.4–48.7] vs. 12.0 months [IQR: 6–23]; p<0.001) (Table I).

Comorbid diseases were observed significantly more frequently in Azerbaijani patients than in Turkish patients (12.5% vs 4.0%, p < 0.001). The most common inflammatory comorbidities in both cohorts were JIA (8.3% in Azerbaijani patients vs 3.4% in Turkish patients, p = 0.055) and IgA vasculitis (4.2% vs 0.6%, respectively; p=0.032).

A family history of FMF was significantly more frequent among Turkish patients than among Azerbaijani patients (67.3% vs 27.8%, p < 0.001). The frequencies of parental consanguinity was similar between Turkish and Azerbaijani patients (25.2% vs 20.8%, p = 0.427) (Table I).

During acute attacks, Turkish patients exhibited significantly higher rates of both chest pain

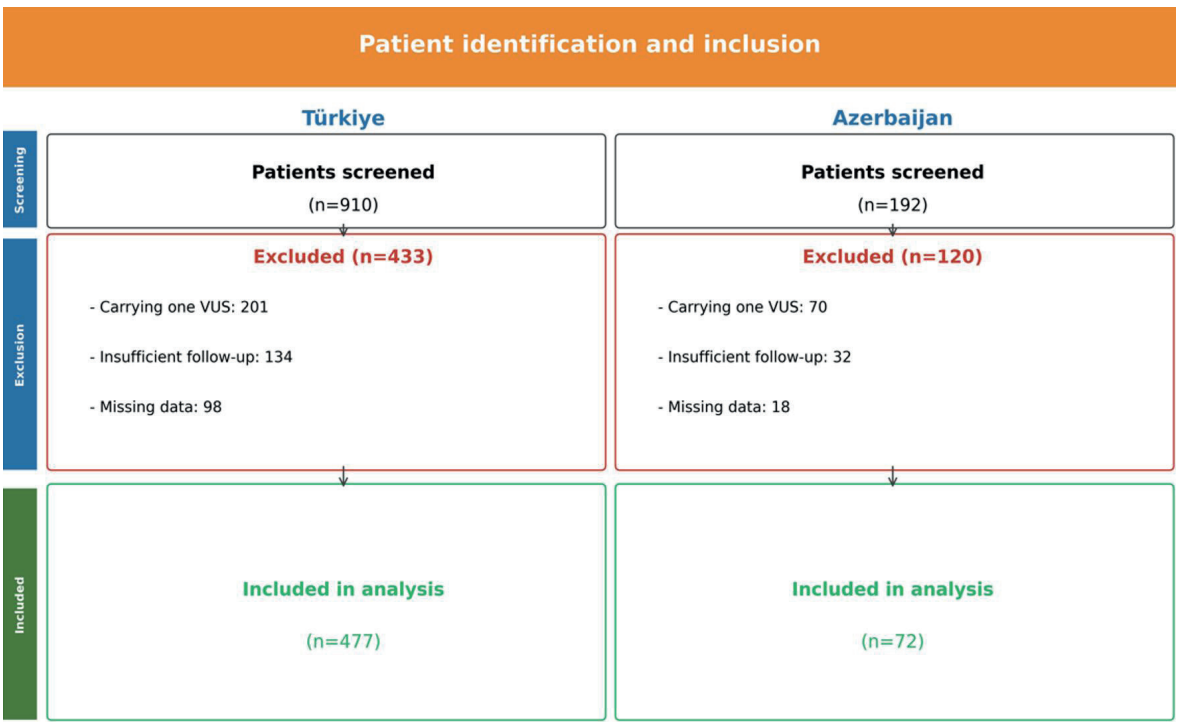

Fig. 1. Flowchart for the selection of the study population.
VUS, variant of uncertain significance.

(22.6% vs. 8.3%, p = 0.005) and arthralgia (52.6% vs. 32%, p =0.001) than Azerbaijani patients. Fever, abdominal pain, arthritis, erysipelas-like erythema, vomiting, diarrhea, and orchitis frequencies were similar between the two groups (Table I).

The median attack duration was longer in the Azerbaijani cohort than in the Turkish cohort [2 (1–5) days vs. 2 (1–4) days, respectively; p=0.027]. Additionally, very short attacks (<24 hours) were more frequently observed in the Azerbaijani cohort than in the Turkish cohort

Table I. Comparison of demographic and clinical features between Turkish and Azerbaijani FMF cohorts.

	Turkish patients (n = 477)	Azerbaijani patients (n = 72)	p value
Demographic features			
Sex			0.131
Female, n (%)	229 (48.0)	28 (38.9)	
Male, n (%)	248 (52.0)	44 (61.1)	
Age at onset (months), median (IQR)	48 (24–72)	30 (16–67)	0.044
Age at diagnosis (months), median (IQR)	63 (40–96)	67.3 (37–117)	0.448
Diagnostic delay (months), median (IQR)	12.0 (6–23)	14 (11.4–48.7)	<0.001
Family history of FMF, n (%)	321 (67.3)	20 (27.8)	<0.001
Parental consanguinity, n (%)	120 (25.2)	15 (20.8)	0.427
Clinical findings			
Fever during attacks, n (%)	423 (88.7)	59 (81.9)	0.104
Abdominal pain, n (%)	393 (82.4)	57 (79.2)	0.507
Chest pain, n (%)	108 (22.6)	6 (8.3)	0.005
Arthritis, n (%)	117 (24.5)	11 (15.2)	0.204
Arthralgia, n (%)	251 (52.6)	23 (32)	0.001
Erysipelas-like erythema, n (%)	61 (12.7)	6 (8.3)	0.208
Vomiting, n (%)	38 (8.0%)	8 (11.1%)	0. 292
Diarrhea, n (%)	66 (13.8%)	4 (5.6%)	0. 050
Orchitis, n (%)	6 (1.3%)	1 (1.4%)	1.000
Amyloidosis, n (%)	4 (0.8)	0	0.031
ISSF score, median (IQR)	2 (1–3)	2 (1–2)	0.002
Annual attack frequency, median (IQR)	12 (6–12)	6 (4-8)	<0.001
WBC ($\times 10^3$ /mm^3), median (IQR)	9.58 (4.97–20.19)	8.52 (4.7–18.9)	0.523
Hemoglobin (g/dL), median (IQR)	12 (6.9–15.7)	12.5 (6.95–15.1)	0.228
Thrombocyte ($\times 10^3/\mu L$), median (IQR)	323 (159–738)	229 (149.5–683)	0.151
CRP during attacks (mg/L), median (IQR)	56 (34–96)	17.9 (3.2–35.6)	<0.001
Serum amyloid A (mg/L), median (IQR)	27.5 (1.7–105.8)	75.3 (30–208)	0.068
Anti–IL-1 therapy, n (%)	55 (11.5)	2 (2.9)	0.028
Colchicine resistance, n (%)	45 (9.4)	5 (6.9)	0.494
Colchicine adverse effects, n (%)	22 (4.6)	2 (2.8)	0.498

Data are expressed as n (%) or median (IQR). Group comparisons were performed using chi-square/Fisher's exact test or Mann–Whitney U test, as appropriate.
p value <0.05 was considered statistically significant.
IQR, Interquartile range; FMF, Familial Mediterranean fever; ISSF, International Severity Score for Familial Mediterranean Fever; WBC, White blood cell count; CRP, C-reactive protein; IL-1, interleukin-1

(26.2% vs. 18.5%). The annual attack frequency was significantly lower in Azerbaijani patients (6 vs 12 attacks/year, p < 0.001).

ISSF scores were significantly higher in Turkish patients than in Azerbaijani patients (median [IQR]: 2 [1–3] vs 2 [1–2], respectively; p = 0.002).

During acute attacks, median CRP levels were significantly higher in Turkish patients than in Azerbaijani patients (56 vs. 17.9 mg/L, p < 0.001), whereas median SAA levels were comparable between the groups (27.5 vs. 75.3 mg/L, p = 0.068).

MEFV genotype distribution

There was a significant difference in the distribution of *MEFV* genotypes between the two cohorts (p< 0.001). Confirmatory genotypes (exon 10 homozygous and compound heterozygote genotypes) were more prevalent in Turkish patients (35.6% and 31%, respectively), while unconfirmatory genotypes (exon 10 heterozygous and other/VUS combinations) were significantly more prevalent in the Azerbaijani cohort (59.7%) (Table II). In terms of allele frequency (calculated from the total of 2n alleles), M694V was the most frequently

Table II. Distribution of *MEFV* genotypes in pediatric Turkish and Azerbaijani FMF patients.

Variant group	Turkish cohort (n=477)	Azerbaijani cohort (n=72)	p
Confirmatory genotypes, n (%)	318 (66.7)	29 (40.3)	<0.001
Homozygous variants	170 (35.6)	16 (22.2)	0.032
M694V/M694V	146 (30.6)	13 (18.1)	
M680I/M680I	15 (3.1)	1 (1.4)	
V726A/V726A	5 (1.0)	1 (1.4)	
R761H/R761H	2 (0.4)	–	
M694I/M694I	1 (0.2)	1 (1.4)	
A744S/A744S	1 (0.2)	–	
Compound heterozygous	148 (31.0)	13 (18.1)	0.026
M680I/M694V	59 (12.4)	–	
M694V/V726A	38 (8.0)	9 (12.5)	
M694V/R761H	15 (3.1)	2 (2.8)	
M680I/V726A	21 (4.4)	1 (1.4)	
M680I/R761H	5 (1.0)	–	
V726A/R761H	4 (0.8)	–	
Other compound heterozygous	6 (1.3)	1 (1.4)	
Non-confirmatory genotypes, n (%)	159 (33.3)	43 (59.7)	<0.001
Single heterozygous / genotype not confirmed	159 (33.3)	43 (59.7)	
M694V	48 (10.1)	6 (8.3)	
M680I	6 (1.3)	3 (4.2)	
V726A	23 (4.8)	5 (6.9)	
A744S	2 (0.4)	1 (1.4)	
Other / VUS combinations	80 (16.8)	28 (38.9)	

Values are presented as n (% within cohort). Confirmatory genotypes comprise exon 10 homozygous and compound heterozygous pathogenic variants; non-confirmatory genotypes comprise single heterozygous and genotype-not-confirmed cases (single pathogenic variant, one pathogenic variant plus a VUS, or two VUS variants). The distribution of confirmatory versus non-confirmatory genotypes differed significantly between cohorts ($\chi 2 = 17.6$, $p < 0.001$). Homozygous and compound heterozygous subgroups were each compared with the remaining genotypes (Fisher's exact test; p = 0.032 and p = 0.026, respectively).
VUS, variant of uncertain significance. FMF, Familial Mediterranean fever

detected allele in both cohorts (Türkiye: n = 452, 47.4%; Azerbaijan: n = 43, 29.9%; p < 0.001), followed by M680I (Türkiye: n = 121, 12.7%; Azerbaijan: n = 6, 4.2%; p = 0.005) and *V726A* (Türkiye: n = 96, 10.1%; Azerbaijan: n = 17, 11.8%; p = 0.621).

Subgroup analysis of confirmatory genotypes

When the analysis was restricted to patients carrying exon 10 homozygous genotypes (Turkish cohort: n=170; Azerbaijani cohort: n=16), Turkish patients demonstrated significantly higher ISSF scores than their Azerbaijani counterparts (median 3 [IQR: 2–4] vs. 2 [IQR: 1–3], p=0.037). Regarding clinical manifestations within this subgroup, the frequencies of fever (88% in Turkish patients vs. 75%, p=0.396) and abdominal pain (83.5% in Turkish patients vs. 81.3%, p=1.000) were similar between the two cohorts; however, arthritis was significantly more frequent among Turkish patients with exon 10 homozygous genotypes (39% vs. 6.3 %, p=0.032).

Treatment outcomes

The response to colchicine treatment was similar between Turkish and Azerbaijani patients (90.6% vs 93.1%, p = 0.422). The frequency of colchicine-related adverse effects did not differ significantly between the two groups (4.6% vs 2.8%, p = 0.498). Colchicine-related adverse effects were observed in 2 Azerbaijani patients, both of whom experienced gastrointestinal symptoms. In the Turkish cohort, 22 patients experienced colchicine-related adverse effects, including elevated liver function tests in 8 patients and gastrointestinal intolerance in 14 patients. The use of anti–IL-1 therapy was significantly higher among Turkish patients than among Azerbaijani patients (11.5% vs 2.9%, p = 0.028). Amyloidosis was present in 4 Turkish patients (0.8%).

Discussion

In this comparative analysis of Turkish and Azerbaijani pediatric FMF patients, the principal finding was a clear difference in overall disease severity between the two cohorts. Azerbaijani patients had an earlier age at symptom onset but experienced significantly lower annual attack frequency and a predominance of unconfirmatory genotypes. In contrast, Turkish patients demonstrated a more severe disease profile, characterized by higher attack frequency and a greater prevalence of confirmatory exon 10 genotypes. In light of these findings, the clinical course of FMF appears to differ meaningfully between the two populations, potentially reflecting differences in underlying genetic architecture and contextual factors.

Notably, although Azerbaijani patients exhibited an earlier age at symptom onset, they experienced a longer diagnostic delay. This discrepancy may partly reflect structural differences in healthcare systems. Pediatric rheumatology has been an established subspecialty in Türkiye since 2011, with wider access to trained specialists, whereas in Azerbaijan the field is not yet formally structured as a subspecialty and the number of pediatric rheumatologists remains limited. In addition, the lower annual attack frequency observed in Azerbaijani patients may further contribute to delayed recognition, as less frequent episodes can obscure the typical recurrent pattern required to establish a clinical diagnosis of FMF.

Another noteworthy finding was the higher frequency of inflammatory comorbidities in the Azerbaijani cohort than in the Turkish cohort. This difference may reflect referral bias (complex cases preferentially reaching tertiary centers), shared genetic susceptibility between FMF and other autoinflammatory conditions, population-specific immune modifiers. Given the smaller size of the Azerbaijani cohort, this finding should be interpreted with caution. A positive family history of FMF was significantly more common among Turkish patients than among those in the Azerbaijani cohort. This disparity may partly reflect greater disease awareness and more structured subspecialty care in Türkiye. Moreover, the

higher prevalence of confirmatory exon 10 genotypes in the Turkish cohort may promote stronger familial clustering due to increased penetrance.[19] Supporting this interpretation, a multicenter analysis from the Eurofever Project identified a positive family history as an independent predictor of FMF severity.[20] In contrast, the lower frequency of reported family history in Azerbaijani patients may relate to a predominance of milder genotypes, reduced intergenerational recognition of disease, or historical limitations in access to rheumatology care and genetic testing.

During acute attacks, Turkish patients more frequently exhibited chest pain and arthralgia, whereas fever and abdominal pain were comparable between the cohorts. This distribution is consistent with previous comparative studies of genetically related FMF populations demonstrating variation in the predominance of serositis and musculoskeletal features.[4,20-22] In a comparative analysis of Turkish and Crimean Tatar patients, chest pain was reported more frequently in Turkish patients, while joint involvement was relatively more prominent in Crimean Tatars.[21] Similarly, a large-scale study comparing FMF patients residing in the Eastern Mediterranean with genetically similar individuals who had migrated to Western Europe showed that those remaining in the Mediterranean region experienced more frequent attacks and higher rates of arthritis and pleurisy.[20] These findings indicate that even among populations with overlapping genetic architectures, the clinical expression of FMF, particularly serosal and musculoskeletal involvement, may be shaped by environmental exposures, healthcare context, and other population-specific modifiers. In this framework, the higher frequency of chest pain and arthralgia observed in our Turkish cohort may reflect an interaction between genetic background and contextual influences rather than genotype alone.[21,23]

In our study, attack characteristics further highlighted this variability: although the median attack duration was only slightly longer in Azerbaijani patients, they experienced significantly fewer attacks per year. Taken together with previous reports, these findings suggest that FMF expression may differ in both symptom profile and attack dynamics among closely related populations, likely reflecting an interaction between genetic background and region-specific modifiers rather than a uniform clinical course.[20-22]

Disease severity indices and acute-phase reactants further supported the overall difference in inflammatory burden between the cohorts. Turkish patients had significantly higher ISSF scores, consistent with a more severe clinical phenotype. This observation aligns with the higher prevalence of *M694V* and other confirmatory exon 10 genotypes in the Turkish cohort. Prior studies have repeatedly demonstrated that M694V, particularly in homozygous or compound heterozygous states, is associated with increased disease severity, higher attack frequency, and greater cumulative inflammatory burden.[4,20,24] In parallel, CRP levels during acute attacks were significantly higher in Turkish patients, reinforcing the impression of a more intense inflammatory response in this group. Taken together, the concordance between genotype distribution, higher ISSF scores, and elevated CRP levels supports the presence of a more inflammatory and genetically driven disease spectrum in the Turkish cohort. Although CRP levels were lower in Azerbaijani patients during acute attacks, SAA levels were comparable between cohorts (p=0.07), likely reflecting SAA's higher sensitivity as an earlier and more pronounced acute-phase marker. Both markers were measured during acute attacks in all patients, ruling out timing bias. Notably, prior studies on autoinflammatory amyloidosis have reported elevated SAA despite normal CRP, suggesting that SAA can capture chronic subclinical inflammation missed by CRP. The relatively higher SAA levels in the Azerbaijani cohort, despite milder clinical features, may reflect persistent subclinical inflammation. However, given the shorter follow-up in this

group, the long-term amyloidosis risk and its link to SAA levels remain unclear.[16]

The significant difference in *MEFV* genotype distribution represents a central finding. Turkish patients more frequently carried confirmatory exon 10 genotypes, whereas unconfirmatory genotypes predominated in the Azerbaijani cohort, consistent with the previously discussed association between genotype burden, higher ISSF scores, and greater inflammatory activity. The frequency of M694V in our Azerbaijani cohort closely mirrors previous reports, including a study of adult FMF patients in Azerbaijan and a large analysis of 1,330 individuals of Azerbaijani ethnicity from northwestern Iran, in which M694V was likewise the predominant mutation (42%), followed by V726A (19%), M680I (14%), and M694I (2%).[8,25] Notably, *V726A*—often reported as highly prevalent in Arab populations—was detected at a relatively higher frequency in our Azerbaijani cohort compared with Turkish patients, suggesting subtle regional differences in allele distribution.[26] The predominance of non-confirmatory or heterozygous genotypes in the Azerbaijani cohort may partially explain the milder and more heterogeneous clinical phenotype observed, given the well-established relationship between exon 10 genotype burden and disease severity.[4,27] This has practical implications, as diagnostic algorithms and clinical thresholds developed in populations with a high prevalence of classical confirmatory genotypes, may perform differently in settings where non-confirmatory genotypes predominate. In addition, some of these genetically unconfirmed patients might initially mimic FMF but could develop clinical features of other periodic fever syndromes during follow-up.

An important observation was that even within the subgroup of patients carrying homozygous exon 10 mutations, Turkish patients exhibited higher ISSF scores and a greater frequency of arthritis than Azerbaijani patients harboring the same high-risk genotype. This is particularly notable because exon 10 variants, especially M694V in the homozygous state, have consistently been associated with more severe disease, earlier onset, and increased musculoskeletal involvement in multiple cohorts, including the seminal work of Livneh and Touitou and subsequent Eurofever analyses.[20,28-30] Nevertheless, previous studies have also demonstrated that genotype–phenotype correlations in FMF are not absolute, and substantial clinical variability can occur even among individuals with identical mutations.[20-22,26,31] The intra-genotype differences observed between the two populations in our study therefore suggest that disease severity is not determined solely by *MEFV* mutation status but is likely modulated by additional factors such as environmental influences, epigenetic mechanisms, healthcare context, and broader genetic background.

Colchicine remains the cornerstone of FMF management, with approximately 90–95% of adherent patients achieving adequate disease control and a small subset requiring biologic escalation.[32] In our study, colchicine response rates were high and comparable between Turkish and Azerbaijani patients (approximately 90–93%), despite differences in genotype distribution and overall disease severity. This preserved efficacy across geographically and genetically distinct cohorts reinforces the central and universal role of colchicine as first-line therapy in pediatric FMF.[33,34] However, anti–IL-1 therapy was used significantly more frequently in Turkish patients than in Azerbaijani patients. This difference likely reflects the greater clinical severity and higher burden of confirmatory exon 10 genotypes in the Turkish cohort, as well as broader access to biologic therapies within the Turkish healthcare system. Given that anti–IL-1 agents are the standard of care for colchicine-resistant or -intolerant FMF, disparities in biologic utilization may also be influenced by differences in referral structures and treatment availability. In Azerbaijan specifically, biologic therapies are not covered by national insurance and remain largely inaccessible due to financial constraints,

which may have further contributed to the lower rate of biologic therapy use in this cohort. The occurrence of amyloidosis exclusively in Turkish patients, albeit infrequent, further parallels the more severe genotype–phenotype profile observed in this group. Together, these findings suggest that while colchicine effectiveness is consistent across populations, escalation to advanced therapies appears to track underlying disease burden and healthcare infrastructure rather than intrinsic differences in colchicine responsiveness.

Study limitations

This study has several limitations. Its retrospective bicentric design, conducted at a single tertiary referral center in each country, may have introduced selection bias and limited the generalizability of the findings, as center-specific factors such as referral patterns, diagnostic thresholds, and local clinical practices may have contributed to the observed differences independently of true population-level variation. The smaller size of the Azerbaijani cohort may further limit generalizability and reduce statistical power for certain analyses, including subgroup comparisons. In addition, because multiple subgroup comparisons were performed without formal adjustment for multiplicity, some statistically significant associations may represent chance findings. Therefore, these results should be considered exploratory and require validation in larger, independent cohorts. Differences in access to biologic therapies and subspecialty care between healthcare systems may also have influenced treatment patterns and complication rates. In addition, environmental and socioeconomic factors, such as infection burden, living conditions, nutrition, and healthcare accessibility, were not systematically evaluated, although they may contribute to inter-population differences in disease expression.

In conclusion, this bicentric study provides the first systematic comparison of pediatric FMF patients from Türkiye and Azerbaijan and demonstrates that, despite shared ethnic and genetic backgrounds, the disease may manifest with distinct clinical and genetic patterns. The observed divergence in severity, genotype distribution, and inflammatory burden indicates that FMF expression is not uniform across closely related populations. While *MEFV* mutation burden remains a key determinant of phenotype, our findings suggest that genetic architecture interacts with healthcare context and population-specific modifiers to shape disease presentation. These results underscore the need to interpret FMF within regional frameworks, acknowledging potential center-specific influences and to incorporate such diversity into future diagnostic strategies and precision medicine approaches in autoinflammatory diseases.

Ethical approval

The study was approved by Istanbul University Ethics Committee (date: June 25, 2025, number: 3429655) and by the Medical Research Ethics Committee of the ''New Clinic'' Public Legal Entity (date: May 15, 2025, number: 013/25).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: NAA, VG; data collection: VG, GV, LS, PPA, BM; analysis and interpretation of results: VG, ÖA, BM, SDA, FGD; draft manuscript preparation: NAA, VG. All authors reviewed the results and approved the final version of 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

Recognizing Stuve–Wiedemann syndrome in childhood: clinical insights from 11 patients with founder and novel *LIFR* variants

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ABSTRACT

Background. Stuve–Wiedemann syndrome is a rare autosomal recessive bent-bone dysplasia characterized by dysautonomia and distinctive skeletal abnormalities, most commonly caused by biallelic *LIFR* variants.

Methods. Eleven patients from ten unrelated families with molecularly confirmed Stuve–Wiedemann syndrome were evaluated. Detailed demographic, perinatal, clinical, radiographic, and molecular data were collected. All patients underwent Sanger sequencing of *LIFR*.

Results. Respiratory problems and episodic hyperthermia were present in all patients, while feeding difficulties, hypotonia, growth failure, developmental delay, craniofacial dysmorphism, oral abnormalities, and ocular involvement were also common. All patients demonstrated long-bone bowing, cortical thickening, and flared metaphyses. A biallelic *LIFR* variant was identified in all patients, occurring in the homozygous state in nine patients and in the compound heterozygous state in two patients. The recurrent c.2074C>T; p.(Arg692Ter) variant was homozygous in seven patients and compound heterozygous in one patient. Three novel *LIFR* variants were also identified.

Conclusion. Stuve–Wiedemann syndrome is characterized by a high mortality rate during the first two years of life due to severe dysautonomia, and orthopedic complications worsen progressively with age; therefore, early diagnosis and lifelong multidisciplinary follow-up are essential. Furthermore, the high rate of consanguinity in Türkiye, together with the recurrent p.(Arg692Ter) variant in *LIFR* identified in multiple unrelated families, supports the possibility of a founder effect and suggests that the frequency of Stuve–Wiedemann syndrome in our population may be higher than expected. Our findings further characterize the previously reported clinical manifestations of Stuve–Wiedemann syndrome while expanding the molecular spectrum through the identification of three novel *LIFR* variants.

Key words: Stuve-Wiedemann syndrome, LIFR, dysautonomia, skeletal dysplasia.

Stuve–Wiedemann syndrome (SWS; OMIM #601559), also referred to as neonatal Schwartz–Jampel syndrome type 2 (SJS2), is a rare autosomal recessive disorder characterized by dysautonomia, episodic hyperthermia, respiratory insufficiency, feeding difficulties, and distinctive skeletal abnormalities. The disorder was first described in 1971 by Stüve and Wiedemann in two female siblings and a male cousin who exhibited congenital bowing of the long bones, hand anomalies, craniofacial abnormalities, and respiratory distress, suggesting autosomal recessive inheritance.[1]

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SJS, also known as chondrodystrophic myotonia, is primarily defined by myotonia and characteristic skeletal abnormalities. A distinct subgroup presenting at birth with prominent skeletal features, including fetal hypokinesia, congenital contractures, shortening and bowing of the long bones, undertubulation of the metaphyses, and osteoporosis, has been described as SJS type 2 (a neonatal-onset form with Pyle disease–like bone dysplasia).[2] Notably, beyond its clinical characteristics, this subgroup has been shown to lack genetic linkage to the classical SJS locus on 1p36–34.[2] Subsequent studies showed that SJS type 2 and SWS share essentially the same clinical spectrum with identical skeletal features and differ only by the presence of myotonia on electromyography in SJS, leading to the conclusion that these two conditions represent a single entity.[3]

In 2004, a study involving 19 affected families demonstrated that null mutations in the leukemia inhibitory factor receptor (LIFR) gene (OMIM *151443) located on 5p13.1 are responsible for the disorder, thereby providing molecular confirmation that the two entities are indeed the same condition.[4] Furthermore, SWS patients negative for *LIFR* mutations have been identified, and in this clinically and molecularly heterogeneous disorder, biallelic loss-of-function variants in *IL6ST* (OMIM *600694) have also been shown to cause the phenotype, leading to the designation of SWS type 2 (OMIM #619751).

It has been reported that while the risk of death due to dysautonomia is high during infancy, this risk decreases in childhood, during which orthopedic complications begin to predominate in the clinical course. Early recognition of SWS is crucial, as timely diagnosis enables appropriate management of dysautonomia and prevention of progressive orthopedic complications.

To date, more than 90 patients with SWS have been reported in the literature.[5-20] Here, we report 11 patients from 10 unrelated families diagnosed with SWS, providing detailed clinical, radiographic, and molecular characterization to further delineate the disorder.

Methods

A total of 11 patients with a molecularly confirmed diagnosis of SWS who were followed at a single tertiary referral center were included in this study. Detailed demographic and clinical data, including perinatal features, respiratory problems, feeding difficulties, dysautonomic episodes, growth and developmental outcomes, skeletal abnormalities, and other associated comorbidities, were collected.

Peripheral blood samples were obtained from all patients and available parents. Genomic DNA was extracted using the standard salt precipitation method after written informed consent had been obtained. All patients underwent Sanger sequencing of the LIFR gene (NM_001127671.2). Specific primers were used to amplify all coding exons and exon–intron boundaries by polymerase chain reaction (PCR). PCR products were subjected to capillary electrophoresis on an ABI 3500 Genetic Analyzer (Thermo Fisher Scientific, Waltham, Massachusetts, USA). Sequence chromatograms were evaluated using standard sequencing analysis software, and genotypes were determined accordingly. Primer pairs are available upon request.

Variants were classified according to the ACMG guidelines using available databases including ClinVar, gnomAD, HGMD, and in silico prediction tools such as MutationTaster, SIFT, and PolyPhen.[21] Segregation analysis was performed whenever parental samples were available.

Statistical analysis

Given the descriptive nature of the study, only descriptive statistical analyses were performed. Continuous variables are presented as median (range), whereas categorical variables are presented as numbers and percentages.

The study was approved by Hacettepe University Ethics Committee (SBA 25/1013, date: 17/12/2025).

Results

Demographic and clinical findings

A total of 11 patients from 10 families, including eight females and three males, were included in the study. The demographic, clinical, and molecular characteristics of the patients are summarized in Table I. Consanguinity was present in 6 of 10 families (60%), and two additional families originated from the same village. A history of sibling death was reported in five (50%) families. The median age at diagnosis was 12 months, ranging from postnatal day 1 to 4 years. Patient 4 died at 7 months of age due to sudden infant death, whereas Patient 6 died suddenly at 4 years of age, with a presumed cerebrovascular event as the cause of death. Prenatal abnormalities were documented in six patients, most commonly limb shortening/bowing and decreased fetal movements.

Respiratory problems and episodic hyperthermia were observed in all patients, while feeding difficulties were present in 10 of 11 patients (90.9%), hypotonia in 9 of 10 patients (90%), and growth failure in 9 of 10 patients (90%). Developmental delay was present in the majority of patients (80%), manifesting as isolated speech delay, motor delay, or global developmental delay. Characteristic craniofacial findings were variably observed and pursed lips were noted in all evaluated patients (10/10, 100%) (Fig. 1). Oral/dental abnormalities were observed in all evaluated patients (9/9, 100%), including oligodontia, multiple dental caries, dry mouth, and atrophy of the lingual papillae. Ocular involvement was frequent (9/10, 90%) and included keratitis, corneal opacity, dry eye, refractive errors, and strabismus.

Radiological and skeletal findings

Among the skeletal findings, bowing of the long bones, cortical thickening, and flared metaphyses were present in all patients, whereas camptodactyly was observed in 8 of 11 patients (72.7%), joint contractures in 9 of 11 (81.8%), scoliosis in 8 of 10 (80%), and bone fractures in 6 of 9 (66.6%) (Fig. 1 and Fig. 2).

Molecular findings

Molecular analysis identified biallelic *LIFR* variants in all patients. The recurrent pathogenic variant c.2074C>T; p.(Arg692Ter) was identified in the homozygous state in patients from seven families, whereas in one patient it was detected in the compound heterozygous state in combination with an additional variant. Overall, the c.2074C>T; p.(Arg692Ter) variant accounted for 15 of 22 disease-associated alleles (68.2%) in the cohort. Moreover, three previously unreported variants in the *LIFR* gene were identified, comprising one nonsense variant, one missense variant, and one frameshift

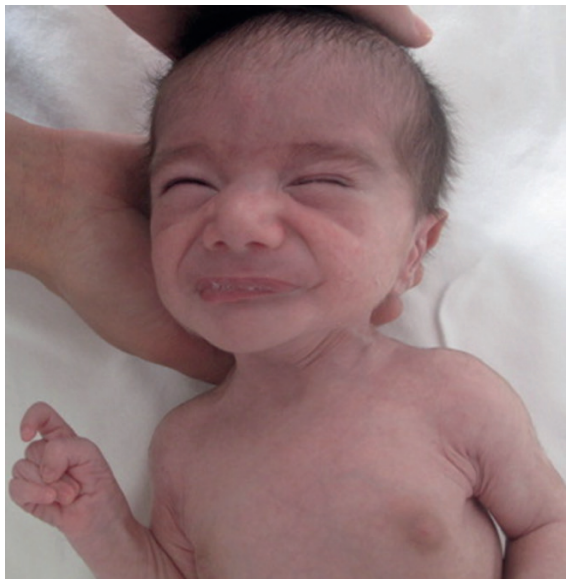

Fig. 1. Clinical image of Patient 2 at 1 month of age showing pursed lips and camptodactyly.

Table I. Demographic, clinical, and molecular characteristics of patients with Stuve-Wiedemann syndrome.

	Family	F1		F2	F3	F4	F5	F6	F7	F8	F9	F10
	Patient ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11
Demographic features	Sex	F	M	F	F	F	F	F	M	F	M	F
	Consanguinity	+	+	+	-	- (Same village)	+	+	+	+	-	- (Same village)
	History of sibling death	-	-	+	+	+	-	+	-	-	+	-
	Age at diagnosis	12 months	3 years	1.5 years	Day 1	4 years	6 months	3 months	3 years	4 months	4 months	2 years
	Survival status	Alive	Alive	Alive	Died at 7 months	Alive	Died at 4 years	Alive	Alive	Alive	n.a.	Alive
Clinical findings	Perinatal features	Increased nuchal translucency, and lower limb bowing and shortening	Limb shortening, and decreased fetal movements	Oligohydramnios, limb shortening, and decreased fetal movements	Limb bowing	- (No prenatal care)	Femoral shortening, and decreased fetal movements	Oligohydramnios, short femoral neck, and decreased fetal movements	-	- (No prenatal care)	- (No prenatal care)	-
	Hypotonia	+	+	+	+	+	+	+	+	-	n.a.	+
	Respiratory problems	+	+	+	+	+	+	+	+	+	+	+
	Feeding difficulty	+	+	+	+	+	+	+	-	+	+	+
	Episodic hyperthermia	+	+	+	+	+	+	+	+	+	+	+
	Growth failure	+	+	+	+	+	+	+	-	+	n.a.	+
	Developmental delay	-	Motor delay	Motor delay	Motor delay	-	Global delay	Global delay	Speech delay	Motor delay	n.a.	Motor delay
	Facial dysmorphism	Bitemporal narrowing, depressed nasal bridge, microretrognathia, and short neck	Depressed nasal bridge and microretrognathia	Bitemporal narrowing, depressed nasal bridge, and short neck	-	Narrow forehead with frontal hypertrichosis	Microretrognathia, prominent metopic suture, frontal bossing, depressed and broad nasal bridge, everted lower lip, high-arched palate	Mild frontal bossing, midfacial hypoplasia, incomplete eyelid closure, bulbous nasal tip, prognathism, short neck	Frontal bossing, hypertrichosis, synophrys, deep-set eyes, bulbous nasal tip, high and narrow palate	Micrognathia	Dolichocephaly	Blepharophimosis, microstomia, micrognathia
	Pursed lips	+	+	+	+	+	+	+	+	+	n.a.	+
	Oral/dental findings	Oligodontia, early dental caries, and atrophy of the lingual papillae	Oligodontia, premature tooth loss, dry mouth, and atrophy of the lingual papillae	Oligodontia, and atrophy of the lingual papillae	n.a.	Premature tooth loss, orthodontic problems and atrophy of the lingual papillae	Malocclusion, atrophy of the lingual papillae	Premature tooth loss, malocclusion, dry mouth, and atrophy of the lingual papillae	Multiple dental caries, dry mouth and atrophy of the lingual papillae	Multiple dental caries, premature tooth loss, and dry mouth	n.a.	Multiple dental caries and premature tooth loss
	Ocular findings	Keratitis, corneal opacity and dry eye	Keratitis, corneal opacity and dry eye	Hypermetropia, keratitis, corneal opacity, dry eye, and strabismus	Dry eye	-	Keratitis, corneal opacity and dry eye	Myopia, keratitis, corneal opacity and dry eye	Keratitis, corneal opacity, and strabismus	Keratitis, corneal opacity, and dry eye	n.a.	Keratitis, corneal opacity, and dry eye

ASD: Atrial septal defect, AR: Aortic regurgitation, F: Female, M: Male, MR: Mitral regurgitation, MVP: Mitral valve prolapse, n.a.:Not available, PAH: Pulmonary arterial hypertension, PEV: Pes equinovarus, PFO: Patent foramen ovale, TR: Tricuspid regurgitation, VUS: Variant of Uncertain Significance. The novel variants are indicated in bold.

Table I. Continued.

	Family	F1		F2	F3	F4	F5	F6	F7	F8	F9	F10
	Patient ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11
Skeletal features	Camptodactyly	+	+	-	+	+	-	+	-	+	+	+
	Joint contracture	+	+	+	+	+	-	+	-	+	+	+
	Scoliosis	+	+	+	-	+	+	+	-	+	n.a.	+
	Osteoporosis/ Bone fracture	+/+	n.a. / +	+ / -	n.a. / n.a.	+/+	+ / +	+ / +	+ / -	+ / -	n.a. / n.a.	+/+
	Bowing of the long bones	+	+	+	+	+	+	+	+	+	+	+
	Cortical thickening of the long bones	+	+	+	+	+	+	+	+	+	+	+
	Wide, flared metaphyses	+	+	+	+	+	+	+	+	+	+	+
	Anesthetic complications	-	-	-	-	-	Respiratory distress after anesthesia	-	-	-	n.a.	-
	Other clinical findings	PEV	Morgagni hernia	Moderate TR, papular skin lesions	-	Papular skin lesions	Microcephaly, mildly thin corpus callosum, PAH, MVP, mild-to-moderate MR, PFO and PEV	Hearing loss, minimal AR, bicuspid aortic valve, and aortic root dilatation	Microcephaly, small ASD, PFO	-	Seizures	-
Molecular findings	LIFR variant NM_001127671.2	c.2074C>T, p.(Arg692Ter)	c.2074C>T, p.(Arg692Ter)	**c.823G>T, p.(Glu275Ter)**	c.274C>T, p.(Gln92Ter) / **c.1429delC, p.(Gln477LysfsTer11)**	c.2074C>T, p.(Arg692Ter)	c.2074C>T, p.(Arg692Ter)	c.2074C>T, p.(Arg692Ter) / c.1105_1106insT, p.(Tyr369LeufsTer5)	**c.890T>A, p.(Val297Asp)**	c.2074C>T, p.(Arg692Ter)	c.2074C>T, p.(Arg692Ter)	c.2074C>T, p.(Arg692Ter)
	Zygosity	Homozygous	Homozygous	Homozygous	Compound heterozygous	Homozygous	Homozygous	Compound heterozygous	Homozygous	Homozygous	Homozygous	Homozygous
	ACMG Classification	Pathogenic	Pathogenic	Likely pathogenic	Likely pathogenic / Likely pathogenic	Pathogenic	Pathogenic	Pathogenic / Likely pathogenic	VUS	Pathogenic	Pathogenic	Pathogenic

ASD: Atrial septal defect, AR: Aortic regurgitation, F: Female, M: Male, MR: Mitral regurgitation, MVP: Mitral valve prolapse, n.a.:Not available, PAH: Pulmonary arterial hypertension, PEV: Pes equinovarus, PFO: Patent foramen ovale, TR: Tricuspid regurgitation, VUS: Variant of Uncertain Significance. The novel variants are indicated in bold.

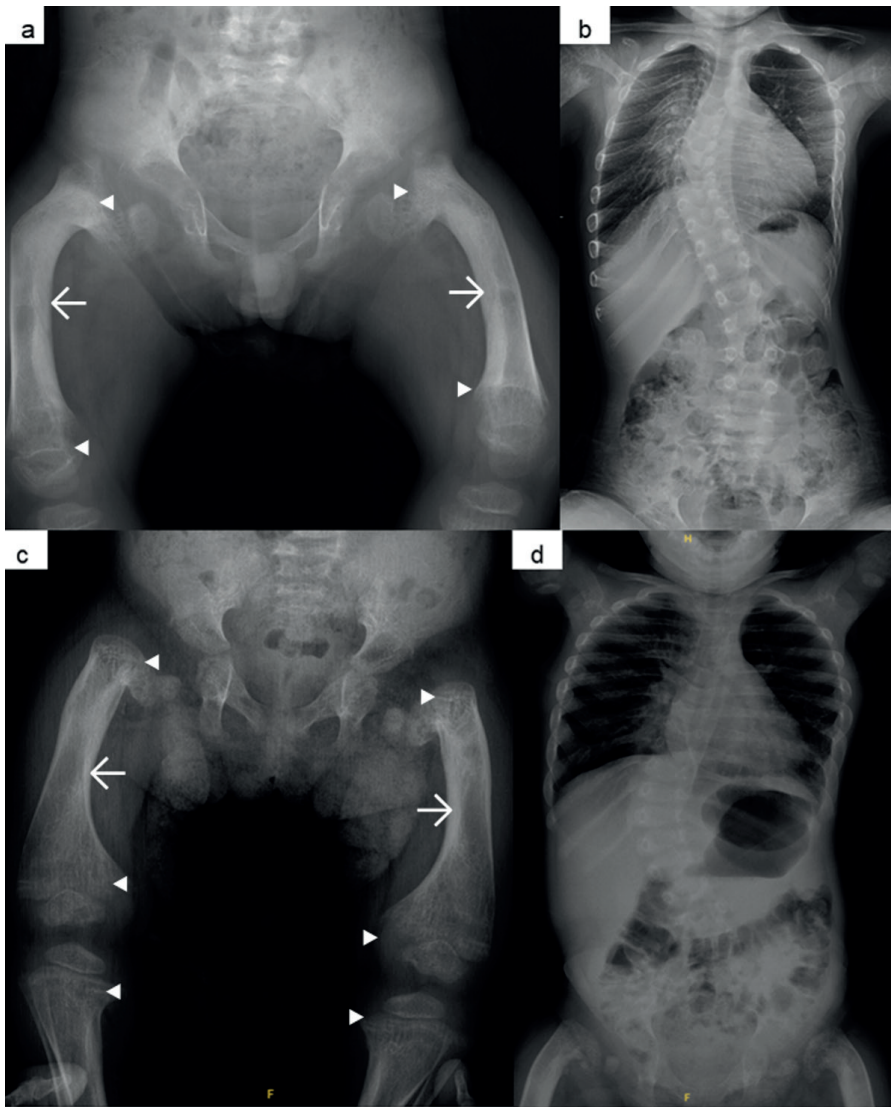

Fig. 2. Radiographs of Patients 2 and 3 demonstrate bowing of the long tubular bones, cortical thickening (arrows), and wide, flared metaphyses (arrowheads) (a: Patient 2 at 5 years; c: Patient 3 at 2 years), as well as scoliosis (b: Patient 2 at 6 years; d: Patient 3 at 2 years).

variant. Among the novel variants detected in our cohort, c.890T>A, p.(Val297Asp), was classified as a variant of uncertain significance (VUS) based on ACMG guidelines; however, several lines of evidence raised the possibility of pathogenicity. This variant is not present in the gnomAD database (PM2_Supporting), and in silico prediction tools suggest a deleterious impact on protein function, as supported by AlphaMissense (score: 0.754; PP3_Supporting) and PolyPhen-2, which classifies it as probably damaging (score: 1.000). In addition, segregation analysis supported an autosomal recessive inheritance pattern, and the patient's phenotype was strongly consistent with SWS, with no alternative molecular diagnosis identified. The novel variants were submitted to the ClinVar database (SUB16043420, SUB16045977, SUB16046006), and all identified variants were marked on the schematic representation of the LIFR protein (Fig. 3).

Fig. 3. Schematic representation of the LIFR protein domains and the distribution of pathogenic variants identified in our cohort. The LIFR protein consists of a signal peptide (SP), cytokine receptor homology domains (CRH1 and CRH2), an immunoglobulin-like domain (Ig), fibronectin type III domains (FNIII), a transmembrane domain (TM), and a cytoplasmic domain (CD). The positions of the variants identified in this study are indicated above the protein schematic. Novel variants identified in the present study are indicated in bold and marked with an asterisk (*).

Discussion

SWS is a rare autosomal recessive disorder characterized by skeletal abnormalities and severe dysautonomic manifestations, particularly during early childhood, whereas orthopedic complications become more prominent with age.[5,9] All patients in our cohort demonstrated the characteristic skeletal phenotype of SWS, including universal bowing of the long bones and frequent camptodactyly, accompanied by varying degrees of autonomic dysfunction (Table I).

Short and bowed limbs have been reported in all patients with SWS, and camptodactyly has been described in approximately 80% of cases.[5] Consistent with these observations, bowing of the long bones was present in all of our patients, while camptodactyly was observed in 72.7% of the cohort. Characteristic radiological findings, including bowed long bones with cortical thickening, enlarged metaphyses, and an abnormal trabecular pattern, as well as scoliosis and osteoporosis-related fractures observed in our patients were consistent with the previously reported clinical spectrum and natural course of the disorder.[5]

Prenatal warning signs include growth restriction, oligohydramnios, reduced fetal movements, and characteristic skeletal findings such as short and bowed long bones, pronounced tibial bowing (greater than femoral involvement), relative sparing of the fibula and upper limb bones, camptodactyly, and talipes.[8,22] It has been emphasized that, in the prenatal differentiation of SWS from other bent-bone disorders, the presence of camptodactyly together with a normal scapula is an important distinguishing feature.[22] In our cohort, six prenatally monitored patients showed findings such as increased nuchal translucency, limb shortening, decreased fetal movements, and oligohydramnios. However, none of the patients received a molecularly confirmed diagnosis of SWS during the prenatal period. This may be attributed to the relatively nonspecific prenatal skeletal findings of SWS, the absence of severe abnormalities suggestive of a lethal skeletal dysplasia leading to limited prenatal recognition, restricted access to prenatal genetic testing, and the lack of a previously diagnosed affected sibling in the family, which may have reduced the likelihood of recommending molecular analysis.

A narrow thorax, one of the main prenatal indicators of lethality in skeletal dysplasias, is typically absent in SWS. Nevertheless, infant mortality remains high because of dysautonomic complications.[8] The disorder is considered potentially fatal before the age of 2 years, primarily because of respiratory distress and episodic hyperthermia. Sudden death and anesthesia-related malignant hyperthermia have also been reported. Mortality is notably high, estimated at approximately 46% overall,

reaching 42% in patients younger than 2 years and 10% in older individuals.[5] In our cohort, two patients died, one following a presumed cerebrovascular event and one because of sudden death. In addition, Patient 4 had two siblings who had previously died with similar clinical features. Anesthetic complications were also documented in one of our patients who subsequently died (Table I, Patient 6). Additionally, pulmonary arterial hypertension, which has been suggested to be associated with poor prognosis, was present in one of our patients, who died at 4 years of age.[5]

Additional features associated with the disorder include corneal involvement, oral and dental abnormalities, and dysmorphic facial features, particularly the characteristic pursed-mouth appearance, as well as neurological manifestations such as hypotonia, seizures, and delayed motor development.[5] Ectodermal findings such as milia, multiple eruptive vellus hair cysts, and dystrophic nails have been reported, and similarly, papular skin lesions were noted in two of our patients.[7] One of our patients was found to have a Morgagni hernia; to the best of our knowledge, this association has not previously been reported and may represent a coincidental finding.

Although the disorder has been reported more frequently in Arab populations, with an estimated prevalence of 0.52 per 10,000 births, recent reports suggest that it may not be as rare in Türkiye as previously assumed.[23,24] This distribution may be related to the high rate of consanguinity in these populations, which increases the prevalence of autosomal recessive disorders. A systematic review published in 2022 reported consanguinity in 65% of families with SWS.[5] In our cohort, the corresponding rate was 60%, further supporting the contribution of consanguinity to disease occurrence. In addition, a founder variant in the Turkish population has been proposed in the *LIFR* gene, and this variant, c.2074C>T; p.(Arg692Ter), was homozygous in seven of our patients, while one patient carried it in trans with another pathogenic *LIFR* variant, consistent with a compound heterozygous genotype.[23] Notably, the fact that this variant accounted for the majority of disease-associated alleles in our cohort and was identified in apparently unrelated families further supports the possibility of a founder effect in the Turkish population. Although this variant has also been reported in other populations, it has been predominantly described in Turkish patients.[19,23,25,26] Moreover, a previous study demonstrated a shared haplotype spanning the *LIFR* locus among affected individuals, supporting a possible founder effect.[23] However, future haplotype analyses would be required to confirm a shared ancestral origin.

Null mutations in *LIFR* disrupt the JAK/STAT3 signaling pathway, and studies in Lifr−/− mice have demonstrated impaired bone remodeling, reduced astrocyte numbers, and perinatal lethality.[4,27] Similar to *CRLF1*-related cold-induced sweating syndrome 1 (Crisponi syndrome; OMIM #272430), SWS belongs to the spectrum of ciliary neurotrophic factor receptor (CNTFR) pathway–related disorders characterized by autonomic nervous system dysfunction.[11,27,28] In the differential diagnosis of SWS, Crisponi syndrome is an important consideration, as it shares multiple clinical features, such as episodic hyperthermia, feeding difficulties, respiratory problems, facial trismus, and camptodactyly. However, bowing of the long bones is highly characteristic of SWS and serves as a key distinguishing feature. Owing to this hallmark feature, SWS is classified within Group 20, the bent-bones dysplasia group, in the current Nosology of genetic skeletal disorders.[29] Nevertheless, the presence of dysautonomic features distinguishes SWS from other entities within this group.

This study has several limitations. First, the sample size was small, which is expected for a rare disorder but limits the generalizability of our findings. Second, the retrospective design resulted in incomplete data for some variables, as reflected by the variable denominators across clinical features. Third, the cohort was drawn from a population with a high rate of consanguinity, which may have influenced

both the frequency of homozygous variants and the apparent predominance of the recurrent p.(Arg692Ter) allele. Finally, although three previously unreported *LIFR* variants were identified, no functional studies were performed; therefore, their pathogenicity relies on ACMG-based interpretation, segregation data, and phenotype correlation.

In conclusion, SWS should be considered in children with dysautonomic manifestations accompanied by long-bone bowing, camptodactyly, and characteristic craniofacial features. Early recognition is essential for appropriate orthopedic surveillance, timely physical therapy, and surgical interventions when necessary. Early calcium and vitamin D supplementation may also help prevent osteoporosis-related fractures. Equally important is the careful assessment of dysautonomia-related symptoms and the prevention of anesthesia-associated complications, including malignant hyperthermia, which may be life-threatening. Our cohort further delineates the phenotypic and molecular spectrum of the disorder and underscores the recurrent p.(Arg692Ter) *LIFR* variant in the Turkish population.

Ethical approval

The study was approved by Hacettepe University Ethics Committee (date: December 17, 2025, number: SBA 25/1013).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: GÜD, GEU, PÖŞK; data collection: GÜD, NBA; analysis and interpretation of results: GÜD, NBA, GEU, PÖŞK; draft manuscript preparation: GÜD, NBA. All authors reviewed the results and approved the final version of 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

Long-term outcomes and prognostic factors in pediatric Wilms tumor: a 47-year single-center experience

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ABSTRACT

Introduction. Wilms tumor is the most common renal malignancy in children. Survival rates now exceed 90% with multimodal therapy. This study aims to retrospectively analyze 104 pediatric Wilms tumor patients diagnosed over a 47-year period at our institution, examining demographic characteristics, tumor staging, treatment modalities, complications, recurrence rates, and survival outcomes.

Materials and Methods. This retrospective single-center study included 104 pediatric patients diagnosed with Wilms tumor between January 1, 1978, and January 31, 2025. Patients were stratified into early (1978–2005) and late (2006–2025) periods. Survival analysis was performed using the Kaplan–Meier method and multivariable Cox proportional hazards regression.

Results. The 5-year overall survival (OS) and event-free survival rates were 61.1% and 57.3% in the early era, 86.8% and 81.5% in the late era, and 73.6% and 65.8% in the overall cohort. OS was significantly lower in patients with anaplasia (p=0.035), advanced-stage disease (p=0.004), and in those treated in the early era (p=0.009). In multivariable analysis, treatment era and metastatic disease at diagnosis were independently associated with poorer survival, whereas anaplasia did not retain statistical significance after adjustment.

Conclusion. Survival outcomes improved substantially over time. Metastatic disease at diagnosis and treatment era were the strongest independent predictors of survival, while advanced stage and anaplasia were associated with outcome in univariable analyses.

Key words: Wilms tumor, pediatric oncology, long-term outcomes, prognostic factors.

Wilms tumor is the most common renal malignancy in children, representing approximately 7.1% of all pediatric cancers in Türkiye.[1,2] Advances in multimodal therapy, incorporating surgery, chemotherapy, and radiotherapy, have significantly improved prognosis, with overall survival rates now often exceeding 90%.[3] However, managing Wilms tumor remains a challenge that requires a precise balance between achieving high cure rates and minimizing long-term treatment-related morbidity.

Clinically, Wilms tumor typically presents as an asymptomatic abdominal mass, often discovered incidentally by parents or during routine physical examinations. Although many cases remain silent at presentation, some patients may exhibit symptoms such as abdominal pain, hematuria, or hypertension.[4] The stage at presentation and histologic subtype remain the most significant predictors of survival.

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Current clinical practice is primarily guided by standardized protocols from the Children's Oncology Group (COG) and the International Society of Pediatric Oncology (SIOP).[1,5] Despite high survival rates, recurrence still occurs in approximately 15% of cases, and survivors remain at risk for late complications such as nephrotoxicity, cardiotoxicity, and secondary malignancies.[6,7] Analyzing long-term institutional data is essential to understanding how evolving treatment strategies influence patient outcomes over several decades.

This study presents a retrospective analysis of 104 pediatric Wilms tumor patients treated at our institution over a 47-year period. We evaluate demographic characteristics, clinical presentation, treatment modalities, and survival outcomes. By documenting nearly five decades of clinical experience, we aim to provide a comprehensive overview of the management and long-term results of pediatric Wilms tumor in a single-center setting.

Materials and Methods

This retrospective single-center study was conducted at the Pediatric Oncology Department of Ondokuz Mayıs University and included 104 pediatric patients diagnosed with Wilms tumor between January 1, 1978, and January 31, 2025. Patients younger than 18 years at the time of diagnosis, with histopathologically confirmed primary renal Wilms tumor and complete diagnostic and treatment records, were included in the study. Patients diagnosed with other tumors involving the renal area, initially considered in the differential diagnosis of Wilms tumor at presentation (7 adrenal neuroblastomas, 3 nephromas, 2 renal cell carcinomas, 1 ganglioneuroma, and 1 malignant mesenchymal tumor), as well as those with insufficient medical records (n=8), were excluded from the analysis.

Demographic characteristics, clinical presentation, physical examination findings, laboratory results, imaging studies, histopathological findings, chemotherapy protocols, treatment-related complications, follow-up duration, long-term sequelae, recurrence, and survival status were retrospectively reviewed. For patients diagnosed prior to the implementation of the hospital's electronic medical record (EMR) system, data were obtained from archived patient files; for more recent cases, data were extracted from the EMR database.

Histopathological evaluations were performed by institutional pathologists based on the original diagnostic reports. No central pathology review or retrospective re-examination of archival slides was conducted for this study. In accordance with established classification, unfavorable histology was defined by the presence of either focal or diffuse anaplasia, collectively categorized as anaplastic Wilms tumor.[8]

Initial diagnostic procedures included ultrasonography (USG), computed tomography (CT), and magnetic resonance imaging (MRI). For patients diagnosed before 1985, due to the unavailability of CT, lung metastasis was assessed using chest radiography. Routine laboratory investigations were performed in all patients prior to chemotherapy initiation. Echocardiographic assessment was performed when available; because echocardiography was not routinely accessible before 1990, systematic baseline evaluation could not be obtained for all early-era patients.

Throughout the study period, patients were managed according to evolving treatment protocols influenced by both the National Wilms Tumor Study (NWTS)/COG and SIOP treatment approaches. Because the study spanned several decades, tumor stage was determined according to the protocol in use at the time of diagnosis. Earlier cases were classified using a SIOP-based stage I–V framework, whereas patients diagnosed from 2006 onward were staged according to NWTS/COG criteria.[1,7,8] Radiotherapy indications and dose planning were also based on these risk-adapted protocols.

Surgical treatment primarily consisted of radical nephroureterectomy (RNU), except in selected cases, and all treatment plans were discussed within multidisciplinary tumor board meetings. In most cases, due to limited availability of advanced pathology infrastructure in earlier years, assessments were based on morphological and immunohistochemical analysis.

The current study integrates two consecutive institutional cohorts of pediatric Wilms tumor: an unpublished series of 56 patients diagnosed between 1978 and 2005 and a more recent cohort of 48 patients diagnosed between 2006 and 2025. For comparative analyses, patients were grouped into an early era (1978–2005) and a late era (2006–2025). Because treatment strategies evolved over time, therapeutic approaches were additionally described according to protocol-defined periods.

Treatment strategies evolved across three sequential periods at our institution. Prior to 1999, patients were managed through an institutional surgery-first approach. Following upfront nephrectomy, children with low-stage, favorable-histology tumors received chemotherapy regimens comprising vincristine and actinomycin D, whereas those with advanced-stage or unfavorable-histology disease were treated with intensified multiagent therapy incorporating doxorubicin and radiotherapy, tailored to the risk-stratification standards of the era. Between 1999 and 2005, management adhered to the Turkish Pediatric Oncology Group (TPOG) Wilms Tumor protocol, which was largely derived from the SIOP treatment approach.[8] For patients undergoing primary nephrectomy, postoperative therapy was determined by tumor stage and histological risk. Stage I tumors (regardless of histology) and Stage IIA favorable-histology tumors received vincristine and actinomycin D. In Stage IIB favorable-histology tumors, radiotherapy was added to this two-drug regimen. For Stage III–IV favorable-histology tumors, the regimen expanded to include vincristine, actinomycin D, and doxorubicin plus radiotherapy. Patients with Stage II–IV unfavorable-histology tumors received a more intensive four-drug combination of vincristine, actinomycin D, doxorubicin, and etoposide in addition to radiotherapy. From 2006 onward, the institutional protocol was harmonized with the risk-stratification and treatment strategies established by NWTS and COG. Survival analyses were conducted according to these protocol-defined cohorts, with further stratification by early versus late era for descriptive comparisons.

Statistical analyses were performed using IBM SPSS version 22. The Mann–Whitney U test was applied for comparisons of non-parametric variables, and the chi-square test was used for categorical data. Survival analysis was performed using the Kaplan–Meier method, and intergroup differences were evaluated using the log-rank test. Univariable and multivariable Cox proportional hazards regression analyses were performed to identify prognostic factors associated with overall survival. Results were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). The Kolmogorov–Smirnov and Shapiro–Wilk tests were used to assess the normality of data distribution. A p-value of <0.05 was considered statistically significant.

The study was approved by the Ondokuz Mayıs University Clinical Research Ethics Committee (Approval No: 2023/115; Date: April 27, 2023).

Results

A total of 104 pediatric patients diagnosed with Wilms tumor were included in the study, consisting of 45 males (43.3%) and 59 females (56.7%). Of these, 56 patients were treated in the early period (1978–2005) and 48 patients in the late period (2006–2025). The detailed demographic and laboratory characteristics of the patients are presented in Table I.

Sixty-five patients (62.5%) were diagnosed before the age of four years. At diagnosis, liver and renal functions were generally within normal limits. Isolated serum creatinine elevation was noted in 8 patients (median 1.35

Table I. Demographic characteristics of the study population.

Parameters	Early Period (1978-2005) (n=56)	Late Period (2006-2025) (n=48)	Total (1978-2025) (n=104)	p
Age (months), median [Q1-Q3] (min-max)	33 [15.8-54.0] (5 - 156)	35.5 [21.3-60.0] (4 - 132)	35.5 [18.0-56.3] (4 - 156)	0.739
Sex, n (%)				0.542
Male	24 (42.9%)	21 (43.8%)	45 (43.3%)	
Female	32 (57.1%)	27 (56.3%)	59 (56.7%)	

mg/dL; interquartile range, 1.19–1.58; range, 1.10–2.00), primarily in the early era, although these cases were not associated with elevated blood urea nitrogen (BUN) levels. The most significant laboratory finding was anemia, with hemoglobin levels below 12 g/dL observed in 90 patients (86.5%). Other hematological parameters, including white blood cell and platelet counts, did not show consistent or clinically significant deviations across the cohort.

The initial clinical presentations of the patients are summarized in Table II. When comparing the two study periods, a significant increase in incidentally detected asymptomatic masses was observed in the late era compared to the early era (8.3% vs 0%, p=0.042). While abdominal mass remained the most common finding in both periods, other symptoms such as abdominal pain and hematuria showed no significant difference between eras (p > 0.05).

Associated congenital anomalies were detected in 11 patients (10.6%). Among these patients, hemihypertrophy and WAGR syndrome were each observed in 3 patients (27.3%), while 9q deletion, phenylketonuria with panhypopituitarism, hypospadias, horseshoe kidney, and Beckwith-Wiedemann syndrome were each observed in one patient (9.1%). Regarding the stage distribution in this subgroup, eight patients (72.7%) were diagnosed with early-stage disease (Stages I–II), while three patients (27.3%) presented with advanced-stage disease (Stages III–IV).

Regarding hematuria status at diagnosis, macroscopic hematuria was present in 14 patients (13.5%), microscopic hematuria in 36 patients (34.6%), and no hematuria was detected

Table II. Presenting complaints of the patients.

Symptom	Early era (1978–2005) (n=56)	Late era (2006–2025) (n=48)	p
Abdominal mass	47 (83.9%)	34 (70.8%)	0.155
Abdominal pain	20 (35.7%)	13 (27.1%)	0.401
Anorexia & weight loss	12 (21.4%)	10 (20.8%)	1.000
Fever	16 (28.6%)	6 (12.5%)	0.056
Macroscopic hematuria	7 (12.5%)	7 (14.6%)	0.781
Nausea & vomiting	7 (12.5%)	2 (4.2%)	0.172
Sweating	6 (10.7%)	3 (6.3%)	0.501
Diarrhea	4 (7.1%)	0 (0.0%)	0.122
Constipation	2 (3.6%)	1 (2.1%)	1.000
Seizure	1 (1.8%)	0 (0.0%)	1.000
Irritability	0 (0.0%)	1 (2.1%)	0.462
Incidentally detected	0 (0.0%)	4 (8.3%)	0.042

Data presented as number (percentage).

in 54 patients (51.9%). Anemia was observed in all patients with macroscopic hematuria (14/14, 100%). Overall, anemia was present in 45 of 50 patients with hematuria and in 45 of 54 patients without hematuria (90.0% vs. 83.3%, p=0.320).

Regarding metastatic status at diagnosis, CT imaging was not available before 1985, and therefore, CT data were lacking for 16 patients. In the early period, pulmonary metastases were detected in 3 patients by chest radiography, and in an additional 5 patients based on subsequent CT imaging. In the late period, 7 patients presented with pulmonary metastases. No extrapulmonary metastases were identified at diagnosis. Overall, pulmonary metastases were present in 15 patients (14.4%) at initial presentation.

Tumor thrombus was identified in 10 patients (9.6%) at diagnosis, including 5 patients from the early period (8.9%) and 5 from the late period (10.4%). Among patients with tumor thrombus, thrombus extended into the renal vein in 3 patients (30.0%), into the inferior vena cava in 5 patients (50.0%), and reached the right atrium in 2 patients (20.0%).

The distribution of tumor stages and histopathological findings according to the study periods is presented in Table III. For the comparative analysis of stage distribution between the two eras, Stage V cases were excluded. Patients were grouped into early-stage (Stages I-II) and advanced-stage (Stages III-IV) disease. While a numerical shift toward earlier-stage tumors was observed in the later era, this trend did not reach statistical significance (p=0.483).

Anaplasia was identified in 8 patients (14.3%) in the early period (1978–2005) and 7 patients (14.6%) in the late period (2006–2025) (p=0.591), yielding an overall anaplasia rate of 14.4% (n=15). Review of pathology reports from the early period showed that diffuse anaplasia was specified in one case and focal anaplasia in one case, whereas six cases were reported as anaplastic without subclassification; in the late period, focal anaplasia was present in three patients and diffuse anaplasia in four patients.

Surgical evaluation revealed that, in the early period, preoperative chemotherapy was administered to 5 patients (8.9%) in accordance with NWTS/COG guidelines for specific indications (one due to tumor thrombus and four due to bilateral tumors), while the remaining 51 patients (91.1%) underwent upfront surgery. Among early-era patients, RNU was performed in 52 cases (92.9%) and partial nephrectomy in 4 cases (7.1%).

In the late period, 7 patients (14.6%) received preoperative chemotherapy due to tumor thrombus or a large inoperable mass. RNU was performed in 45 patients (93.8%), while partial nephrectomy was performed in 2 patients (4.2%) with unilateral Wilms tumor associated with a genetic syndrome. One patient (2.1%)

Table III. Comparison of tumor stage and anaplasia between groups diagnosed in 1978-2005 vs. 2006-2025.

		Early Period (n=56) (1978-2005)	Late Period (n=48) (2006-2025)	Total (n=104) (1978-2025)	p
Stage	I	3 (5.4%)	19 (39.6%)	22 (21.2%)	0.012
	II	23 (41.1%)	8 (16.7%)	31 (29.8%)	
	III	21 (37.5%)	14 (29.2%)	35 (33.7%)	
	IV	5 (8.9%)	7 (14.6%)	12 (11.5%)	
	V	4 (7.1%)	0 (0.0%)	4 (3.8%)	
Anaplasia	Present	8 (14.3%)	7 (14.6%)	15 (14.4%)	0.591
	Absent	48 (85.7%)	41 (85.4%)	89 (85.6%)	

Data presented as number (percentage).

in the late period refused surgical treatment and subsequently died. Additionally, 10 patients (9.6%) underwent two or more surgical procedures due to tumor relapse.

Radiotherapy was administered according to institutional protocols, with dose adjustments based on disease stage and histology. For flank or whole-abdomen irradiation, cumulative doses typically ranged from 9 Gy to 21.6 Gy, delivered in standard fractions. In cases of pulmonary metastases, whole-lung irradiation was performed at doses between 10.5 and 12 Gy. During the early study period, 19 patients (33.9%) underwent radiotherapy at our institution; of these, 13 received abdominal irradiation (68.4%) and three received combined abdominal and lung irradiation (15.8%). Radiotherapy data were unavailable for three patients (15.8%) referred to external centers prior to 1987, when our institutional radiotherapy unit became operational. The stage distribution for this radiotherapy cohort included 5 patients with Stage II disease (26.3%), 10 with Stage III disease (52.6%), and 4 with Stage IV disease (21.1%).

In the late period, 22 patients (45.8%) received radiotherapy, while 26 patients (54.2%) did not. Radiotherapy indications included 3 patients with Stage II disease (13.6%), 13 with Stage III disease (59.1%), and 6 with Stage IV disease (27.3%). Notably, one patient with Stage IV disease in the late period refused both surgical and radiotherapy treatment.

The median follow-up time for the entire cohort was 53 months (interquartile range, 15.0–148.5; range, 1–314). At the time of analysis, 38 of 56 patients (67.9%) in the early period and 42 of 48 patients (87.5%) in the late period were alive, resulting in a crude survival rate of 76.9% (80 of 104 patients) for the entire cohort. A total of 24 patients (23.1%) died during the follow-up period. Of the 24 deaths, 21 (87.5%) were directly attributable to progressive disease and systemic metastases. Treatment-related mortality occurred in 3 cases (12.5%), including two deaths due to neutropenic sepsis and one due to hepatic veno-occlusive disease (VOD). No deaths related to late toxicities were observed during follow-up.

Relapse was observed in 18 patients (17.3%), including 8 patients from the early period (14.3%) and 10 patients from the late period (20.8%). The most common sites of relapse were the liver or diffuse abdominal area in 12 patients (66.7%), followed by the contralateral kidney region in 3 patients (16.7%) and the ipsilateral kidney region in 3 patients (16.7%). All relapsed patients received the ICE (ifosfamide, carboplatin, and etoposide) regimen as salvage therapy. In three patients with suboptimal response (16.7%), treatment was switched to a cyclophosphamide–topotecan protocol. Surgical resection of localized recurrent lesions was performed in 10 patients (55.6%). At the time of final analysis, 8 patients (44.4%) were alive, whereas 10 patients (55.6%) died due to progressive disease. Autologous stem cell transplantation was not utilized in our cohort.

According to the Kaplan-Meier analysis, the estimated 5-year overall survival (OS) and event-free survival (EFS) rates for the entire cohort were 73.6% and 65.8%, respectively. Survival outcomes were significantly associated with the stage at diagnosis (p=0.004); specifically, the 5-year OS rates for Stage I, II, III, and IV were 92.3%, 82.6%, 65.2%, and 41.7%, respectively. When stratified by treatment era, the 5-year OS was 61.1% in the early era and 86.8% in the late era (p=0.009), while the 5-year EFS was 57.3% and 81.5%, respectively (p=0.126). In a further granular analysis, the estimated 5-year OS rates were 70.5% for patients diagnosed during the 1999–2005 period and 86.8% for those diagnosed during the 2006–2025 period; however, the difference in OS between these two periods was not statistically significant (log-rank p=0.333).

Kaplan–Meier analysis showed significantly lower OS in patients with anaplasia (p=0.035), in those with advanced-stage disease compared with early-stage disease (p=0.004), and in patients treated in the early treatment era compared with the late treatment era (p=0.009).

No significant difference in OS was observed according to age at diagnosis (<2 years vs ≥2 years) (p=0.840). Kaplan–Meier survival curves illustrating these findings are presented in Fig. 1.

Cox proportional hazards regression analysis was performed to identify prognostic factors associated with overall survival (Table IV). In univariable Cox analysis, early treatment era (HR=3.18; 95% CI: 1.26–8.06; p=0.014), advanced-stage disease (HR=3.60; 95% CI: 1.43–9.09; p=0.007), anaplasia (HR=2.49; 95% CI: 1.03–6.02; p=0.042), and metastatic disease at diagnosis (HR=5.18; 95% CI: 2.29–11.63; p<0.001) were significantly associated with poorer overall survival. In the multivariable Cox regression model including metastatic status, early treatment era (HR=3.12; 95% CI: 1.23–7.94; p=0.017) and metastatic disease at diagnosis (HR=4.17; 95% CI: 1.56–11.11;

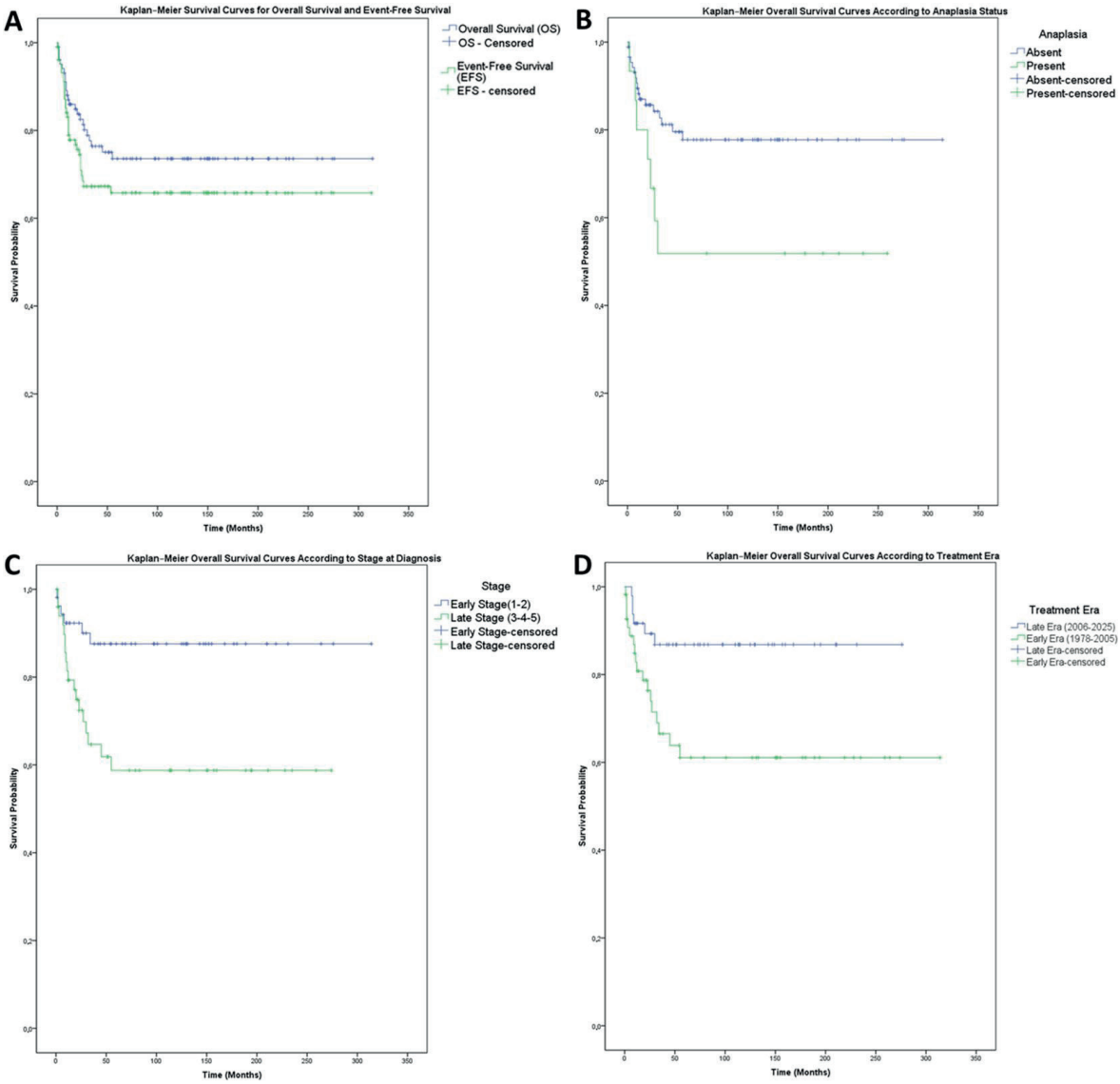

Fig. 1. Kaplan–Meier survival curves. (A) Overall and event-free survival, (B) Overall survival according to anaplasia status, (C) Overall survival according to stage at diagnosis, (D) Overall survival according to treatment era.

Table IV. Univariable and multivariable Cox proportional hazards regression analysis of prognostic factors for overall survival.

Variable	Reference category	Univariable model			Multivariable model		
		HR	95% CI	p	HR	95% CI	p
Sex, male	Female	0.95	0.42–2.14	0.902			
Age at diagnosis	Per month increase	1.004	0.993–1.016	0.467			
Early treatment era	Late treatment era	3.18	1.26–8.06	0.014	3.12	1.23–7.94	0.017
Advanced stage	Stage I–II	3.6	1.43–9.09	0.007	2.02	0.66–6.21	0.219
Tumor thrombus	Absent	0.77	0.18–3.27	0.722	—	—	—
Anaplasia	Absent	2.49	1.03–6.02	0.042	1.82	0.72–4.61	0.205
Metastatic disease	Absent	5.18	2.29–11.63	<0.001	4.17	1.56–11.11	0.004

CI: confidence interval, HR: hazard ratio.

p=0.004) remained independently associated with poorer overall survival. Advanced stage, anaplasia, sex, and age at diagnosis were not independently associated with overall survival in this model.

Given the close relationship between advanced stage and metastatic disease, an alternative multivariable Cox model excluding metastatic disease was constructed. In this model, advanced stage at diagnosis (HR=3.19; 95% CI: 1.17–8.70; p=0.023) and early treatment era (HR=2.96; 95% CI: 1.17–7.46; p=0.022) remained independently associated with poorer overall survival, whereas anaplasia did not retain statistical significance.

Treatment-related complications observed during the study period are summarized in Table V. Scoliosis was reported in five patients, with four belonging to the early era. Cardiac functions were monitored using echocardiography at the initiation of therapy and at regular intervals during clinical follow-up. A decline in left ventricular ejection fraction (EF < 60%) was identified in three patients. Two patients from the early era were asymptomatic at the time of their last echocardiogram, while the third patient from the late era exhibited clinical signs of heart failure, specifically exertional dyspnea. These three patients had received cumulative doxorubicin doses of 360, 375, and 330 mg/m^2, respectively.

Table V. Acute and long-term treatment-related complications.

Early treatment complications	n (%)	Late treatment complications	n (%)
Hepatitis	2 (1.9%)	Scoliosis	5 (4.8%)
Veno-occlusive disease	2 (1.9%)	Delayed puberty & growth retardation	4 (3.8%)
Vincristine extravasation	2 (1.9%)	Chronic kidney disease	3 (2.9%)
Ureteral injury	1 (1.0%)	Cardiotoxicity	3 (2.9%)
Postoperative hypertension	1 (1.0%)	Chemotherapy-induced neuropathy (ptosis)	2 (1.9%)
Contrast extravasation with compartment syndrome	1 (1.0%)	Hypertension	2 (1.9%)
		Adrenal insufficiency	1 (1.0%)
		Osteoporosis	1 (1.0%)
		Depression & anxiety disorder	1 (1.0%)

Percentages were calculated using the total study population (n=104). Patients could experience more than one complication. No secondary malignancy was observed in any patient.

Discussion

Over the past several decades, survival outcomes in pediatric Wilms tumor have improved dramatically, with current OS rates approaching 90% in developed healthcare settings. This remarkable progress reflects a transition from the era of surgery-only approaches to risk-adapted, multimodal treatment strategies.[9] Our study provides a longitudinal perspective on the evolution of Wilms tumor over a 47-year period, offering valuable insights into changes in presentation, treatment, and outcomes across two distinct eras.

In our cohort, a slight female predominance (56.7%) was observed. This contrasts with the nearly equal sex distribution reported in the TPOG's 2006 multicenter study.[8] However, similar female predominance has been noted in several studies from Asian populations[1,10], while other reports describe slight male or female dominance depending on regional or institutional variations.[11,12] These findings suggest that while Wilms tumor does not exhibit a universally consistent sex predilection, demographic differences may emerge in specific populations or healthcare settings.

In our study, 62.5% of patients were diagnosed before the age of four, consistent with the well-established observation that Wilms tumor primarily affects younger children. Previous national and international studies have similarly reported that the majority of patients are diagnosed before the age of five.[8,11]

A striking finding in our cohort was the high prevalence of anemia at diagnosis, observed in 86.5% of patients. Although anemia was frequent in both patients with and without hematuria and the overall difference did not reach statistical significance (90.0% vs. 83.3%, p = 0.320), all patients presenting with macroscopic hematuria had anemia. This descriptive finding suggests that clinically apparent hematuria may have contributed to anemia in a subset of patients, although it does not fully explain the overall high anemia burden in the cohort. Therefore, anemia at diagnosis is likely multifactorial, potentially reflecting chronic tumor-related blood loss, nutritional iron deficiency, anemia of inflammation, tumor burden, or impaired erythropoiesis.[13,14] However, the retrospective design of our study limited a detailed etiologic analysis, as complete iron studies were not available for all participants.

In our cohort, the majority of patients presented with abdominal mass, aligning with existing literature that identifies this symptom as the most common initial manifestation of Wilms tumor.[11] Notably, in the later period of our study, we observed an increase in incidentally diagnosed cases. This trend may be attributed to advancements in imaging technologies, such as USG and CT, as well as improved accessibility to healthcare services, facilitating earlier detection of asymptomatic tumors.[11,15]

Regarding associated anomalies, 10.6% of our patients had congenital anomalies, which falls within the range reported in the literature, varying from 2.8% to 17%.[11,12] These anomalies often include genitourinary malformations and are sometimes linked to syndromic conditions such as WAGR and Beckwith-Wiedemann syndromes, which are known to predispose individuals to Wilms tumor.[11,12] In our cohort, the majority of patients with such anomalies (72.7%) were diagnosed at an early stage (Stages I-II). This finding underscores the importance of thorough clinical evaluation and genetic counseling, as clinical vigilance and screening in predisposed individuals facilitate early detection and management.

Over the course of our study, when comparing early-stage (Stages I-II) and advanced-stage (Stages III-IV) disease (excluding Stage V), we observed a numerical shift toward earlier-stage tumors in the later period. Although this trend did not reach statistical significance (p=0.483), it aligns with the significant increase in incidentally detected asymptomatic masses (p=0.042) observed in our later cohort. This pattern likely reflects improvements in early detection and easier access to diagnostic

services, both within our institution and across the broader healthcare system.[16] In contrast, the proportion of patients presenting with advanced-stage disease remained relatively stable over time, suggesting that a subset of tumors may still present with more aggressive clinical behavior and rapid progression despite improved diagnostic accessibility.

The rate of bilateral Wilms tumor in our early cohort was comparable to the 5.9% reported in the 2010 multicenter study conducted by the TPOG.[8,11] Although we observed a lower frequency of bilateral Wilms tumor in the later period, this likely represents a coincidental variation or reflects the specific characteristics of our late-era study population. In contrast, the significant increase in Stage I diagnoses during the late era represents a distinct stage shift. This trend likely reflects the impact of improved imaging resolution and earlier clinical identification, which facilitate the detection of unilateral disease at a more localized stage before it progresses to advanced levels.

The overall rate of anaplasia in our series was 14.4% (early: 14.3% vs. late: 14.6%; p=0.591), which is higher than the 9.7% reported in the TPOG study.[8] This finding must be interpreted with caution due to the historical heterogeneity in pathology reporting across our 47-year study period. The lack of consistent focal versus diffuse subclassification, particularly during the early era, introduces a degree of reporting variability that likely affects cross-study comparisons and the precision of anaplasia-related risk estimates in our cohort.

In our cohort, 11.5% of patients received preoperative chemotherapy, which is lower than the rates reported in previous national studies, including 20% in the TPOG multicenter analysis and 19% in another large Turkish series.[8,11] However, we observed a clear increase in the use of preoperative chemotherapy in the later period of our study. This trend likely reflects the gradual adoption of evolving treatment protocols and increasing clinical experience in tailoring therapy based on tumor complexity and operability.

Overall, the stage distribution in our cohort remained consistent with those reported in the literature.[11] As in many centers worldwide, nephron-sparing surgery (NSS) was selectively performed in appropriate cases. In our study, NSS was primarily used in patients with bilateral Wilms tumor or in those with unilateral tumors associated with predisposing syndromes, in line with current recommendations.[11,12]

The 5-year OS and EFS rates in our cohort (73.6% and 65.8%, respectively) are broadly consistent with established national and international reports.[8] Notably, outcomes improved substantially over time, with OS increasing from 61.1% in the early era to 86.8% in the late era (p=0.009). Specifically, the lack of a significant survival difference between the 1999–2005 and 2006–2025 periods (log-rank p=0.333) highlights the early impact of the Turkish Wilms Protocol. This indicates that the most substantial breakthrough in survival was achieved through the standardization of therapy and improved supportive care by the late 1990s, reaching a high-quality plateau that has been consistently maintained. While EFS also showed an upward trend (81.5% vs. 57.3%), the lack of statistical significance (p=0.126) suggests that while our primary and salvage strategies have enhanced ultimate survival, preventing initial relapses remains a challenge that warrants further optimization of frontline therapies.

The frequency and distribution of distant metastasis at diagnosis were also comparable to existing literature, with the lungs remaining the most common site of metastatic involvement.[8] Despite improvements in primary treatment, disease relapse remains a major clinical challenge. In our study, the relapse rate was 17.3%, aligning with the range of 20% to 25.9% reported in other series.[11,12] In our cohort, the liver and diffuse abdominal area were the most frequent sites of relapse. While this frequency appears higher than typically reported, it

should be interpreted within the context of our small relapse subgroup (n=18), where each patient significantly impacts the percentage. Additionally, our classification combined isolated liver relapses with diffuse abdominal recurrences, which contributed to this perceived prevalence. In our center, the management of relapsed Wilms tumor primarily focused on intensified chemotherapy and surgical interventions. Although international high-risk protocols often incorporate autologous stem cell transplantation, our strategy relied on the ICE regimen combined with the surgical resection of accessible lesions. This approach, applied to the majority of our relapsed cases, was dictated by institutional protocols and available clinical resources during the study period. The achieved post-relapse survival rate of 44.4% is consistent with existing literature for patients managed with conventional salvage modalities in the absence of high-dose therapy and transplant.[17]

In our cohort, mortality was primarily associated with progressive disease rather than treatment-related toxicity. The fact that 87.5% of deaths were attributable to progressive disease, while only a small fraction (12.5%) resulted from acute complications such as neutropenic sepsis or VOD, marks a significant clinical observation. These findings suggest that, although modern supportive care has reduced lethal toxicities, further survival gains may depend on more effective strategies for patients with progressive or treatment-refractory disease rather than on further nonspecific intensification of conventional therapy.

Our multivariable Cox regression analysis further underscores this evolution, as both treatment era and metastatic disease emerged as the strongest independent predictors of overall survival. The robust prognostic value of the treatment era (HR=3.12; 95% CI: 1.23–7.94) highlights the cumulative success of institutional experience, improved radiotherapy planning, and more effective salvage regimens over nearly five decades. Consistent with previous reports, metastatic presentation remains the most formidable barrier to survival, carrying an approximately four-fold higher hazard of death in our series (HR=4.17; 95% CI: 1.56–11.11).[8,11] Interestingly, while advanced stage and anaplasia were significant in univariable Cox analyses, they did not retain independent significance when adjusted for metastatic status and treatment era. This likely reflects strong collinearity between these variables, as distant metastasis is the defining feature of Stage IV disease. Consequently, in comprehensive multivariable models, the prognostic impact of advanced stage is often statistically superseded or captured by the presence of metastasis. Supporting this interpretation, advanced stage became independently associated with poorer overall survival in the alternative multivariable Cox model excluding metastatic disease (HR=3.19; 95% CI: 1.17–8.70). Regarding anaplasia, its lack of independent significance after adjustment may be partly explained by the historical heterogeneity in pathology reporting over the 47-year study period. As discussed earlier, the lack of detailed subclassification in early-era cases might have diluted the independent prognostic weight of anaplasia compared to more objective markers like metastatic status.

While overall survival in our cohort aligns with international standards, the persistently poor outcomes in these subgroups highlight an ongoing unmet clinical need and underscore the importance of future research efforts targeting these patients.

The spectrum of treatment-related complications in our cohort was largely consistent with established reports in the literature.[8] A notable trend was the decreased incidence of scoliosis among patients treated in the later period, which is likely attributable to advancements in radiotherapy techniques—specifically refined targeting and planning that minimize musculoskeletal sequelae. Additionally, vincristine-induced neurotoxicity, such as ptosis, remains a recognized clinical challenge.[12,18] Beyond these acute or subacute complications, the concept of survivorship, encompassing long-term quality of life, has

become paramount in pediatric oncology. Our findings concerning cardiotoxicity and endocrine late effects, such as growth retardation, underscore the clinical necessity for lifelong, multidisciplinary surveillance to address the evolving health needs of Wilms tumor survivors.

This study has several notable strengths. First, its extensive 47-year span offers a valuable opportunity to evaluate long-term trends in the management and outcomes of pediatric Wilms tumor. Second, the available clinical and therapeutic records enabled a longitudinal overview and comparative evaluation of treatment strategies across different eras. Additionally, the use of multivariable regression analysis contributed to the identification of independent prognostic factors within our cohort. However, certain limitations should be acknowledged. The retrospective design inherently carries the risk of missing data, particularly for patients treated before the implementation of electronic health records. Additionally, histopathological variables were derived from contemporaneous pathology reports, and archived slides/blocks were not systematically re-reviewed; therefore, histologic subclassification (including focal versus diffuse anaplasia) may be subject to historical reporting variability and potential misclassification, particularly in earlier decades. Variations in diagnostic methods, staging classifications, and treatment protocols over time may have introduced heterogeneity across cohorts. Finally, as a single-center study, the generalizability of the findings may be limited, although the consistency of results with national and international data supports their external validity.

In conclusion, our findings confirm that survival outcomes in Wilms tumor have improved significantly over the past decades, in parallel with advances in multimodal therapy, early detection, and clinical expertise. Nevertheless, metastatic disease at diagnosis and treatment era were the strongest independent predictors of survival in our cohort, while advanced stage and anaplasia were associated with outcome in univariable analyses and should be interpreted in the context of disease burden and evolving pathology reporting over time. The observation that mortality was predominantly associated with progressive disease rather than treatment toxicity suggests that future survival gains in our setting may depend on improved risk stratification and more effective treatment approaches for patients with metastatic or treatment-refractory disease, rather than further nonspecific intensification of standard regimens.

Ethical approval

The study was approved by Ondokuz Mayıs University Clinical Research Ethics Committee (date: April 27, 2023, number: 2023/115).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: OSD, AU, AD, MEÖÇ, İK; data collection: OSD; analysis and interpretation of results: OSD, AD; draft manuscript preparation: OSD, AU, MEÖÇ, İK. All authors reviewed the results and approved the final version of 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

Esophageal atresia and nutritional outcomes: the influence of anastomotic stricture and gastroesophageal reflux

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ABSTRACT

Background. Esophageal atresia (EA) is a congenital malformation often associated with long-term gastrointestinal complications and impaired growth. This study aimed to evaluate anthropometric outcomes in children with EA, with particular attention to the impact of associated conditions such as anastomotic stricture and gastroesophageal reflux (GER).

Methods. We conducted a retrospective analysis of patients with type C EA who underwent primary anastomosis between 2005 and 2021. Anthropometric data were collected at four age intervals (<1 year, 1–4 years, 5–11 years, >11 years) and standardized using validated growth charts. Associations between anthropometric parameters and the presence of stricture or GER were analyzed.

Results. Fifty-seven patients met the inclusion criteria. Stricture and GER were identified in 32% and 30% of patients, respectively. Infants (<1 year) with stricture had significantly lower BMI Z-scores -2.5 ± 0.7 than those without stricture (-1.1 ± 1.1; p=0.0093), while those with GER had significantly lower weight Z-scores (-2.1 ± 1.0) than those without GER (-1.2 ± 1.1; p=0.0443). Although most patients showed improvement in anthropometric parameters with age, early growth impairment was consistently observed in association with these complications.

Conclusions. Children with EA are at risk of impaired growth during early childhood, particularly when stricture or GER is present. Regular anthropometric monitoring and early nutritional intervention are crucial, especially within the first year of life. Long-term multidisciplinary follow-up is recommended to optimize developmental outcomes.

Key words: esophageal atresia, esophageal stricture, gastroesophageal reflux, growth, nutritional status.

Esophageal atresia (EA) is a congenital anomaly occurring in approximately 1 in 2,500 to 3,000 live births.[1] According to Gross's classification, type C—characterized by a proximal esophageal atresia with a distal tracheoesophageal fistula (TEF)—is the most prevalent form, accounting for about 85% of cases.[2]

Patients with EA often experience both short- and long-term comorbidities.[3-5] From a gastrointestinal perspective, common

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complications include esophageal stricture, gastroesophageal reflux (GER), and dysphagia.[6,7]

Esophageal stricture, the most frequent postoperative complication, affects up to 60% of patients.[6] This condition often necessitates endoscopic intervention and can lead to symptoms such as dysphagia, vomiting, coughing, recurrent respiratory infections, and impaired weight gain.[8-10]

In addition to esophageal stricture, GER is also prevalent among patients with EA, with a reported incidence ranging from 20% to 63%, depending on age and diagnostic methods.[6,11] Complications arising from GER, including anastomotic stenosis, esophagitis, and Barrett's esophagus, can manifest throughout development.[12,13]

Studies have reported lower height and weight-for-age values in children with EA compared with healthy age-matched populations.[3,14,15] However, the influence of comorbidities on these anthropometric measures remains underexplored.[16]

Therefore, the aim of this study was to evaluate longitudinal anthropometric outcomes (weight, height/length, and Body Mass Index [BMI]) in children with repaired type C EA, and to assess the association of anastomotic stricture and GER with growth trajectories within a repeated-measures follow-up dataset, while also exploring clinically relevant factors such as prematurity.

Materials and Methods

This retrospective study analyzed the medical records of all surviving patients who underwent primary anastomosis surgery for type C EA at our institution between 2005 and 2021. To reduce potential confounding factors, patients with non-type C atresia or long-gap EA were excluded due to their distinct clinical presentations, including a tendency toward higher complication rates and the need for multiple surgeries.[17,18] Additionally, individuals with incomplete medical records, those lost to postnatal follow-up, or those who died in the immediate perinatal period were not included in the study. Sample size was determined by the availability of eligible cases.

Patient data were categorized into four age groups following the age intervals used by Coppens et al.[19] in the study that informed the design of the present study. The groups included infants younger than 1 year, children aged 1 to 4 years, those aged 5 to 11 years, and adolescents older than 11 years. EA type was classified according to Gross's classification system.[2]

Data collection

Demographic, clinical, perinatal, surgical, and postoperative data were extracted from patient records. Raw anthropometric data (weight and height) for each patient were collected at each of the four age intervals, for age-specific analyses within the longitudinal repeated-measures dataset. These values were subsequently entered into a nutritional calculator, a software application that adjusts measurements according to age- and sex-specific reference growth curves and converts them into Z-scores and percentiles.

Anthropometric measurements were standardized using the SEGHNP nutritional calculator.[20] Weight and length/height were converted to Z-scores and percentiles using the reference growth curves by Carrascosa et al. (2010)[21], and BMI Z-scores were obtained using the same tool.

As each patient's data corresponded to different dates, these were standardized using the nutritional calculator, into which we entered both the date of birth and the date of each anthropometric measurement. The calculator determined each patient's age at the time of measurement and compared the values with the corresponding age-matched reference curves. For the purposes of this study, Z-scores were chosen as the primary metric because

they provide a more precise quantification of deviation from the reference population.

Although Z-scores were used as the primary analytic measures, raw anthropometric values are provided for transparency. Supplementary Table S1 summarizes weight (kg) and length/height (cm) by age interval.

Diagnostic evaluations

Patients presenting with dysphagia underwent an initial contrast esophagography. If a stricture was detected, upper endoscopy was performed for evaluation and, if necessary, dilation. Patients with symptoms suggestive of GER or positive reflux findings on esophagography underwent 24-hour esophageal pH monitoring or upper endoscopy with esophageal biopsy, as indicated when suspicious findings were encountered. There was no protocol for prophylactic proton pump inhibitor (PPI) administration in patients under one year of age, because patients in the study were treated over a relatively long time span and such a protocol was implemented only in more recent years.

Statistical analysis

Data were analyzed using IBM SPSS Statistics version 29 and R software version 4.1.1. Descriptive statistics were used to summarize the characteristics of the cohort. The distribution of continuous variables was assessed for normality using the Shapiro-Wilk test. Variables with a normal distribution are presented as mean ± standard deviation (SD), whereas non-normally distributed variables are expressed as median and interquartile range (Q1-Q3). However, in selected cases, mean ± SD was also reported for variables that did not follow a normal distribution, as extreme values were considered part of the expected clinical variability in this population rather than true outliers. This approach was intended to better reflect the real-world distribution of anthropometric outcomes in patients with postoperative complications. Categorical variables are reported as frequencies and percentages.

Anthropometric Z-scores are summarized using mean ± SD for variables compatible with normality and median (Q1–Q3) for non-normally distributed variables. For transparency, Table II reports both summaries by age interval. When subgroup sizes were very small, results are presented descriptively and interpreted as exploratory.

Longitudinal changes in anthropometric Z-scores (weight, height/length, and BMI) across age intervals were analyzed using the Friedman test. When the overall test was statistically significant, post hoc pairwise comparisons were performed using the Wilcoxon signed-rank test. For age-specific comparisons between patients with and without anastomotic stricture or GER, Welch's t-test (R) for normally distributed variables and the Mann-Whitney U test (R) for non-normally distributed variables were used when subgroup sizes were sufficient; when very small subgroups ($n<5$) were present, results were reported descriptively without p-values.

Associations between categorical variables were assessed using Chi-square tests, and Fisher's exact test was applied to 2×2 contingency tables when expected frequencies were small. Potential confounders and modifying factors (including prematurity and associated anomalies) were explored by comparing groups using Fisher's exact test. A p-value < 0.05 was considered statistically significant, except where adjusted for multiple comparisons as described above. We explored multivariable repeated-measures approaches; however, sparse data in several age-by-complication strata and unbalanced follow-up precluded stable model estimation.

Results

A total of 76 clinical records were reviewed, of which 19 were excluded. Seven were incomplete, and six corresponded to patients who died in the immediate perinatal period due to associated life-threatening conditions. Another six patients were excluded because they presented with a different type of EA: three had type A, one had

type D, and two had type C with long-gap EA requiring delayed surgery. After exclusions, 57 patients met the study's inclusion criteria.

After categorizing the 57 patients by age group, anthropometric and clinical data were available for 56 of <1 year, 51 of 1-4 years, 30 of 5-11 years and 12 of > 11 years.

This was influenced by the patients' ages at the time of the study (conducted between 2021 and 2022) and loss to follow-up.

Although all patients (n=57) were alive at the end of the first year, the number of patients is reflected as 56 because data from the first year were unavailable for one patient.

An open surgical approach was used in 56 patients, with only one case managed thoracoscopically. Twenty patients were premature and 37 patients were born at term with mean gestational ages of 34.05 and 38.89 weeks respectively.

Associated anomalies were present throughout the sample in various forms across the sample: There were 7 cases of vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal defects, and limb defects (VACTERL) association and 1 case of trisomy 21. Eighteen cases had cardiac anomalies (defined as such in the immediate neonatal period based on preoperative cardiac ultrasound) consisting of 12 ostium secundum atrial septal defects, 4 ventricular septal defects and 2 cases of mild valvular insufficiency, while patent ductus arteriosus and patent foramen ovale were considered as minor findings and were excluded. Information regarding subsequent cardiac surgical interventions was not systematically collected. Urological anomalies were present in 7 cases including hypospadias, urinary tract dilatation, renal agenesis or hypoplasia and horseshoe kidney.

Potential confounding and modifying factors related to growth and nutritional outcomes were also recorded. Prematurity was present in 20 patients (35.1%). Low birth weight (<2500 g) was observed in 26 patients (46%). GER requiring surgical treatment occurred in 5 patients during the first year of life and in 4 patients during the 1–4-year interval. Nutritional support measures included gastrostomy in 2 patients during the first year and 3 patients during the 1–4-year interval (2 of whom were the same patients recorded in the <1-year group), while nasogastric tube feeding was required in 5 and 1 patients (with the latter patient continuing from the previous <1 year age group), respectively. Four patients in the <1-year group and one patient in the 1–4-year group were unable to maintain full oral feeding at some point during follow-up. Consequently, oral feeding was achieved in 52/56 patients in the <1-year group, 50/51 in the 1–4-year group, and in all patients in the older age groups (30/30 aged 5–11 years and 12/12 aged >11 years).

Anastomotic stricture was present in 32% of patients (n = 18), and GER in 30% (n = 17), with both conditions varying across age groups, as shown in Table I.

Anastomotic stricture in the < 1-year group was present in 8 cases, 5 of which persisted into the 1-4 years period, during which 7 new cases were diagnosed. In the 5- 11 years group, 4 strictures corresponded to recurrences (having been present in any of the previous age groups) and 3 were newly-diagnosed.

Anthropometric parameters (weight, height, and BMI) from the entire sample are expressed as standardized Z-scores and are shown in Table II; data availability varied across age intervals due to differences in follow-up. Raw

Table I. Prevalence of complications by age group.

Age Group	Stricture (%)	GER (%)
< 1 year (n=56)	14% (n=8)	14% (n=8)
1–4 years (n=51)	26% (n=13)	14% (n=7)
5–11 years (n=30)	23% (n=7)	17% (n=5)
> 11 years (n=12)	0% (n=0)	17% (n=2)

Prevalence of complications: Presence or esophageal stricture or gastroesophageal reflux in each of the age groups.
GER: Gastroesophageal Reflux.

Table II. Mean and median anthropometric values according to age groups.

Age group	Weight Z-score (mean ±SD)	Height Z-score (mean ±SD)	BMI Z-score (mean ±SD)	Weight Median (Q1–Q3)	Height Median (Q1–Q3)	BMI Median (Q1–Q3)	N
<1y	-1.3 ± 1.1	-0.8 ± 1.4	-1.3 ± 1.1	-1.3 (-2.0 – -0.5)	-0.7 (-1.6 – 0.4)	-1.3 (-2.0 – -0.4)	56
1-4y	-1.0 ± 1.2	-0.9 ± 1.5	-0.7 ± 1.1	-0.8 (-1.8 – -0.3)	-0.8 (-1.7 – 0.3)	-0.6 (-1.4 – -0.1)	51
5-11y	-0.3 ± 1.2	-0.3 ± 1.4	-0.2 ± 1.2	-0.1 (-1.0 – 0.3)	-0.2 (-1.6 – 0.5)	-0.32 (-0.9 – 0.03)	30
> 11 y	-0.1 ± 1.4	± 1.2	-0.1 ± 1.5	-0.5 (-1.1 – 0.3)	0.2 (-0.4 – 0.8)	-0.4 (-0.9 – -0.0)	12

Anthropometric values: Weight, height and BMI showing a normalizing trend along with growing age. Not normally distributed values according to Shapiro-Wilk test are shown in bold.
SD: Standard Deviation. Q1-Q3: First and third Quartile values. BMI: Body Mass Index. N: Number of patients.

anthropometric measurements (weight in kg and length/height in cm) are presented in Supplementary Table S1.

Normality of the anthropometric variables was assessed using the Shapiro–Wilk test. Several distributions deviated significantly from normality, particularly in the older age groups, justifying the use of non-parametric methods. The Friedman test revealed statistically significant differences across age groups for weight Z-scores ($\chi^2(3) = 15.278$, $p = 0.002$) and BMI Z-scores ($\chi^2(3) = 23.29$, $p = 0.001$), while height Z-scores showed no significant differences ($\chi^2(3) = 4.909$, $p = 0.179$). Post hoc pairwise comparisons using the Wilcoxon signed-rank test identified significant improvements in weight and BMI during early childhood. The results of these analyses are summarized in Table III.

There was a trend toward normalization of Z-scores with age as shown in Fig. 1.

To assess the distribution of possible confounders (prematurity, low birth weight) and modifying factors (cardiac, digestive and urological anomalies, and the presence of VACTERL association), Fisher's exact test was applied to 2×2 contingency tables, individually evaluating the presence or absence of these conditions in patients with or without stricture and with or without GER. Prematurity was the only factor showing an unequal distribution

Table III. Post hoc pairwise comparisons of anthropometric Z-scores across age groups using the Wilcoxon signed-rank test.

Variable	Age Group Comparison	Z value	p value
Weight Z-score	<1 vs 1–4	2.322	0.02
Weight Z-score	<1 vs 5–11	3.887	<0.001
Weight Z-score	<1 vs >11	2.987	0.003
Weight Z-score	1–4 vs 5–11	-2.884	0.004
Weight Z-score	5–11 vs >11	-1.362	0.173
BMI Z-score	<1 vs 1–4	3.078	0.002
BMI Z-score	<1 vs 5–11	4.096	<0.001
BMI Z-score	<1 vs >11	3.263	0.001
BMI Z-score	1–4 vs 5–11	-0.487	0.627
BMI Z-score	5–11 vs >11	0.198	0.845
Height Z-score	All comparisons	-	0.179

Z values and p-values are shown for each comparison. Descriptive statistics for each age interval are reported in Table II and should be interpreted alongside these post hoc comparisons.
BMI: Body Mass Index.

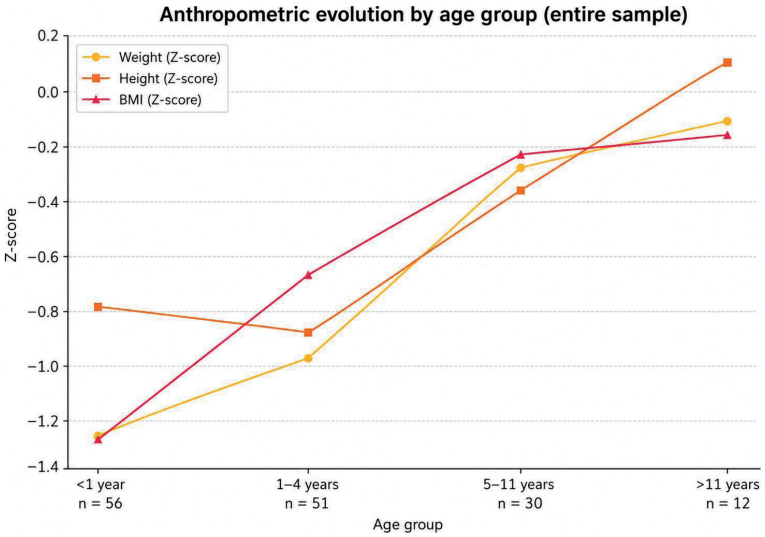

Fig. 1. Evolution of weight, height and BMI Z-scores by age interval in the full cohort.

between comparison groups: in the 5–11-year interval, stricture was more frequent among premature patients (5/10) than among term patients (2/20; p= 0.026). No other statistically significant imbalances were observed for the remaining factors assessed.

We explored the feasibility of a linear mixed-effects model to account for within-subject correlation across repeated measurements and to evaluate the effects of anastomotic stricture and GER over time. However, due to unbalanced follow-up across age intervals and sparse data in several age-by-complication combinations, the model did not converge and produced unstable estimates. Accordingly, we did not report mixed-effects results and proceeded with the complementary approaches described below.

As an alternative, we employed two complementary approaches. First, we aggregated anthropometric Z-scores (weight, height, and BMI) across all time points for each patient and compared the mean values between those who had a stricture or gastroesophageal reflux at any time and those who did not. The Shapiro–Wilk test was used to assess normality, and Welch's t-test was applied to compare means between groups without assuming equal variances. No statistically significant differences were found in average weight Z-score (p=0.989), height Z-score (p = 0.342), or BMI Z-score (p = 0.454) between patients with and without stricture.

In the case of GER, a significantly lower mean height Z-score was observed in patients with GER compared to those without (p = 0.037), while differences in weight (p = 0.140) and BMI (p = 0.547) were not statistically significant.

Second, anthropometric outcomes were compared between patients with and without stricture or GER within each age group, again using Welch's t-test (for normally distributed values) or Mann-Whitney U test (for non-normally distributed values) to account for possible differences in variance.

When comparing anthropometric parameters between patients with and without stricture, statistically significant differences were found only in BMI values for those under 12 months of age (Table IV). No other statistically significant differences were found in the remaining age groups or parameters (Supplementary Table S2).

When comparing patients with and without GER, statistically significant differences were

Table IV. Mean anthropometric measures by stricture presence (<1 year).

Anthropometric value	Group	N	Z-score (mean± SD)	p-value
Weight <1y	No Stricture	48	-1.2 ± 1.1	0.125
	Stricture	8	-1.8 ± 1.0	
Height <1y	No Stricture	48	-0.8 ± 1.5	0.854
	Stricture	8	-0.8 ± 0.7	
BMI <1y	No Stricture	48	-1.1 ± 1.1	0.009
	Stricture	8	-2.5 ± 0.7	

Anthropometric measurements in the < 1-year group comparing values (normal distribution) with Welch's t-test in patients according to the presence or absence of esophageal stricture. Z-score values are presented as mean ± standard deviation. BMI: Body Mass Index. SD: Standard Deviation. N: Number of patients.

found only in weight for patients under 12 months of age (Table V). No other statistically significant differences were observed across age groups or variables (Supplementary Table S3). The very wide ranges observed in the >11-year GER-positive subgroup were driven by the extremely small sample size (n = 2). All extreme values were verified against source records and considered clinically plausible

Respiratory symptoms (bronchitis, pneumonia) were very frequent in patients with GER (7/8 patients with GER in the < 1 year-group had respiratory symptoms, as did 6/7 in the 1-4 years group, 5/5 in the 5-11 year-group and 2/2 in the >11 year-group).

Although the data may suggest more complete follow-up of complicated cases, data availability varied for each age group due to the timing of the study (years 2021-2022). At the time, the oldest patients were 15-16 years old data were available for 12 / 17 patients in the > 11-year-age group.

Discussion

This study evaluated the long-term nutritional status of children with EA, emphasizing the impact of associated complications such as anastomotic stricture and GER. Our findings show that while overall growth parameters tend to normalize with age, children under 12 months of age appear to be more vulnerable to nutritional compromise, especially in the presence of stricture or GER.

In our cohort, 32% of patients presented with stricture and 30% with GER. These complications were more frequently observed in the first few years of life and were associated with lower weight and BMI Z-scores. Although statistical significance was reached only for BMI (for stricture) and weight (for GER) among infants under 1 year, we observed a non-

Table V. Anthropometric measures by GER presence (<1 year).

Anthropometric value	Group	N	Z-score mean± SD	p-value
Weight <1y	No GER	48	-1.2 ± 1.1	0.044
	GER	8	-2.1 ± 1.0	
Height <1y	No GER	48	-0.6 ± 1.5	0.104
	GER	8	-1.3 ± 0.9	
BMI <1y	No GER	48	-1.2 ± 1.1	0.264
	GER	8	-1.7 ± 1.2	

Comparison of anthropometric measurements (normal distribution) with Welch's t-test in the < 1-year group according to the presence or absence of gastroesophageal reflux. Z-score values are presented as mean ± standard deviation. SD: Standard Deviation GER: Gastroesophageal Reflux. BMI: Body Mass Index. N: Number of patients.

significant trend toward lower anthropometric parameters across all age groups when these conditions were present. These findings align with studies by Legrand et al.[3] and Puntis et al.[14], which underscore the contribution of reflux and stricture to early growth impairment.

Importantly, Depoortere et al.[22] conducted a large, population-based prospective cohort study and found that at 1 year of age, 15% of patients with EA were undernourished and 19% showed stunting, with no significant catch-up growth observed between 6 and 12 months. These results reinforce the idea that the first year of life is a critical window for nutritional monitoring and intervention. They also emphasize the role of comorbidities such as low birth weight, prematurity, and associated anomalies, which were also present in a significant proportion of our cohort.

Similarly, Maan et al.[23] reported that 30% to 40% of children aged 1–5 years who had undergone EA/TEF repair were underweight, stunted, or wasted compared with healthy controls. Interestingly, they noted that children who underwent primary repair had better nutritional outcomes than those who had staged repairs—highlighting the influence of surgical strategy on growth. In our study, most patients underwent open primary repair, which may partly explain the positive long-term trends observed in older age groups.

Feeding difficulties are another major factor that contributes to growth delays in patients with EA. Studies have shown that these difficulties often persist into childhood and are multifactorial, involving dysmotility, aspiration, inflammation, and behavioral components.[6,13,14] Although our study did not formally assess feeding behavior, the presence of GER and stricture—both known contributors to feeding difficulties—likely played a role in early nutritional deficits.

Despite the relatively high rate of early complications, long-term growth outcomes in our study are encouraging. Patients aged 5-11 years and older than 11 years showed near-normal Z-scores for weight, height, and BMI, echoing the findings of other longitudinal studies that describe gradual catch-up growth.[24,25] Nevertheless, the absence of consistent catch-up growth in some subsets—particularly those with more complex cases or delayed surgery—remains a concern and justifies long-term multidisciplinary follow-up.

This study has several limitations that should be acknowledged. First, its retrospective design inherently limits the ability to control for confounding variables and introduces potential biases related to data completeness and accuracy. Second, the study was conducted at a single center, which may affect the generalizability of the findings to other populations or healthcare settings. Third, the sample includes patients treated over a relatively long time span, during which changes in surgical techniques, nutritional protocols, and follow-up practices may have occurred. This temporal heterogeneity could have introduced variability in outcomes that was not fully captured or adjusted for in the analysis. Although prematurity was assessed as a potential confounder through subgroup distribution testing, the sample size and sparse strata limited further multivariable adjustment, and residual confounding cannot be excluded. Additionally, in patients with VACTERL association or associated anomalies, growth-restricting genetic factors may be present.

Finally, imbalances in group size in some age comparisons (Table IV, Supplementary Table S2, Table V) and very small subgroups in others (e.g., n = 2 in Supplementary Table S3) represent a further limitation. These issues are inherent to the rarity of the condition and the retrospective nature of the cohort. Although statistical tests were applied with caution, results from these small subgroups should be interpreted as exploratory and descriptive. Additionally, although some continuous variables did not follow a normal distribution, we reported mean ± standard deviation in addition to median (Q1-Q3) to provide a comprehensive description of anthropometric outcomes. This decision,

discussed in the methods section, was based on the clinical relevance of extreme values, which were not considered outliers but rather part of the expected variability in this patient population.

In conclusion, our findings support the growing consensus that children with EA require early and long-term nutritional surveillance, especially during the first year of life. The inclusion of comorbidity screening and feeding assessments into follow-up protocols may allow for more personalized management. Further prospective, multicenter studies are needed to better characterize long-term growth trajectories and define optimal nutritional strategies for this complex population.

Supplementary materials

Supplementary materials for this article are available online at https://doi.org/10.24953/turkjpediatr.2026.6347

Ethical approval

The study was approved by Research Ethics Committee of the Community of Aragón (CEICA), with Institutional Review Board (IRB) (date: September 24, 2021, number: C.P.-C.I. PI21/400).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: PSA, PBR, CCB; data collection: PSA, PV, RFA, IRA; analysis and interpretation of results: PSA, CCB, PBR, RGR; draft manuscript preparation: PSA, CCB, PBR, RGR. All authors reviewed the results and approved the final version of 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

Frequency of gastroptosis and gastroparesis in children with treatment-resistant dyspepsia and duodenogastric reflux: a prospective study

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ABSTRACT

Background. Studies on gastroptosis and gastroparesis in children are limited. This prospective study aimed to evaluate the frequency of gastroptosis and gastroparesis and their association with duodenogastric reflux (DGR) and treatment-resistant dyspeptic symptoms in children.

Methods. The study evaluated pediatric patients aged 2-18 years with dyspepsia who underwent upper gastrointestinal endoscopy between March 2020 and June 2022. Fluoroscopy and gastric emptying scintigraphy were performed in 88 patients (50 with DGR and 38 with treatment-resistant dyspepsia).

Results. The mean age of the patients was 13.7±3.6 years, and 62 (70.5%) were girls. Gastroptosis was detected in 22 (25%) and gastroparesis in 24 (27%) of all 88 patients. Gastroptosis was present in 10 (20%) and gastroparesis in 20 (40%) of the 50 patients with DGR. Gastroptosis was present in 12 (32%) and gastroparesis in 4 (11%) of the 38 patients with treatment-resistant dyspepsia. Gastroparesis was more common in those with DGR (40%) than in those with treatment-resistant dyspepsia (11%) (p=0.09). Gastroptosis was also detected in 14 (58.3%) patients with gastroparesis. The median body mass index (BMI) z-score of those with gastroptosis was significantly lower than those without gastroptosis (p=0.002).

Conclusions. Gastroptosis and gastroparesis were frequently identified in children with treatment-resistant dyspeptic symptoms or DGR. These conditions should be considered and investigated in this patient population.

Key words: dyspepsia, duodenogastric reflux, fluoroscopy, gastroparesis, gastroptosis, scintigraphy.

Functional dyspepsia is a common gastrointestinal symptom with an overall prevalence of 7.6% in children.[1] According to the Rome IV criteria, functional dyspepsia is characterized by one or more bothersome symptoms, including postprandial fullness, early satiation, or epigastric pain or burning not associated with defecation. These symptoms should be present at least once a week, with symptom onset at least 6 months before diagnosis and the diagnostic criteria fulfilled during the last 3 months, after appropriate evaluation excludes another medical condition.[2] Pathophysiological factors causing dyspeptic symptoms include abnormal gastric accommodation, delayed gastric emptying, visceral hypersensitivity, gastrointestinal infections, *Helicobacter pylori* infection, psychological factors, duodenal increased sensitivity to acids and lipids, and duodenojejunal motility disorder.[3]

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Gastroptosis is characterized by the abnormal downward displacement of the stomach, which can lead to constipation, tenesmus, dyspepsia, belching, loss of appetite, nausea and vomiting.[4,5] Other than case reports, two studies have investigated the relationship between gastroptosis and dyspepsia. One study conducted in adults reported that dyspeptic symptoms were significantly less common in patients with gastroptosis.[6] In contrast, a pediatric study published by Tangul et al. demonstrated that alkaline gastroesophageal reflux is more frequently observed in gastroptosis cases and that its incidence increases with the severity of gastroptosis.[7] Gastroparesis is a gastric motility disorder characterized by postprandial epigastric pain, halitosis, bloating, postprandial fullness, weight loss, and vomiting.[8] In childhood, gastroparesis is extremely rare and mainly occurs in premature infants, when the gastrointestinal tract is immature or due to an allergy to cow's milk protein. The majority of gastroparesis cases are idiopathic or postviral. Delayed gastric emptying may be associated with diabetes mellitus, hypothyroidism, eosinophilic gastroenteropathy, celiac disease, cystic fibrosis, muscular dystrophy, or vagotomy.[9] Gastroparesis and gastroptosis can be easily misdiagnosed. In the presence of persistent dyspepsia in children, especially in girls, patients should be examined in detail for the possibility of gastroparesis. Delayed or misdiagnosed gastroparesis may lead to secondary gastroptosis.[4]

Duodenogastric reflux (DGR) is the reverse flow of duodenal fluid composed of bile acid, pancreatic secretions, and intestinal secretions into the stomach due to impaired antroduodenal motility and pyloric function. Inflammation and ulceration of the gastric mucosa and intestinal metaplasia in the stomach may result from DGR,[10] which causes not only reflux gastritis but also mucosal damage that can be related to esophagitis, gastric ulcers, and gastric and esophageal carcinoma.[11] The aim of this study was to evaluate the frequency of gastroptosis and gastroparesis and their association with DGR and treatment-resistant dyspeptic symptoms in children with dyspepsia who had either DGR or persistent symptoms despite treatment.

Materials and Methods

Ethical approval was obtained from the Clinical Research Ethics Committee of Gülhane Training and Research Hospital (Decision No. 2020/111, dated March 17, 2020), and the study adhered to the principles of the Declaration of Helsinki. A total of 920 children aged 2 -18 years with complaints of dyspepsia (patients with epigastric pain, bloating, postprandial fullness, early satiety, nausea, vomiting, burping, and epigastric burning) were evaluated at the Gülhane Training and Research Hospital Pediatric Gastroenterology Outpatient Clinic between March 2020 and June 2022. Gastroptosis and gastroparesis were investigated in 88 of 920 patients who underwent endoscopy (DGR = 50, treatment-resistant dyspepsia = 38). Patients were categorized according to their clinical presentation as either DGR or treatment-resistant dyspepsia, and gastroptosis and gastroparesis were evaluated as diagnostic outcomes within these groups.

Under deep sedation induced by an anesthetist, an upper gastrointestinal (UGI) tract endoscopy was performed by 2 pediatric gastroenterologists using an Olympus X260 scope (Olympus Optical Corporation, Japan). Biopsy samples from the esophagus, stomach, and duodenum were delivered to pathology in a formalin fixation solution. Biopsy specimens were stained with hematoxylin-eosin and evaluated by light microscopy. Given the lack of access to advanced diagnostic tools such as Bilitec 2000, the diagnosis of DGR was based on a combination of endoscopic, histopathological, and clinical findings. During endoscopy, patients with hyperemia, fragility, edema, bile acid pool, and solid bile wastes in the gastric mucosa (Fig. 1), together with histopathological findings including inflammation and foveolar

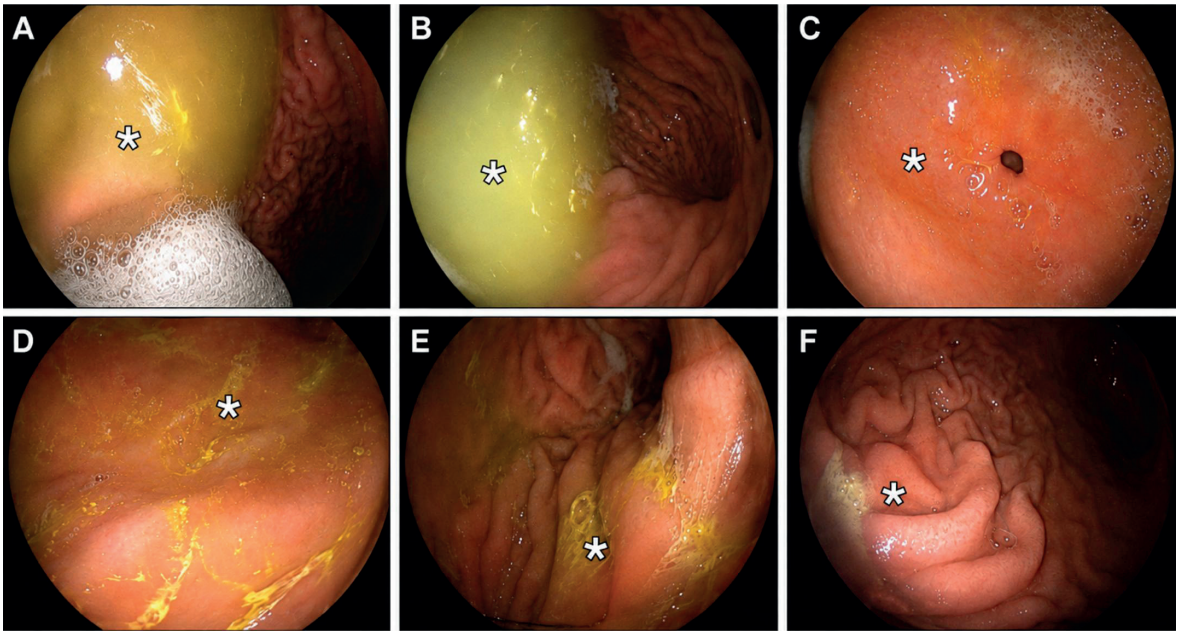

Fig. 1. Endoscopic findings in pediatric patients with duodenogastric reflux. Asterisks (*) indicate the representative endoscopic lesions. **A-B.** Presence of bile acid pool in the gastric mucosa. **C.** Antrum with hyperemic and edematous mucosa. **D-E.** Solid bile wastes adherent to the gastric mucosa. **F.** Corpus with hyperemic and edematous mucosa.

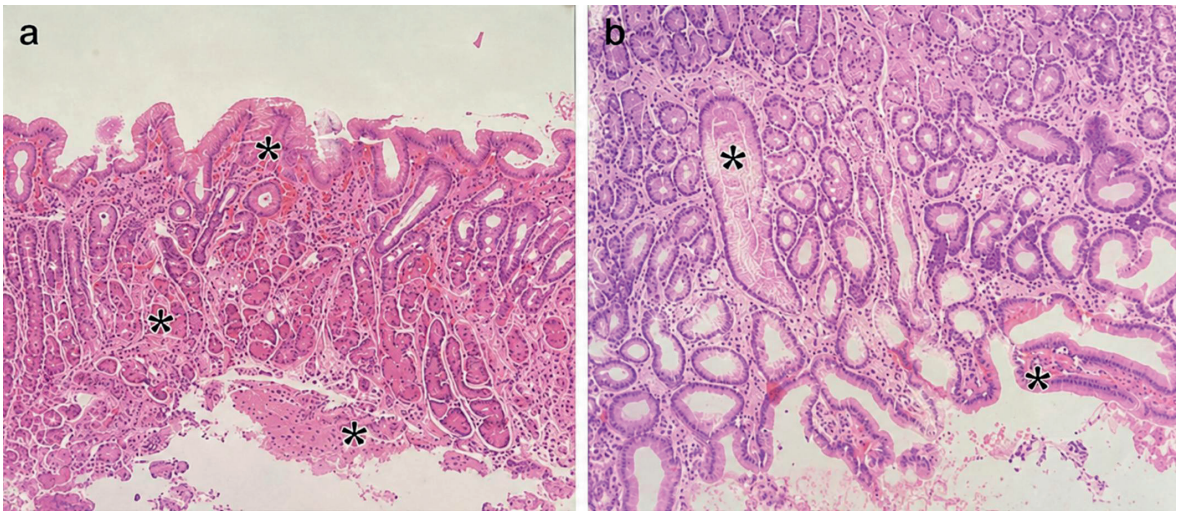

Fig. 2. Histopathological findings in pediatric patients with duodenogastric reflux. Asterisks (*) indicate the representative histopathological findings. **a.** Prominent vascular congestion in the lamina propria, foveolar hyperplasia on the surface, and mild fibrosis. **b.** Foveolar hyperplasia and mild chronic inflammation (H&E staining, ×100 magnification).

Cropped and adapted from Figure 2a-c in[12]: 12. Türker SN, Barış Z, Şeker NS, Aydemir Y. Histopathological differences in pediatric duodenogastric reflux: a comparative study. Eur J Pediatr 2025; 184: 343.

hyperplasia in gastric biopsies (Fig. 2), were evaluated as having DGR.[12] Histopathological findings were not considered diagnostic alone but were interpreted together with endoscopic bile-related findings and clinical presentation to support the diagnosis of DGR. Because a fasting period (8 hours) before the endoscopy can also lead to bile pooling in

the stomach, the mere detection of a bile pool was considered insufficient for the definition of DGR; the presence of solid bile wastes adherent to the stomach wall, and endoscopic and histopathological evidence of bile-related inflammation in the mucosa were also required.

For the purposes of this study, treatment-resistant dyspepsia was defined as persistence of dyspeptic symptoms despite at least 8 weeks of proton pump inhibitor (PPI) therapy. To detect underlying gastroptosis and gastroparesis, UGI fluoroscopy examinations and gastric emptying scintigraphy were performed in patients with treatment-resistant dyspepsia or in patients with DGR. Gastroptosis was diagnosed by UGI fluoroscopy either with barium or water-soluble iodinated contrast according to the evaluation of the radiologists (Fig. 3). In the UGI fluoroscopy examination, elongation of the stomach's greater curve down to the level of the iliac crests was considered gastroptosis.[13] Gastroparesis was diagnosed by gastric emptying scintigraphy performed using a standardized solid-phase radiolabeled meal consisting of technetium-99m sulfur colloid–labeled eggs (equivalent to two eggs), accompanied by bread and water, in accordance with established gastric emptying scintigraphy protocols. Gastric emptying time was considered delayed if there was retention > 90% 1 hour after the meal, > 60% 2 hours, and > 10% 4 hours after.[14]

The anthropometric measurements, including body mass index (BMI) z-scores, were obtained from the patients' medical records. BMI z-scores were calculated using the World Health Organization (WHO) growth assessment software.[15] Patients who underwent endoscopy for dyspepsia and were found to have gastric inflammation were treated with PPIs. Those diagnosed with DGR received a combination of PPI and ursodeoxycholic acid. Prokinetic treatment (domperidone) was added in selected patients with gastroptosis and/or gastroparesis who had persistent dyspeptic symptoms or DGR. However, treatment response was not assessed using a standardized symptom severity scoring system, which is acknowledged as a limitation of the study.

Statistical analysis

Statistical data were evaluated using the Statistical Package for the Social Sciences (SPSS) for Windows version 20.0. Descriptive statistics

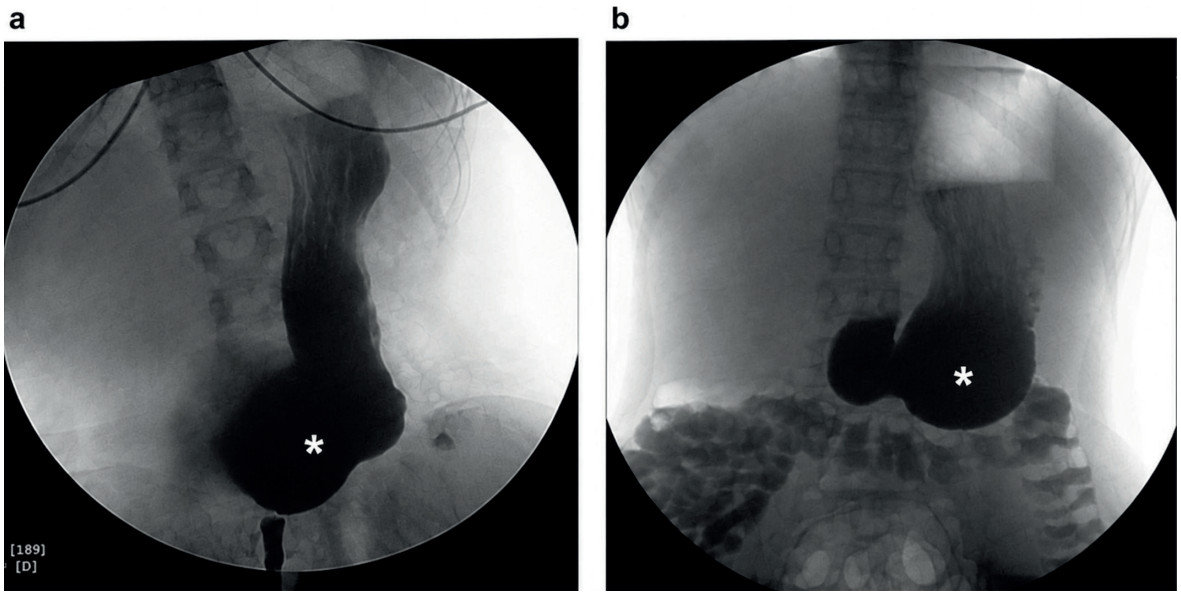

Fig. 3. Typical upper gastrointestinal fluoroscopy findings in pediatric gastroptosis. Asterisks (*) indicate the representative fluoroscopic findings. **a-b.** Elongation of the greater curvature of the stomach extending down to the level of the iliac crests.

were presented as numbers and percentages for categorical variables. Continuous variables were presented as mean ± standard deviation if normally distributed and as median (Q1–Q3) if the distribution was non-normal. The normality of numerical variables was assessed using the Kolmogorov–Smirnov test. Comparisons of normally distributed continuous variables were performed using the Student's t-test, whereas non-normally distributed variables were compared using the Mann–Whitney U test. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. A p value <0.05 was considered statistically significant.

Results

Gastroptosis and gastroparesis were investigated in 88 of 920 patients who underwent endoscopy with dyspepsia (DGR = 50, treatment-resistant dyspepsia = 38). The mean age of the patients was 13.7 ± 3.6 years, and 62 (70.5%) were girls. Gastroptosis was detected in 22 (25%) and delayed gastric emptying (gastroparesis) in 24 (27%) of all 88 patients. Gastroptosis was present in 10 (20%) and gastroparesis in 20 (40%) of the 50 patients with DGR. Gastroptosis was present in 12 (32%) and gastroparesis in 4 (11%) of the 38 patients with treatment-resistant dyspepsia. Gastroparesis was more common in those with DGR (40%) than in those with treatment-resistant dyspepsia (11%), (p = 0.09). (Table I). A notable overlap was observed between gastroptosis and gastroparesis, with gastroptosis present in 14 (58.3%) patients with gastroparesis.

The median BMI z-score of those with gastroptosis was significantly lower than those without (p = 0.002). There was no statistically significant difference in median BMI z- scores according to the presence of gastroparesis (p = 0.92) (Table II). While 12% of those with DGR were underweight according to their BMI z-score, there were no patients in the underweight category among those with treatment-resistant dyspepsia (p = 0.03). There was no significant difference between the mean ages according to the presence of gastroptosis (14.45 ± 3.05 vs. 13.52 ± 3.80 years, p = 0.38); however, the mean age of those with gastroparesis was significantly lower than those without (13.13 ± 1.95 vs. 14.48 ± 3.77 years, p = 0.03) and the mean age of those

Table I. The frequency of gastroptosis and gastroparesis among patient groups.

Variables	Duodenogastric reflux, n (%)	Treatment-resistant dyspepsia, n (%)	p-value
Upper gastrointestinal fluoroscopy			0.21
Normal	40 (80)	26 (68)	
Gastroptosis	10 (20)	12 (32)	
Gastric emptying scintigraphy			0.09
Normal	30 (60)	34 (89)	
Gastroparesis	20 (40)	4 (11)	

Chi-square test or Fisher's exact test, as appropriate.

Table II. Comparison of BMI z- scores of patients with gastroptosis or gastroparesis with those without.

Normal UGI fluoroscopy (n = 66)	Gastroptosis (n = 22)	
-0.505 (−0.928, 0.166)	-1.421 (−1.737, −0.584)	p=0.002
Normal gastric emptying scintigraphy (n = 64)	Gastroparesis (n = 24)	
-0.705 (−1.596, 0.013)	-1.085 (−1.647, 0.018)	p=0.920

Mann–Whitney U test. BMI z-scores given as median (Q1, Q3)
BMI: body mass index, UGI: upper gastrointestinal

with DGR was significantly higher than those without (14.68 ± 2.64 vs. 12.53 ± 4.38 years, p = 0.02). There was no statistically significant difference in the frequency of gastroptosis between girls and boys (16/62 [25.8%] vs. 6/26 [23.1%], p = 0.787). Similarly, the frequency of gastroparesis did not differ significantly between girls and boys (18/62 [29.0%] vs. 6/26 [23.1%], p = 0.567).

Discussion

Gastroptosis is infrequently reported in the literature, particularly in pediatric populations, and its true prevalence remains unclear.[16] Sukimo et al. reported that gastroptosis was seen in 12% of men and 43% of women.[17] In a study in which Kusano et al. screened approximately 12,000 people in 2 years, gastroptosis was found in 500 women and 167 men.[6] In our study, there was no significant difference between the frequency of gastroptosis according to age and sex, but similar to the literature, girls were the majority of patients with gastroptosis (16 girls, 6 boys).

It is believed that gastroptosis is due to the weakening and relaxation of the abdominal wall muscles, reduction of abdominal fat (especially the lesser omentum), and relaxation of the gastrohepatic and gastrocolic ligaments. The most important theory regarding its etiology is asthenic body structure and weak development of muscle and connective tissues (undifferentiated connective tissue dysplasia).[18,19] Consistent with this theory, our study found that children with gastroptosis had significantly lower BMI z-scores than those without, supporting the hypothesis that reduced nutritional status or body mass may play a role in the development or worsening of gastroptosis.

In an adult study, Kusano et al. investigated the relationship between gastroptosis and dyspepsia in the Japanese population and found that dyspeptic symptoms were significantly less common in patients with gastroptosis.[6] They hypothesized that since there is a close relationship between high BMI and gastroesophageal reflux disease, and patients with gastroptosis have lower BMIs than controls, subjects with gastroptosis monitor their weight and diet more carefully.[6] In contrast, our findings showed gastroptosis in 32% of children with treatment-resistant dyspeptic complaints, with significantly lower BMI z-scores compared to those without gastroptosis. This indicates that dietary modification alone may be insufficient in pediatric dyspepsia, particularly when gastroptosis coexists. Moreover, a recent pediatric study demonstrated that alkaline reflux was more prevalent in children with gastroptosis, and its frequency increased with the severity of gastroptosis.[7] In our cohort, gastroptosis was present in 20% of patients with DGR, supporting a potential association between gastric displacement and alkaline reflux.

Gastroparesis is a gastric motility disorder characterized by delayed gastric emptying in the absence of mechanical obstruction, for which the gold standard for diagnosis is gastric emptying scintigraphy.[20] Large pediatric cohorts report a roughly equal sex distribution,[21] consistent with our findings. While gastroparesis and functional dyspepsia are noticed more frequently in adults, the overall prevalence in children is unknown.[22] The clinical presentations of patients with gastroparesis and functional dyspepsia are significantly similar.[23] Gastric motility disorders, including delayed gastric emptying and reflux of duodenal contents into the stomach, are known to cause significant clinical problems.[24] In our study, gastroparesis was identified in 11% of children with treatment-resistant dyspeptic symptoms. Notably, it was more prevalent in patients with DGR, being detected in 40% of these cases. These findings suggest that underlying gastric motility disturbances may contribute to the pathophysiology of DGR and persistent dyspeptic symptoms in children.

It has been suggested that delayed or misdiagnosed gastroparesis may contribute to the development of gastroptosis. The coexistence of gastroptosis and gastroparesis has been shown in only one case in the literature.[4] In our study, gastroptosis was detected in 58.3% of patients with gastroparesis. This high rate of coexistence suggests a potential pathophysiological link between the two conditions, which has not previously been demonstrated in a pediatric population.

Nowadays, surgical treatment of gastroptosis is limited to a small number of complicated cases. Current treatment includes prokinetic drugs and adequate nutrition.[18] Management of gastroparesis includes dietary modifications (small volume and frequent meals with low content in fat and non-digestible fibers), medical treatments (prokinetic drugs, antiemetics, PPIs, intrapyloric injection of botulinum toxin) and surgical interventions.[20] In our study, prokinetic treatment with domperidone was used in selected patients with gastroptosis and/or gastroparesis who had persistent dyspeptic symptoms or DGR. These findings indicate that identifying underlying gastroptosis or gastroparesis may have practical implications for the clinical management in children with persistent symptoms. However, treatment response was assessed clinically during follow-up visits without the use of a standardized symptom severity scoring system, which represents an important limitation of the study.

The most reliable of the currently available tools for excessive bile reflux detection is the recent Bilitec 2000 method (Synectics Medical) consisting of a fiberoptic probe connected to a portable bilimeter which allows 24 h continuous endoluminal monitoring of bilirubin exposure based on its spectrophotochemical properties.[25] The other limitation of our study is that this method could not be used to define DGR in our study, and the endoscopic and histopathologic findings may not fully reflect the 24-hour variability of DGR.

In conclusion, gastroptosis and gastroparesis were frequently identified among children with treatment-resistant dyspeptic complaints or DGR. Evaluating these conditions in this patient population may improve diagnostic accuracy, facilitate appropriate management, and help reduce complications related to delayed diagnosis.

Ethical approval

The study was approved by Clinical Research Ethics Committee of Gülhane Training and Research Hospital (date: March 17, 2020, number: 2020/111).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: MA; data collection: MA, EDB, CFÖ, ND; analysis and interpretation of results: MA, ND; draft manuscript preparation: MA, NB. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Case Report

Phenotypic characteristics and clinical management of Alagille syndrome with multiple intracranial aneurysms: a case report and literature review

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ABSTRACT

Background. Alagille syndrome (ALGS) is an autosomal dominant multisystem developmental disorder associated with *JAG1* and *NOTCH2* mutations. Although vascular involvement is recognized, life-threatening intracranial hemorrhage as the initial presentation is extremely rare.

Case Presentation. A 5-year-old male presented with a severe headache and was diagnosed with intracerebral and subarachnoid hemorrhage caused by multiple ruptured intracranial aneurysms. Genetic testing confirmed a pathogenic *JAG1* mutation, establishing the diagnosis of ALGS. The patient, who had known aortic stenosis, developed infective endocarditis—raising the possibility that infection was driving the aneurysms. After two microsurgical craniotomies, he ultimately died of multi-organ failure.

Conclusions. This case highlights a rare presentation of ALGS involving acute rupture of multiple intracranial aneurysms, complicated by cardiac malformation and infective endocarditis, with newly formed aneurysms highly suspected to be infection-driven. ALGS should be considered in young children presenting with early intracranial hemorrhage, particularly when cardiac anomalies coexist. Early multidisciplinary intervention may prevent the catastrophic sequelae of ALGS-associated intracranial aneurysms.

Key words: Alagille syndrome, multiple intracranial aneurysms, intracranial hemorrhage, infective endocarditis, infectious intracranial aneurysms.

Alagille syndrome (ALGS) is a rare autosomal dominant, multisystem developmental disorder linked to mutations in *JAG1* and *NOTCH2*.[1] Classic features include sparse or hypoplastic intrahepatic bile ducts, congenital heart defects, spinal deformities, characteristic facial features, ocular manifestations, and vascular anomalies.[1] The incidence is reported to ranger from 1:30,000 to 1:100,000, with mortality rates of 10–20 %.[2,3] In addition to severe hepatic and cardiac disease, intracranial hemorrhage is a major cause of death. Isolated reports have associated ALGS with multiple intracranial aneurysms. We describe the diagnostic and therapeutic course of a 5-year-old patient with ALGS and multiple intracranial aneurysms and discuss the genetic profile, possible pathogenesis, and management strategies for this rare comorbidity.

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Case Presentation

A 5-year-old right-handed boy presented with coma (Glasgow Coma Scale score of 9). The computed tomography angiography (CTA) showed a right frontoparietal hematoma of >35 mL and a right middle cerebral artery (MCA) aneurysm (Fig. 1a and Fig. 1b); clot evacuation and clipping were performed within 4 hours, and he was discharged 1 month later.

Two weeks later, his headache recurred and progressed to deep coma with herniation. A left hematoma of >25 mL and a left MCA aneurysm (Fig. 1c and Fig. 1d) prompted emergency craniectomy with clipping. Given the recurrent intracranial multi-aneurysmal hemorrhage in a child accompanied by cardiac pathology (aortic stenosis) and aortic valve vegetations (Fig. 1e and Fig. 1f), a multisystem disorder was suspected. The foremost

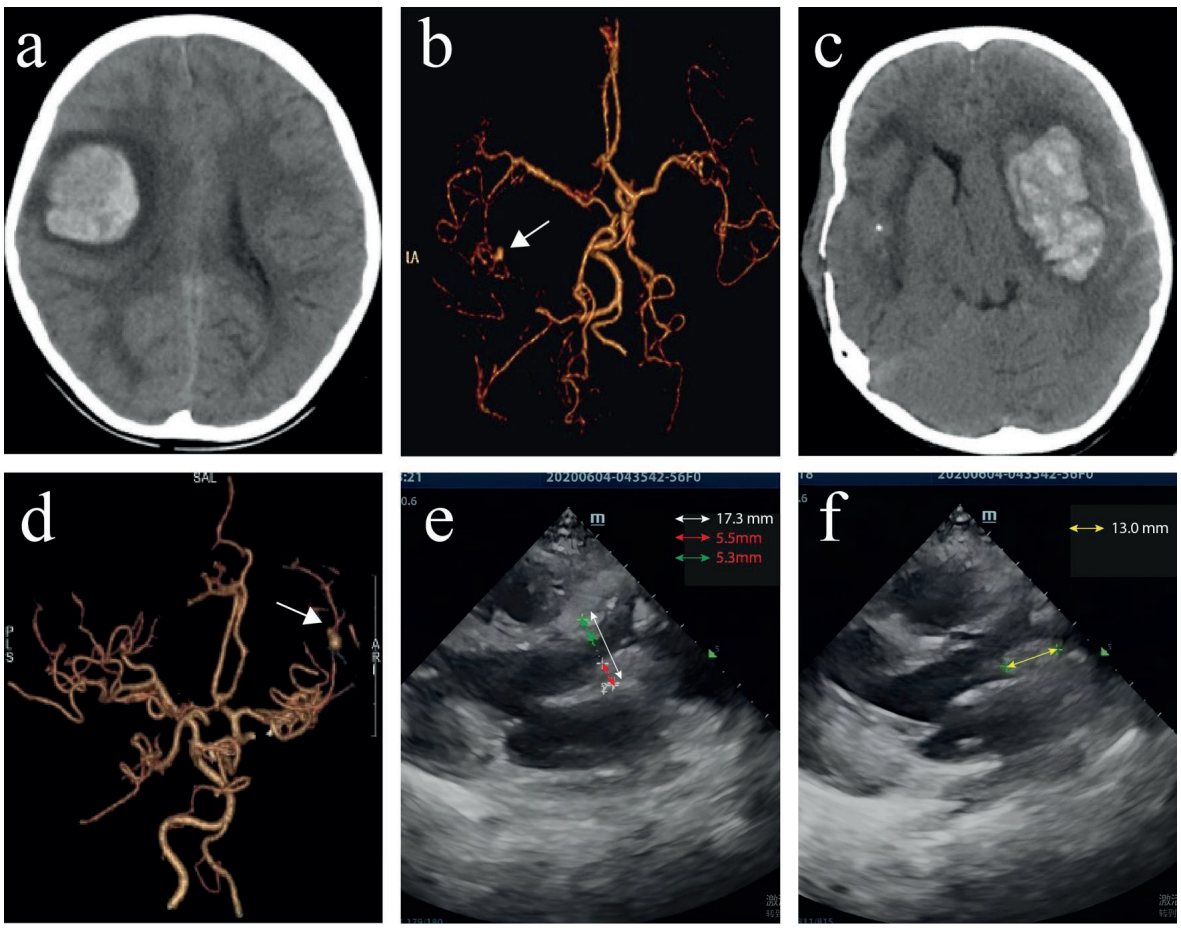

Fig. 1. a) Computed tomography (CT) showing the hematoma in the right frontoparietal lobe. **b)** CT angiography showing a right MCA aneurysm (arrow). **c)** CT showing the hematoma in the left frontoparietal lobe. **d)** CTA showing a left MCA aneurysm (arrow). **e, f)** Echocardiography images demonstrating that the right coronary cusp and non-coronary cusp of the aortic valve are both thickened, with vegetations present on the aortic valve, resulting in significantly restricted valve opening. The white double arrow (e) indicates the anteroposterior diameter of the aortic root (17.3 mm). The red double arrow (e) marks the distance from the non-coronary cusp to the posterior aortic wall (5.5 mm), i.e., the vegetation thickness. The green double arrow (e) indicates the distance from the right coronary cusp to the anterior aortic wall (5.3 mm). The yellow double arrow (f) indicates the vegetation length (13.0 mm). The aortic valve opening diameter is 6.5 mm (calculated as 17.3 mm - 5.5 mm - 5.3 mm).

consideration was infective endocarditis (IE) superimposed on congenital heart disease, most likely a dysplastic aortic valve or coarctation, while connective-tissue disorders and vasculitides remained in the differential. Inflammatory markers and the autoimmune antibody screen were unremarkable, shifting suspicion toward a heritable connective tissue disorder. However, the combination of aortic stenosis (a cardiac lesion less typical of classic connective tissue disorders such as Marfan or Ehlers-Danlos syndromes) and recurrent aneurysmal hemorrhage in a child raised the possibility of other genetic syndromes. Among these, Alagille syndrome (ALGS), caused by pathogenic variants in *JAG1* or *NOTCH2*, was considered, as it can present with congenital heart defects (including aortic stenosis and peripheral pulmonic stenosis), intracranial aneurysms, and multisystem involvement. Although the patient lacked overt cholestasis or characteristic facial features, the absence of inflammatory and autoimmune markers, together with the specific cardiac and vascular findings, prompted targeted *JAG1* sequencing. Peripheral blood DNA samples were obtained from the patient and both parents for Sanger sequencing analysis. The results revealed that the patient harbored a heterozygous frameshift variant NM_000214.2:c.3218dupT (p.(Ser1074Glufs*35)) in *JAG1*, which was absent in both parents, indicating that this was a pathogenic variant of the gene (Fig. 2). Post-operative fever and blood cultures positive for *Streptococcus viridans*, together with valvular vegetations on echocardiography (Fig. 1e and Fig. 1f), confirmed infective endocarditis. The *JAG1* mutation and the cardiac findings satisfied the diagnostic criteria for ALGS. After antibiotics and rehabilitation, right-sided strength recovered, and the child could walk.

Three weeks after the second discharge, a third hemorrhage was managed conservatively with external ventricular drainage. A fourth hemorrhage followed, leaving the patient in deep coma with high fever and rigid limbs; cerebrospinal fluid culture grew *Acinetobacter baumannii*, and multi-organ failure ensued, leading to death.

The study was approved by the appropriate ethics review board (approval number: KYLL-2025-2608). Informed consent for publication was obtained from the patient's legal guardian.

Discussion

The *JAG1* gene encodes Jagged1, a critical ligand in the Notch signaling pathway, whose dysfunction leads to multisystem developmental disorders such as ALGS.[4] Located at 20p12.2, this gene regulates cell fate determination and organogenesis during embryonic development by binding to Notch receptors (primarily Notch2).[5] Approximately 94% of patients with ALGS carry pathogenic *JAG1* variants, with haploinsufficiency representing the core pathogenic mechanism.[4]

JAG1 pathogenic variants are diverse, with about 70% being truncating variants (nonsense, frameshift, splice-site) that reduce functional protein by 50% through nonsense-mediated mRNA decay.[6,7] The present c.3218dupT (p.(Ser1074Glufs*35)) frameshift variant falls into this category. Missense variants account for approximately 30%, mainly affecting protein folding and stability.[7] No mutational hotspots exist, but pathogenic variants cluster in functional domains such as the Delta-Serrate-LAG-2 (DSL) domain and epidermal growth factor (EGF)-like repeats.[7]

Clinical phenotypes of *JAG1* pathogenic variants demonstrate highly variable expressivity and incomplete penetrance. Classic ALGS involves five systems: the liver (cholestasis), heart (pulmonary stenosis), skeleton (butterfly vertebrae), eyes (posterior embryotoxon), and characteristic facial features.[8] Family members carrying identical variants may exhibit markedly divergent severity, including asymptomatic carriers, which may be attributable to genetic background modifiers and environmental factors.[4] Beyond classic ALGS, *JAG1* variants can cause non-syndromic

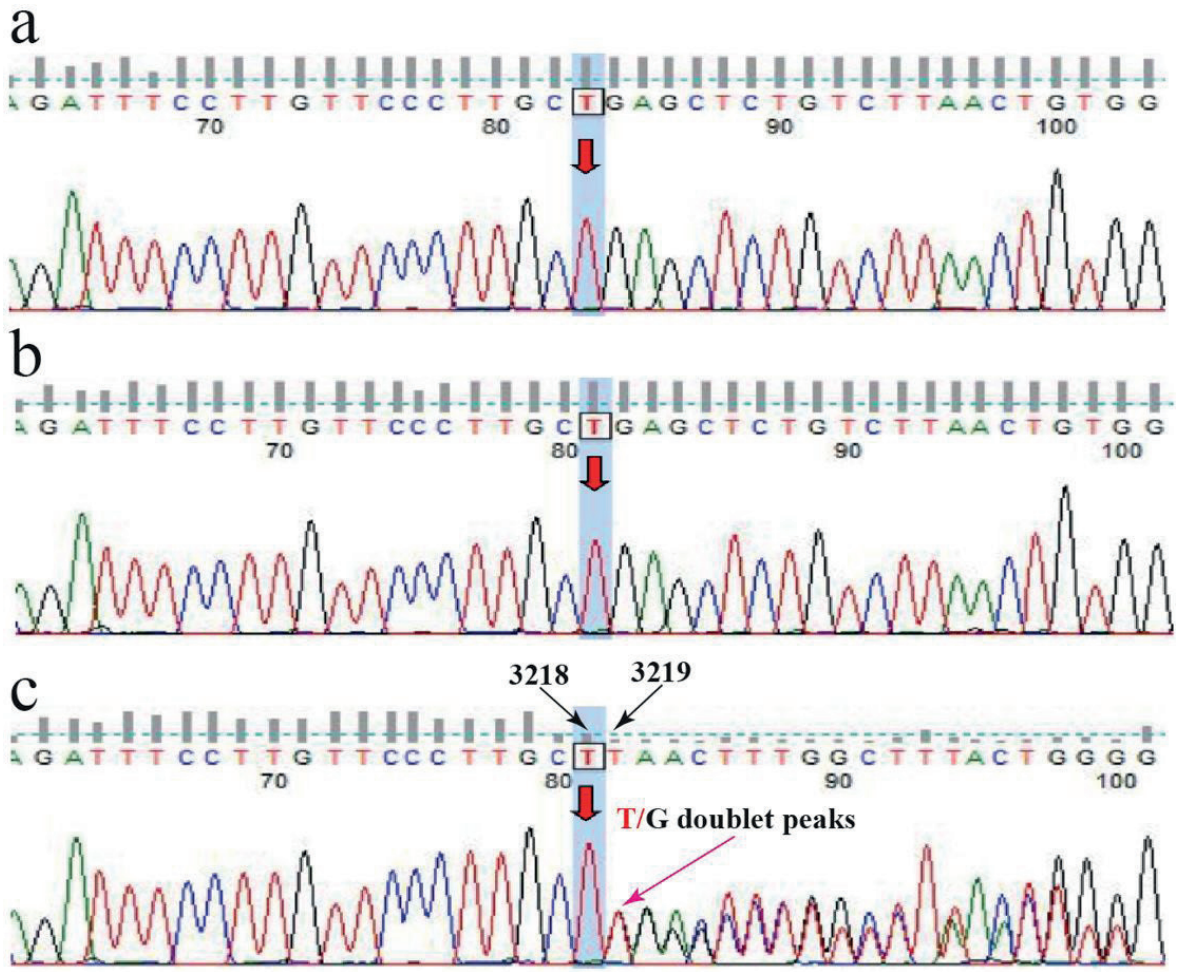

Fig. 2. Sanger sequencing chromatograms of the *JAG1* gene.

(a, b) Parents: wild-type sequence. At position c.3218, a single T peak is present; at position c.3219, a homozygous G peak is observed. No c.3218dupT mutation is detected.

(c) Proband: heterozygous frameshift mutation c.3218dupT (p.(Ser1074Glufs*35)). Due to the T duplication at c.3218 (marked "3218"), the expected homozygous G at c.3219 is replaced by a T/G doublet peak (labeled "T/G doublet peaks" and marked "3219"), indicating a reading frame shift from this point onward.

presentations including isolated bile duct paucity and specific congenital heart defects, though cerebrovascular involvement remains rarely reported.[9]

A loss of *JAG1* expression in endothelial cells may inhibit Notch signaling and disrupt angiogenesis.[10] Homozygous *JAG1*-knockout mice exhibit embryonic lethality and severe cardiovascular malformations, highlighting the critical role of *JAG1* in vascular development.[11,12] Under normal physiological conditions, endothelial *JAG1* drives the recruitment of vascular smooth muscle cells and pericytes.[13] Its absence results in flawed vessel wall architecture and irregular luminal surfaces, predisposing patients to aneurysm formation, although the detailed molecular mechanisms remain to be fully elucidated. Previous reports[14-16] indicate that 1.1% of individuals with ALGS develop intracranial aneurysms, compared with 0.8% to 5% in the general pediatric population, where aneurysms are typically large or giant saccular lesions—the leading cause of aneurysmal subarachnoid hemorrhage in children. This combination significantly increases the risk of hemorrhagic events in ALGS patients, with

Table I. 17 patients with Alagille syndrome and intracranial aneurysms.

Authors, years	Sex	Age (years)	Location of Intracranial Aneurysms	Other comorbidities	Hunt-Hess Grade	Treatment Modality	Outcome
Moreau et al., 1999[28]	M	17	Right C4	CD	0	Endovascular therapy	Survived
Kamath et al., 2004[14]	NA	NA	BA	CD, Jaundice, FD	0	NA	Survived
	NA	NA	BA	CD, Jaundice, FD, AS	0	NA	Survived
	NA	NA	Left MCA	CD, Jaundice	5	NA	Died
Schlosser et al., 2004[26]	F	30	Right C4, C5, Left C5, C6, BA	family history, Dysplasia of the bile duct, FD, AS, aneurysms of the right renal artery	5	Craniotomy clipping	Survived
Cowan et al., 2004[27]	M	23	BA, Left C7	Aortic dissection, AS	2	Craniotomy clipping	Survived
Emerick et al., 2005[25]	F	20	Left MCA	PS, IDDM, Chronic renal insufficiency, Cholestasis, FD, CD	5	NA	Died
	F	11	BA	Cholestasis, CD, FD	0	NA	Survived
	F	1.7	Right C5×2	CD, FD, MMD (Bilateral ICA and MCA stenosis)	0	NA	Survived
Tumialán et al., 2006[24]	F	21	BA	Ascending aortic aneurysm, Jaundice, CD, FD	0	Endovascular therapy	Died
Gaba et al., 2008[23]	F	28	Right Vertebrobasilar Junction	Jaundice, CD, FD, MMD (CAS)	2	Endovascular therapy	Survived
O'Connell et al., 2012[22]	F	17	Right ICA, Left SCA	Cholestasis, PS, FD	2	Endovascular therapy	Survived
Doberentz et al., 2015[18]	F	25	BA	Liver transplantations, FD, PS, Vertebral anomalies	5	NA	Died
Pavanello et al., 2015[21]	F	10	BA	Dysplasia of the bile duct, FD, retinitis pigmentosa, MMD (CAS), PS	0	Endovascular therapy	Survived
Fiorda-Diaz et al., 2017[20]	F	17	Left PCoA	Tetralogy of Fallot, PS	2	Endovascular therapy	Survived
Wali et al., 2021[19]	M	11	Left MCA	Pancytopenia, peripheral pulmonary stenosis	0	Craniotomy clipping	Survived
Present case	M	5	Left MCA, Right MCA	AS	4	Craniotomy clipping	Died

Hunt-Hess Grade: Grade 0: Unruptured aneurysm; Grade 1: Asymptomatic or mild headache only, without meningeal irritation signs and neurological deficits; Grade 2: Moderate to severe headache, with meningeal irritation signs and cranial nerve palsies; Grade 3: Consciousness disorder, with focal neurological signs; Grade 4: Coma, with severe hemiplegia, and early decerebrate rigidity or autonomic dysfunction; Grade 5: Deep coma, decerebrate rigidity, moribund state.
ACA, anterior cerebral artery; ACoA, anterior communicating artery; AS, aortic stenosis; CAS, carotid artery stenosis; CD, cardiac disease; FD, facial dysplasia; F, female; ICA, internal carotid artery; IDDM, insulin dependent diabetes mellitus; M, male; MCA, middle cerebral artery; MMD, moyamoya disease; NA, not available; PCoA, posterior communicating artery; PS, pulmonary stenosis.

bleeding rates ranging from 9% to 16% and mortality rates reaching as high as 25% to 67%.[2,14,17,18]

As of 2025, we reviewed 12 published studies on ALGS complicated by intracranial aneurysms.[14,18-28] Including the present case, a total of 17 patients were analyzed in this literature summary (Table I). Among the 14 cases with available data on sex and age, the male-to-female ratio was 4:10, with a mean age of 16.91 ± 8.38 years (ranging from 1.7 to 30 years); notably, 57.14% were minors. Out of the 17 cases, 5 patients (29.41%) presented with multiple intracranial aneurysms. In total, 25 aneurysms were identified: 10 in the internal carotid artery (including 1 posterior communicating artery aneurysm), 5 in the middle cerebral artery, and 10 in the basilar artery (including 1 vertebrobasilar junction and 1 superior cerebellar artery aneurysm). Nine patients (52.94%) experienced aneurysmal rupture, including 1 case that occurred postoperatively, and 5 patients (29.41%) died. Previous reports[14] indicate that 34% of patients with ALGS succumb to vascular complications. All 17 patients had associated cardio- or cerebrovascular pathology: 3 (17.65%) had moyamoya disease, and 10 (58.82%) had arterial stenosis. Furthermore, most children with ALGS have congenital heart disease—most commonly pulmonary stenosis, coarctation of the aorta, and Tetralogy of Fallot. Aortic coarctation has been established as a risk factor for cerebral aneurysm formation, observed in 0.19% to 1.9% of adults with unruptured aneurysms and 4.8% in those with ruptured aneurysms.[27,29]

The primary surgical approaches for intracranial aneurysms include endovascular therapy, microsurgical clipping, and combined procedures.[30,31] The selection of treatment is influenced by several factors, including the aneurysm's type, location, size, morphology, rupture status, the presence and volume of associated intracranial hematoma, the patient's overall systemic condition, and the available local technical expertise.[30,32,33]

These same criteria apply to aneurysms related to ALGS. Among the 9 cases of ALGS reported in previous studies[19-24,26-28], 66.7% (6 cases) were treated with endovascular methods, while 33.3% (3 cases) underwent clipping. The endovascular group demonstrated a survival rate of 83.33% (5 out of 6), with a mortality rate of 16.67% (1 out of 6). In contrast, the clipping group achieved a 100% survival rate (3 out of 3). In our case, both episodes of aneurysm rupture were accompanied by large intracerebral hematomas, providing a clear indication for open surgery. Additionally, both aneurysms originated from the middle cerebral artery, which led us to opt for microsurgical clipping. Regrettably, the child ultimately succumbed to the combined effects of recurrent hemorrhage and sepsis.

ALGS is a multisystem disorder that necessitates a thorough systemic evaluation when managing intracranial aneurysms in affected patients. This should include assessments of cardiac, hepatic, renal, and ocular function, as well as a spinal radiography and an evaluation of nutritional status and developmental levels. Ursodeoxycholic acid is recommended for the treatment of jaundice, and liver transplantation should be considered for patients with end-stage liver disease.[2,34] Most vertebral anomalies and ocular manifestations do not require surgical intervention.[34] Given that biliary stasis-related vitamin K malabsorption or decompensated liver disease can trigger coagulopathy, coagulation tests are essential.

In this case, intracranial aneurysms and cerebral hemorrhage were accompanied by aortic stenosis and IE. A fusiform aneurysm developed within days, likely due to emboli from IE vegetation (Ando et al.[35] reported rupture within 35 days). In patients with congenital heart disease complicated by infective endocarditis (IE), 2%–9% develop infectious intracranial aneurysms (IIAs), and once these rupture, mortality exceeds 80%.[36,37] IE is a bacterial infection of the endocardium—usually the valves—and one of its most feared complications is the formation of septic emboli.[38] These emboli

can dislodge and disseminate throughout the systemic circulation; when they reach cerebral vessels, they directly invade the wall and incite a local inflammatory response that degrades the vascular matrix, weakening the wall and producing a focal, pathological dilatation—an infectious cerebral aneurysm.[39,40] Such aneurysms are exquisitely fragile and prone to catastrophic intracranial hemorrhage. Although uncommon in the pediatric population, IIAs represent a severe cerebrovascular complication of IE, accounting for roughly 0.5–6.5% of all intracranial aneurysms in children.[39] In this context, the vegetations on the aortic valve are the hallmark of IE, and the infection can also distort valvular anatomy, leading to aortic stenosis or insufficiency.[41,42] When surgery is required to eradicate the infected valve, the presence of a concurrent intracranial aneurysm makes the timing and approach extremely challenging. Treatment for IE should combine antibiotics with surgery when necessary, with the goals of eradicating pathogens, preserving valve function, and preventing sudden death.

The limitations of this study include the fact that the marked phenotypic variability of ALGS precludes determining the association between this variant and the severity of the cerebrovascular phenotype from a single case. The coexistence of infective endocarditis in the patient makes it difficult to disentangle the relative contributions of *JAG1*-related vasculopathy and infectious factors to aneurysm formation.

In summary, ALGS should be considered in children who present with intracranial hemorrhage or aneurysms, especially when congenital cardiac anomalies coexist. If IE is present, vigilance for the occurrence of IIAs is warranted. Immediate antimicrobial therapy should be initiated, and surgical intervention performed when necessary, to reduce rupture risk and improve survival.

Ethical approval

The study was approved by Ethics Committee of Ningxia Medical University General Hospital (date: November 21, 2025, number: KYLL-2025-2608). Before the commencement of the study, informed consent was obtained from the patient's legal guardian, who also consented to the release of the patient's identifiable information.

Author contribution

The authors confirm contribution to the paper as follows: : Study conception and design: YW, YS; data collection: YW, YS, JC; analysis and interpretation of results: DH, ZY, DW; draft manuscript preparation: YW, YS. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Case Report

Hirschsprung's disease and a rare mutation of the *PIGO* gene: Mabry syndrome

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ABSTRACT

Background. Mabry syndrome is a very rare condition characterized by cognitive impairment, distinctive facial features, hypotonia, elevated alkaline phosphatase (ALP) levels in the blood (hyperphosphatasia), and recurrent generalized tonic-clonic seizures. It can be accompanied by gastrointestinal anomalies such as Hirschsprung's disease (HD). In this study, we aim to present a case of hyperphosphatasia with impaired intellectual development syndrome 2 (HPMRS2) from Türkiye, featuring a novel homozygous p.Arg445Pro variant in the *PIGO* gene, occurring in association with HD.

Case Presentation. A two-year-old male patient was referred to the pediatric neurology clinic with decreased responsiveness to the environment, lack of trunk control, and failure to respond to his name. ALP value was 613 IU/L. No pathology was detected in metabolic tests, vitamin D levels, or cranial magnetic resonance imaging, and electroencephalography (EEG). At 11 months of age, he had a generalized tonic-clonic seizure without fever. Since no abnormalities were detected in chromosome analysis and array analysis, whole exome sequencing (WES) was performed. A homozygous mutation was detected in the *PIGO* gene (NM_032634.4): c.1334G>C (p.Arg445Pro). Sanger analysis revealed heterozygous carrier status in both parents. The patient had constipation that was unresponsive to medical treatment since birth. Physical examination revealed abdominal distension. Rectal examination revealed an explosive discharge of gas and stool. A rectal biopsy was performed. The pathology result was ganglion-negative, and the patient was diagnosed with HD. After definitive surgery, spontaneous defecation has been achieved during follow-up, except for rare episodes of enterocolitis.

Conclusions. It should be remembered that Mabry syndrome can be accompanied by gastrointestinal anomalies, primarily HD. This case highlights the increased phenotypic variability associated with *PIGO* mutations and demonstrates the importance of genetic assessment in atypical neurodevelopmental conditions.

Key words: seizures, constipation, Hirschsprung's disease, Mabry syndrome, child.

Mabry syndrome, which is a very rare condition, is also known as hyperphosphatasia with impaired intellectual development syndrome-2 (HPMRS2). Its metabolic pathophysiology is based on glycosylphosphatidylinositol (GPI) deficiency. The clinical presentation often includes intellectual developmental delay, marked hypotonia, delayed walking, hypertelorism, and facial dysmorphism characterized by long palpebral fissures. Seizures are frequently recurring generalized tonic-clonic seizures accompanied by loss of consciousness, and are often unresponsive to single medical therapy. Rarely, cardiac and gastrointestinal (anal atresia, Hirschsprung's disease) anomalies may accompany. Serum alkaline phosphatase (ALP) levels are significantly elevated in most patients, and

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hyperphosphatasemia is the main biochemical marker of Mabry syndrome.[1-3]

In this study, we aim to report a rare case of HPMRS2 in a Turkish patient, identified with a novel homozygous p.Arg445Pro variant in the *PIGO* gene. The clinical phenotype is characterized by hypotonia, refractory epilepsy, and Hirschsprung's disease (HD). This report seeks to expand the known clinical phenotypic diversity associated with this syndrome.

Case Presentation

A nine-month-old male patient was admitted to the pediatric neurology clinic with complaints of delayed head control, lack of body control without support, failure to respond to his name, decreased eye tracking, and chronic constipation. His prenatal and natal history was unremarkable, and the baby was born at term with a birth weight of 2900 grams. From the neonatal period, the patient had severe constipation and required rectal stimulation for defecation. Spontaneous defecation was not observed, and progressive abdominal distension was recorded during infancy. Physical examination revealed facial dysmorphism (micrognathia, wide and flat nose, long philtrum, and low-set ears) and generalized hypotonia. No organomegaly was detected. At one year of age, the patient's measurements were as follows: length 70 cm (10th–25th percentile), weight 7.6 kg (3rd–10th percentile), and head circumference 44 cm (10th percentile).

At 11 months of age, he had an afebrile generalized tonic-clonic seizure. No abnormalities were observed on electroencephalography (EEG). Levetiracetam was initiated after seizure recurrence during drug-free follow-up. However, seizures persisted, and the medication dose was adjusted to 60 mg/kg/d. Serum ALP levels were found to be elevated at 613 IU/L (reference range 0–240 IU/L). There was no vitamin D deficiency, which could cause elevated ALP levels. Metabolic tests, including those for liver disease and increased bone metabolism, were also normal. The patient's forearm radiographs showed no abnormalities. The hand radiograph revealed hypoplasia in the distal phalanx of the 5th finger (Fig. 1). Cranial magnetic resonance imaging revealed no pathology. Since no abnormalities were detected in chromosome analysis and array analysis, whole exome sequencing (WES) was performed. A homozygous mutation was detected in the *PIGO* gene (NM_032634.4): c.1334G>C (p.Arg445Pro). Sanger sequencing revealed heterozygous carrier status in both parents.

The Ankara Developmental Screening Inventory (AGTE) was administered at 18 months of age. Developmental age equivalents were 12 months in the Language–Cognitive domain, 14 months in the Fine Motor domain, 14 months in the Gross Motor domain, and 12 months in the Social–Self-Care domain. The patient was referred to the pediatric surgery clinic with complaints of constipation unresponsive to medical treatment. Physical examination revealed abdominal distension, but the abdomen was soft. Rectal examination revealed an explosive discharge of gas and stool. An upright abdominal X-ray showed that the pelvis contained almost no intestinal gas, but there were dilated bowel loops (Fig. 2). Contrast-enhanced colonography demonstrated a transition zone suggestive of HD (Fig. 3). A rectal biopsy confirmed the absence of ganglion cells in the submucosal plexus, and the patient was diagnosed with HD (Fig. 4). The aganglionic segment was limited to the distal sigmoid colon. The patient subsequently underwent transanal endorectal pull-through surgery. Histopathological examination of the resected specimen confirmed the aganglionic distal segment and normal ganglion cells in the proximal bowel. During follow-up, the patient achieved spontaneous defecation, except for rare episodes of enterocolitis.

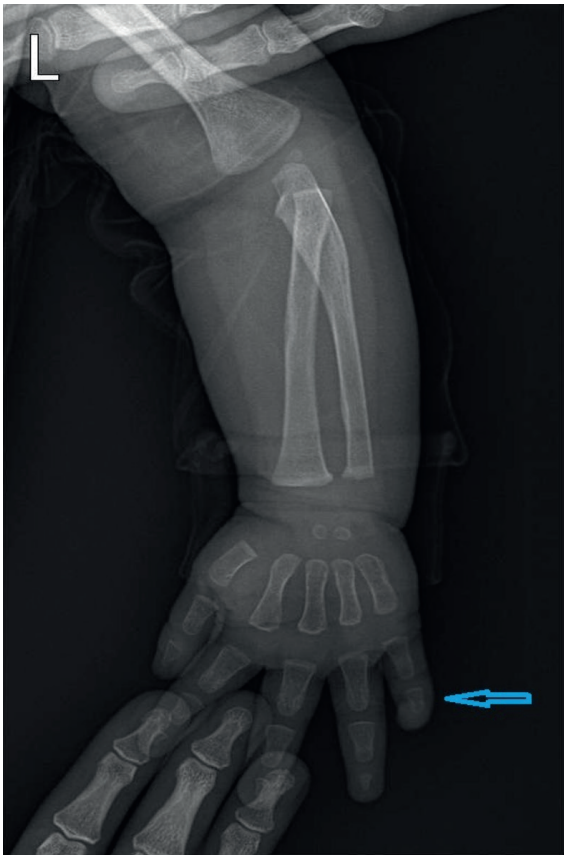

Fig. 1. In an X-ray obtained at the age of 9 months, the forearm is normal, but hypoplasia of the distal phalanx of the 5th finger of the hand is noted (arrow).

Informed consent for the publication of this case report was obtained from the patient's parents. However, clinical photographs could not be included because parental consent for the publication of facial images could not be obtained.

Discussion

Mabry syndrome is a rare, autosomal recessive disease characterized by moderate/severe psychomotor developmental delay, refractory seizures, facial dysmorphism, brachytelephalangy, and hyperphosphatasemia.[1,2] It develops as a result of mutations in genes that are involved in the biosynthesis of GPI anchors. The biosynthesis, protein binding, maturation, and intracellular transport of GPI anchors involve a complex process involving more than 30 genes.

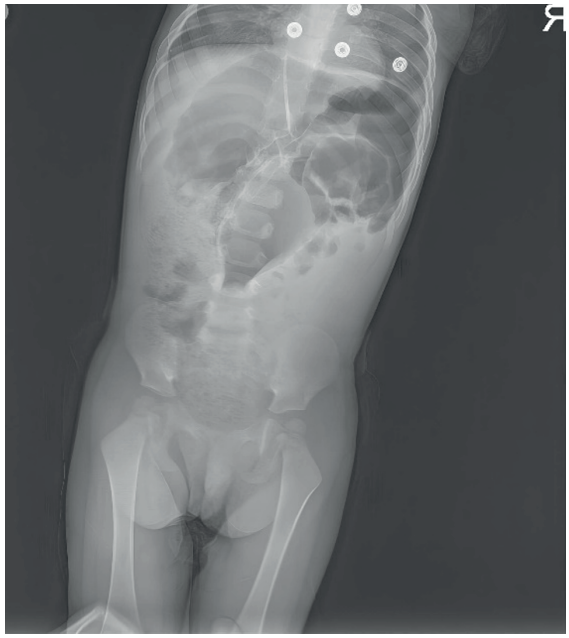

Fig. 2. Upright abdominal X-ray showed that there was no intestinal gas in the pelvis, and there were dilated bowel loops.

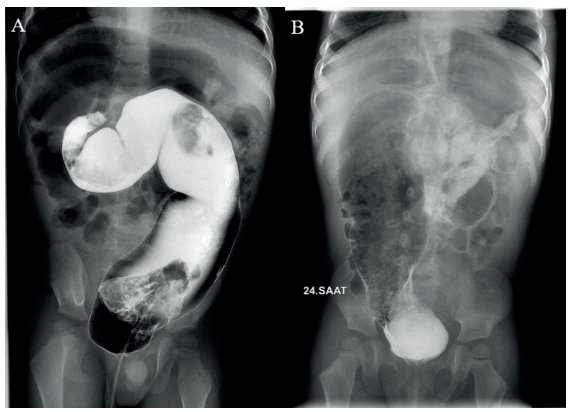

Fig. 3. Contrast-enhanced colonography.
A) Increased colon diameter. B) Incomplete emptying of the colon at 24 hours.

Hirschsprung's disease is a congenital aganglionosis characterized by the absence of ganglion cells in the distal intestine due to a failure in the migration, proliferation, differentiation, or survival of vagal and sacral neural crest cells, which form the precursor cells of the enteric nervous system (ENS)

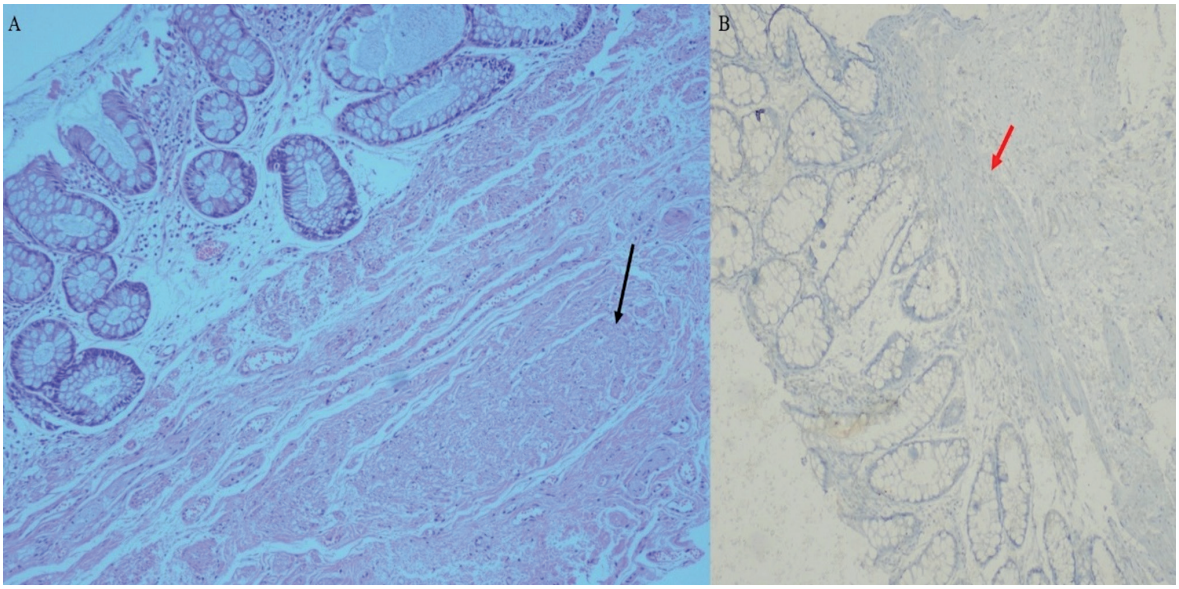

Fig. 4. Histopathological findings of the rectal mucosa.
A) The illustration shows aganglionic rectal mucosa and hypertrophic nerve fibers (black arrow) (H&E, original magnification x20). B) Negative calretinin immunstaining of rectal mucosa (red arrow) (Calretinin IHC, original magnification x 20).

during the embryonic period. GPI-anchored proteins regulate signaling pathways that are important in the migration and differentiation of neural crest cells. Therefore, GPI biosynthesis deficiencies may be associated with HD because they can disrupt the normal development of the ENS.[4,5]

GPI-anchored proteins play a critical role in cell surface adhesion, signal transduction, and neurodevelopmental processes. The *PIGO* gene encodes one of the ethanolamine phosphate transferase enzymes responsible for the addition of ethanolamine phosphate to the GPI anchor, and mutations can lead to multisystem involvement.[6,7] Few patients with *PIGO* mutations have been described in the literature, and the clinical spectrum is quite broad. In our case, a homozygous mutation of c.1334G>C (p.Arg445Pro) was detected in the *PIGO* gene (NM_032634.4), which has not been previously identified in Türkiye. Based on the assessment conducted in accordance with the ACMG guidelines, the identified variant was classified as a variant of uncertain significance. Nevertheless, the clinical constellation of hyperphosphatasia, hypotonia, intellectual disability, epilepsy, and HD observed in our patient exhibits a high degree of phenotypic specificity characteristic of HPMRS2 associated with *PIGO* mutations. In this context, the fulfillment of the PP4 criterion significantly bolsters the likelihood of pathogenicity and reinforces the correlation between the molecular findings and the clinical presentation. Comprehensive literature and database queries, including PubMed and ClinVar, confirmed that this variant has not been previously reported. Consequently, this study represents an original case report that contributes to the existing literature and provides critical diagnostic data for the future identification of similar cases.

According to the population data criterion (PM2), the variant is exceedingly rare and, to the best of our knowledge, is being reported for the first time in the literature. Although data regarding the clinical effects of the p.Arg445Pro variant are limited, no functional study directly evaluating this specific amino acid substitution in PIGO has yet been reported. Nevertheless, when considered together with previously published functional and structural data on *PIGO* variants, as well as the well-established

helix-disrupting biochemical property of proline, the arginine-to-proline substitution is biologically highly likely to exert a deleterious effect on protein stability and/or conformation, and consequently on PIGO function.[8] The present case is also thought to expand the clinical spectrum of Mabry syndrome, particularly with respect to the presence of refractory seizures, hypotonia, intellectual disability, hyperphosphatasemia, and its association with HD.

Holtz et al., in their study summarizing a literature review, evaluated 18 cases with *PIGO* mutations in detail, and observed developmental delay and hyperphosphatasemia in all cases. The most common dysmorphic features were distal digital hypoplasia (77.8%), seizures that usually began before the age of 2 years (66.7%), and nail anomalies (55.6%). Although variable, the most common facial dysmorphisms were ear anomalies (44.4%), and tent-shaped upper lip (33.3%). Hearing loss was also reported in 50% of cases. ALP levels exceeded 1000 U/L in 55.6% of the cases.[1] Another study reported that GPI deficiencies were seen in a very wide clinical spectrum.[2] In the presented case, digital anomalies and facial dysmorphism were present, consistent with the literature, but hearing loss was not detected and the serum ALP level was 613 IU/L.

In their study, Holtz et al. found gastrointestinal anomalies in 55.6% of the cases. The anomalies detected were anal atresia (33.3%), HD (33.3%), and esophageal atresia (11.1%).[1] The significant number of gastrointestinal anomalies in Mabry syndrome suggests that *PIGO* mutations may have an impact on neuroenteric development. In the presented case, HD was identified, and definitive surgery was performed. In this respect, it is one of the first cases of HD caused by the *PIGO* mutation reported from Türkiye.

In conclusion, Mabry syndrome should be considered in cases of hypotonia, refractory seizures beginning before the age of 2, and unexplained hyperphosphatemia. It should be kept in mind that serious gastrointestinal abnormalities, particularly HD, may be present. This case highlights the increased phenotypic variability associated with *PIGO* mutations and demonstrates the importance of genetic assessment in atypical neurodevelopmental conditions.

Ethical approval

Informed consent for the publication of this case report was obtained from the patient's parents.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: TT, SK; data collection: TT, SK, MC; analysis and interpretation of results: TT, SK, MC; draft manuscript preparation: TT, SK. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Case Report

A case of neonatal galactosemia presenting with rare hematologic problems: factor V deficiency and hemophagocytic lymphohistiocytosis

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ABSTRACT

Background. In the neonatal period, classical galactosemia usually presents with nonspecific clinical signs such as feeding intolerance, jaundice, lethargy, hypotonia, vomiting, and failure to thrive. Hemophagocytic lymphohistiocytosis (HLH) is very rare, with only a few case reports. The mechanism of HLH in metabolic disorders is unclear. It is thought to be related to tissue damage and impaired lymphocyte and histiocyte function, or some form of macrophage activation through metabolite accumulation. Various exogenous agents can inhibit factor V (FV) secretion or reduce its activity by inhibiting sulphatization, glycosylation, or phosphorylation.

Case Presentation. Here we report the case of a newborn who presented with elevated prothrombin time and activated partial thromboplastin time in the setting of liver failure and transient low FV levels and was subsequently diagnosed with HLH secondary to galactosemia.

Conclusion. Neonatal galactosemia can lead to secondary HLH and transient FV deficiency. Our experience suggests that FV deficiency in neonates with galactosemia may develop secondary to liver damage and/or impaired glycosylation, and resolves with adequate treatment of the underlying disease.

Key words: galactosemia, factor V, hemophagocytic lymphohistiocytosis, neonate.

Galactosemia is an autosomal recessive (AR) congenital inborn disorder of carbohydrate metabolism characterized by an inability to convert galactose to glucose due to a deficiency of one of the enzymes galactose-1-phosphate uridylyltransferase (GALT), galactokinase or galactose-4-epimerase. Galactosemia is most commonly caused by a deficiency of the enzyme GALT and is known as classical galactosemia. The incidence of galactosemia varies between 1/40,000-1/60,000.[1-3]

Infants with classical galactosemia present with various findings including jaundice, vomiting, hepatomegaly, failure to thrive, poor feeding, and sepsis.[3] Hemophagocytic lymphohistiocytosis (HLH) associated with classic galactosemia is exceedingly rare. To the best of our knowledge, only three cases have been reported in the literature to date.[4-6] Only one case of classical galactosemia with coagulopathy due to factor V (FV) deficiency has been reported in the literature.[7]

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We present this case to emphasize that neonatal galactosemia can lead to secondary HLH and transient FV deficiency.

Case Presentation

A male infant was born with a birth weight of 3340 g at 37 weeks of gestation by elective Caesarean section to a 25-year-old mother. APGAR scores were 9 and 10 at 1 and 5 minutes of life. The infant was admitted to the neonatal intensive care unit because of tachypnea, grunting and cyanosis, which improved with nasal continuous positive airway pressure (CPAP) within 24 hours. The parents were first cousins. The obstetric history was notable for three prior pregnancy losses, while one sibling was healthy. The mother had used low molecular weight heparin during pregnancy due to heterozygous polymorphisms in the *MHTFR* (1298A>C), *F12* (factor XII; V34L) and *PAI1* (plasminogen activator inhibitor-1; 4G/5G) genes. Hemogram, acute phase reactants (procalcitonin and C-reactive protein), blood glucose, electrolytes, renal and hepatic function tests were within normal limits at 24 hours of life. The patient could not be discharged due to poor sucking and was fed via orogastric tube. On postnatal day 6, he developed jaundice, mild hypotonia, hepatomegaly, and >15% weight loss.

Laboratory tests revealed (normal values in parentheses): white blood cell count 14.08 $x10^3$/μL, hemoglobin 17 g/dL, platelets $216x10^3$/μL, alanine aminotransferase (ALT): >700 U/L (0-41 U/L), aspartate aminotransferase (AST): 1955 U/L (0-40 U/L), total bilirubin (TB): 11.2 mg/dL, direct bilirubin (DB): 2.15 mg/dL, gamma glutamyltransferase (GGT): 125 U/L (0-60 U/L), alkaline phosphatase: 1089 U/L (122-469 U/L), lactate dehydrogenase (LDH): 2271 U/L (0-250 U/L), total protein: 4.8 g/dL (4.6-7 g/dL), albumin: 3.7 g/dL (3.8-5.4 g/dL), prothrombin time (PT): 56 s (9.9-11.8 s), activated partial thromboplastin time (aPTT): >100 s (23-31.9 s), international normalized ratio (INR): 5.69 (0.7-1.2). Mixing test showed improvement. Vitamin K and fresh frozen plasma (FFP) were administered and ursodeoxycholic acid (UCDA) was initiated. Although transaminases decreased, direct bilirubin and coagulation parameters remained abnormal. Hepatobiliary and cranial ultrasonography (US) were normal. Echocardiography showed a patent foramen ovale, and patent ductus arteriosus. Toxoplasma, rubella, cytomegalovirus, herpes simplex virus, Ebstein-Barr virus, parvovirus B19 and mumps virus serologies were negative. Blood and urine cultures were negative. Metabolic screening revealed normal ammonia, lactate, and pyruvate levels but positive urine reducing substances. Thin-layer chromatography was performed. Among the common pathway factors, factor I (1.07 g/L), FV (15% and 9.8%) and factor X (65.3%) were tested, revealing a low FV activity.

On postnatal day 13, ALT: 90 U/L, AST: 240 U/L, TB: 11.2 mg/dL, DB: 5.3 mg/dL were found. Laboratory analysis revealed bicytopenia (hemoglobin: 9.9 g/dL, platelets: 86 $x10^3$/μL), low fibrinogen (1.07 g/L), high ferritin (1510 ng/mL) and high LDH (1364 U/L) levels. Monocytosis, vacuolization of monocytes and atypical lymphocytes were seen on peripheral blood smear. Bone marrow aspirate (Wright-Giemsa stain) showed no storage cells. Blasts and atypical lymphocytes were less than 5% but hemophagocytosis (red blood cell, nucleated erythrocyte precursors and granulocytes) was observed in each quadrant of the bone marrow aspirate. The patient was diagnosed with HLH and treated with intravenous immunoglobulin (IVIG) and prednisolone, resulting in laboratory (bicytopenia, AST, ALT, LDH and ferritin) improvement. Blood and urine amino acid analysis showed generalized elevations, particularly glycine, phenylalanine and tyrosine, which were normalized on follow-up. Therefore, transient generalized amino acid elevation secondary to liver failure rather than inherited metabolic diseases was considered. On postnatal day 24, bilateral nuclear sclerosis in the eye lens was found, and urine galactose testing was positive. A galactose-free formula was started. Genetic analysis identified

a homozygous NM_000155.4: c.563A>G (p.Gln188Arg) mutation in exon 6 of the *GALT* gene.

The second FV activity measurement was found to be lower than the first one (15% vs 9.8%). The infant started to gain weight after galactose-free formula and was discharged on the 38th day of life. No perforin gene (*PRF1*) mutations were present in the analysis performed for familial HLH. In addition, FV activity was found to be within normal limits (67.7%) in the pediatric hematology outpatient follow-up (controls were performed at 2nd, 3rd, 4th and 6th months). Bilateral nuclear sclerosis regressed on follow-up. At 20 months of age, the patient demonstrated appropriate neurodevelopmental milestones.

Informed consent was obtained from the parents of the case for the publication.

Discussion

In this report, we describe a neonate with classical galactosemia who developed early liver dysfunction accompanied by severe coagulopathy, transient FV deficiency, and secondary HLH. Although hepatic involvement is well recognized in galactosemia, the coexistence of HLH and marked coagulation abnormalities appears to be uncommon and may complicate the initial clinical evaluation.

Classical galactosemia in the neonatal period may initially manifest with mild and nonspecific symptoms. However, if left untreated, the clinical course can rapidly progress to severe systemic complications. These include hepatomegaly, acute liver failure, renal dysfunction, encephalopathy, and an increased risk of *Escherichia coli* sepsis, potentially leading to shock and death.[2,3] Symptoms typically become evident within the first one to two weeks after the initiation of milk feeding. Coagulopathy secondary to liver involvement may also occur and can be managed with vitamin K and FFP. Early recognition and prompt initiation of a galactose-restricted diet are therefore crucial to prevent life-threatening outcomes.[8]

In galactosemia-associated liver injury, supportive treatment alone is usually insufficient for meaningful hepatic recovery.[9,10] In our case, although liver failure signs partially improved with supportive therapy, cholestasis and coagulation parameters did not improve until a galactose-free diet was initiated, highlighting the critical role of dietary management in reversing hepatic dysfunction.

Galactose levels can be mildly elevated in normal newborns (6–10 mg/dL), which may lead to false-positive results. Other causes of elevated galactose include liver dysfunction due to conditions such as portosystemic vascular shunts, biliary atresia, and Fanconi–Bickel syndrome.[11-13] In our case, hepatobiliary ultrasonography showed no pathological findings.

Hemophagocytic lymphohistiocytosis is a rare, life-threatening hyperinflammatory disease caused by impaired function of natural killer cells and cytotoxic T cells and overactivation of macrophages and T lymphocytes. Primary HLH, also known as familial HLH, is an autosomal recessive disease that is more common when there is consanguinity between parents. Secondary HLH occurs following severe immunologic activation such as immunodeficiency, systemic infection, autoimmune diseases, metabolic diseases or malignancy.[6,14] The mechanism of HLH in metabolic diseases is not clear. It is thought to be related to tissue damage and impaired lymphocyte and histiocyte functions or somehow activation of macrophages through accumulation of metabolites.[15,16] The association between galactosemia and HLH has been reported in only three cases to date, with the third case described by Kundak et al.[4-6] In that report, the patient with HLH secondary to galactosemia presented with fever, hemophagocytosis, hypofibrinogenemia, pancytopenia, splenomegaly, and hyperferritinemia, and was treated with IVIG.[6] In our case, when HLH was

diagnosed on day 13, galactosemia had not yet been confirmed. Therefore, it was unclear whether the HLH was primary or secondary. Current consensus guidelines recommend early treatment for familial HLH and suggest that prompt immunomodulatory therapy may also be beneficial in secondary HLH.[17] Although neonatal data are limited, therapy targeting hyperinflammation should be initiated without delay after diagnosis.[18]We initiated immunomodulatory therapy to stabilize the patient during the acute phase. To our knowledge, this represents the fourth reported case of this association in the literature.

No perforin (*PRF1*) gene mutation was identified in our patient. However, the absence of further genetic testing, including analysis of other HLH-related genes or whole-exome sequencing, represents a limitation of this report.

Factor V has both procoagulant and anticoagulant functions within the coagulation cascade. Although mild mucosal bleeding is the most common clinical manifestation, life-threatening bleeding may also be observed.[7,19] Approximately 75-80% of FV is synthesized in hepatocytes and hereditary deficiency is extremely rare (1 per million).[19,20] Therefore, when low FV levels are detected, liver disease, disseminated intravascular coagulation, and FV inhibitors should be considered first.[20] Numerous posttranslational changes can be observed in the FV pro-peptide, including sulphatization, phosphorylation, glycosylation and formation of disulfide bridges. Various exogenous agents can inhibit FV secretion or reduce its activity through inhibition of sulphatization, glycosylation or phosphorylation.[20]

Only one case of galactosemia associated with FV deficiency has been reported in the literature prior to ours. Mansouritorghabeh et al.[7] reported a newborn diagnosed with "hereditary" FV deficiency who died of pulmonary hemorrhage before initiation of a lactose-free diet. Notably, no genetic analysis confirming hereditary deficiency was provided and the transient or secondary nature of the deficiency could not be excluded.[7] In contrast, FV levels normalized after treatment of galactosemia in our patient, supporting the interpretation that the deficiency was secondary to liver dysfunction rather than a true hereditary defect. Nevertheless, as only common pathway factors were evaluated, the potential involvement of other coagulation factors remains a limitation of our report.

In conclusion, based on the follow-up of our case, FV deficiency in neonates with galactosemia may develop secondary FV deficiency related to liver damage and/or impaired glycosylation, and improve with adequate treatment of the underlying disease.

Ethical approval

Informed consent was obtained from the patient's parents for the publication.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: ŞT, SA, UK, MA, HFG; data collection: UK, SA, MA, HFG; analysis and interpretation of results: XX; draft manuscript preparation: ŞT, UK, SA. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Case Report

Infection-triggered neurological deterioration and immunodeficiency in a case of RNU4ATAC-opathy

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ABSTRACT

Introduction. RNU4ATAC-opathy is a rare autosomal recessive disorder characterized by a wide clinical spectrum, including brain anomalies, seizures, strokes, immunodeficiency, and cardiac defects. Other manifestations include ophthalmologic, dermatologic, renal, gastrointestinal, auditory, and endocrine involvement. Here, we report the identification of pathogenic *RNU4ATAC* variants through whole exome sequencing in an infant presenting with microcephaly, growth failure, and immunodeficiency.

Case Presentation. We describe an 11-month-old infant who had been followed since 4 months of age for growth failure and developmental delay. During follow-up, the patient experienced episodes of neurological deterioration triggered by febrile illnesses associated with SARS-CoV-2 and respiratory syncytial virus infections (RSV) at 9 and 11 months of age, respectively. Immunological evaluation showed normal immunoglobulin levels, a marked reduction in switched memory and memory B cells, impaired T-cell activation, and decreased T-cell subpopulations, suggesting combined immunodeficiency that may have contributed to increased susceptibility to viral infections. Whole exome sequencing subsequently identified compound heterozygous pathogenic variants in the *RNU4ATAC* gene, confirming the diagnosis of RNU4ATAC-opathy.

Discussion. RNU4ATAC-opathy should be considered in cases with microcephaly, growth failure, immunodeficiency, and skeletal abnormalities. Our case shows that RNU4ATAC-opathy may present as infection-related encephalopathy, together with combined T- and B-cell dysfunction. Early immunological assessment and timely initiation of prophylactic therapy could play a key role in improving survival. Genetic and immunological evaluations are essential for accurate diagnosis, early intervention, and effective management. Further research is needed to clarify the syndrome's impact on immune function and guide targeted therapies.

Key words: RNU4ATAC-opathy, immunodeficiency, encephalopathy, microcephaly.

RNU4ATAC-opathy encompasees the phenotypic spectrum associated with biallelic *RNU4ATAC* likely pathogenic or pathogenic variants, which include the clinical phenotypes of microcephalic osteodysplastic primordial dwarfism type I/III (MOPDI; OMIM#210710), Roifman syndrome (RFMN; OMIM #616651), and Lowry-Wood syndrome (LWS; OMIM #226960).[1] RNU4ATAC-opathy is an autosomal recessive inherited disorder

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characterized by a broad clinical spectrum, including brain anomalies, seizures, strokes, immunodeficiency, and cardiac anomalies, as well as ophthalmologic, skin, renal, gastrointestinal, hearing, and endocrine involvement.[1] MOPD1 is characterized by severe disease, prominent brain abnormalities, and early mortality within the first three years of life.[2,3] RFMN is strongly associated with immunodeficiency, leading to frequent hospital admissions due to recurrent infections. In contrast, immunodeficiency has been reported less frequently in patients with LWS than in those with RFMN.[3,4] In the 2024 update of the International Union of Immunological Societies Expert Committee classification, MOPD1 deficiency, caused by *RNU4ATAC* gene defects, has been included in the group of immuno-osseous dysplasias. The reported immunological features comprise decreased natural killer (NK) cell function, reduced total and memory B cells, hypogammaglobulinemia, and variably reduced specific antibodies.[5] In this study, we report *RNU4ATAC* variants identified through whole exome sequencing (WES) in an infant presenting with microcephaly, growth failure, and immunodeficiency.

Case Presentation

A four-month-old male patient was admitted with acute gastroenteritis. He was born at 36 weeks with a birth weight of 1.5 kg (Z-score –3.32) to a non-consanguineous Turkish family, and a history of intrauterine growth restriction. He required a 33-day neonatal intensive care stay, including one day of intubation. No infections were reported until 4 months of age. Before this admission, he had been evaluated for microcephaly and growth failure, and was diagnosed with atopic dermatitis due to persistent eczematous lesions.

During the evaluation of growth failure, cytomegalovirus (CMV) IgM was positive and CMV PCR was 495 IU/mL; however, congenital CMV infection was not considered, given normal hearing, absence of retinitis, and unremarkable brain magnetic resonance imaging (MRI) findings. Neuroimaging revealed a thin corpus callosum and shallow gyral pattern (Fig. 1a and Fig. 1b). Metabolic tests are summarized in Supplementary Table S1.

At 8 months, he was rehospitalized due to a generalized eczematous rash and fever. Examination showed diffuse xerosis with fine scaling, consistent with ichthyosis. Laboratory evaluation revealed leukocytosis, eosinophilia, anemia, elevated IgE, and elevated liver transaminases (Table I). Skin biopsy confirmed atopic/contact dermatitis, and the rash improved with antibiotics, supportive care, and moisturizers (Fig. 2c-e). During hospitalization, he developed diarrhea and a generalized tonic–clonic seizure. Diffusion-weighted imaging revealed punctate diffusion restriction in the splenium of the corpus callosum, periventricular subependymal regions, and right corona radiata, while MR angiography showed normal results (Fig. 1c and Fig. 1d). Electroencephalography revealed focal epileptiform anomalies originating from the frontal and frontocentral regions of the left hemisphere, and levetiracetam was started. A skeletal survey revealed mild spondyloepiphyseal dysplasia (Supplementary Fig. S1). The patient's leukocytosis and eosinophilia resolved in the follow-up.

At the age of 9 months, he was hospitalized for dehydration due to gastroenteritis and coronavirus disease 2019 (COVID-19). He developed seizures and decorticate posturing. Emergency neuroimaging revealed hemorrhagic areas, raising suspicion of mitochondrial disease, acute hemorrhagic encephalomyelitis, and acute necrotizing encephalopathy (ANEC) as primary differential diagnoses (Fig. 1e-j). MR spectroscopy of the basal ganglia revealed an increased choline/creatine (Cho/Cr) ratio, decreased N-acetyl aspartate (NAA) values, and a lactate peak, leading to the suspicion of mitochondrial disease (Fig. 2a and Fig. 2b). A mitochondrial cocktail was started, consisting of thiamine (10 mg/kg/day), riboflavin (10 mg/kg/day), coenzyme Q10 (10 mg/kg/day), biotin

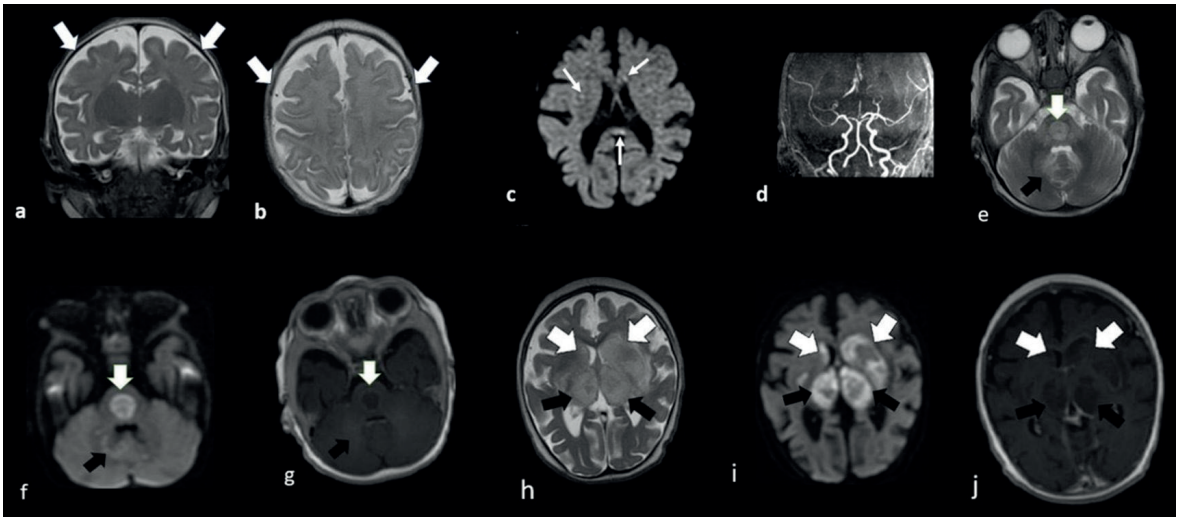

Fig. 1. a, b. Brain magnetic resonance imaging (MRI) coronal (a) and axial (b) T2-weighted (T2W) sequence. The gyral pattern appeared shallow for the patient's age and may be associated with prematurity (white arrows). **c.** Diffusion-weighted image (DWI) revealed punctate restricted diffusion values in the posterior and midline of the splenium of the corpus callosum, as well as in the subependymal areas adjacent to the lateral ventricle (white arrows). **d.** MR angiography was performed, which yielded normal results. **e-g.** Axial T2W (e), DWI (f) and post-contrast T1-weighted (T1W) images (g) show hyperintense edema with diffusion restriction, hemosiderin deposits, and peripheral enhancement in pons (white arrows) and dentate nucleus (black arrows). **h-j.** Axial T2W (h), DWI (i), and post-contrast T1W (j) images demonstrate hyperintense edema with diffusion restriction, hemosiderin deposition, and peripheral enhancement in both thalami (black arrows), and bilateral basal ganglia (white arrows).

(5 mg twice daily), carnitine (40 mg/kg/day), and vitamin E (20 IU/kg, three times per week).

The patient was monitored in the pediatric intensive care unit (PICU) after the clinical deterioration. Ceftriaxone and acyclovir treatments were initiated for encephalitis. Immunological investigations showed normal immunoglobulin levels, normal numbers of T, and B cells and decreased NK cell counts. However, lymphocyte activation was reduced, along with decreases in memory B cells, switched memory B cells, marginal zone B cells, CD8 naive T cells, CD8 central memory T cells, CD8 effector memory T cells, and CD4 central memory T cells (Table I). Intravenous immunoglobulin (IVIG) therapy was administered at 0.4 g/kg/day for 5 days, along with pulse steroid therapy (methylprednisolone 30 mg/kg/day) for 5 days. On the 10th day of intensive care, with clinical improvement under treatment, a follow-up MRI showed decreased edematous appearance and atrophic changes in the described areas. During this hospitalization, the patient lost the ability to sit unsupported and could no longer hold their head up. After discharge from the PICU, monthly IVIG therapy, acyclovir and trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis were started for a probable syndromic combined immunodeficiency diagnosis. Levetiracetam and the mitochondrial cocktail were continued.

At 11 months of age, the patient was hospitalized again due to respiratory syncytial virus (RSV) pneumonia requiring intubation. During hospitalization, transaminase levels were mildly elevated, without hepatosplenomegaly or hyperbilirubinemia, and resolved after ursodeoxycholic acid (UDCA) treatment. The patient's echocardiography was normal, but sinus bradycardia was observed, and resolved without any treatment. During this hospitalization, WES revealed compound heterozygous pathogenic variants in the *RNU4ATAC* gene (see below), confirming the

Table I. The hematological, biochemical, and immunological results of the patient.

Tests		Reference range
Hemoglobin (g/dL)	7.5	11 – 13.5
MCV (fL)	52.3	74 – 88
RBC (x 10^6/μL)	5.07	3.9 – 5
Leukocyte (x 10^3/μL)	33.61	3.5 – 11.0
Platelet (x 10^3/μL)	720	150 - 450
Neutrophil (x 10^3/μL)	15.4	1.5 – 8.0
Lymphocyte (x 10^3/μL)	12.28	1.5 – 4.0
Eosinophil (x 10^3/μL)	1.43	0.1 – 0.4
AST (U/L)	277	<82
ALT (U/L)	164	< 56
ALP (U/L)	179	110 – 302
GGT (U/L)	21	< 204
Bilirubin (total) (mg/dL)	0.28	< 2
Bilirubin (direct) (mg/dL)	0.22	<0.35
CRP (mg/L)	50.18	0 – 5
ESR (mm/h)	101	0 – 15
Immunoglobulins		
IgA (g/L)	0.38	0.05 – 0.85
IgM (g/L)	3.68	0.26 – 1.46
IgG (g/L)	13.26	2.68 – 8.98
Total IgE (IU/mL)	526	< 100
Lymphocyte subsets		
CD3, %	68	49-76
CD4, %	42	31-56
CD8, %	22	12-24
CD16-56, %	2	3-15
CD19, %	14	14-37
Lymphocyte activation		
CD3 CD25 Cells, %	19	52.4 - 94.7
CD3 CD69 Cells, %	28	47.9 - 84.8
B Cell Panel		
Memory B Cells, %	2.1	9.5 - 26.5
Switched Memory B Cells, %	2.1	3.9 - 13.6
Marginal Zone B Cells, %	0	4.1 - 13.9
Naive B Cells, %	89	68 - 89.3
Active B Cells, %	2.2	1 – 5.7
Plasmoblasts, %	2.2	0 - 5.3
Transitional B Cells, %	32.1	3.3 - 16.5
T Cell Panel		
CD4 T Cells, %	38	29 – 59
CD4 Naive T Cells, %	74.7	57 - 84.9
CD4 Central Memory T Cells, %	8.8	11.3 - 26.7
CD4 Effector Memory T Cells, %	10.6	3.3 - 15.2
CD4 Temra T Cells, %	5.8	0.4 - 2.6
CD8 T Cells, %	31	19 – 29
CD8 Naive T Cells, %	18.2	28.4 - 80.6
CD8 Central Memory T Cells, %	0.1	1 – 4.5
CD8 Effector Memory T Cells, %	2.8	6.2 - 29.3
CD8 Temra T Cells, %	78.8	9 - 49.1
RTE (Recent Thymic Emigrants), %	58	40 – 100

ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; GGT: Gamma-glutamyl transferase; MCV: Mean corpuscular volume; RBC: Red blood cell; RTE: Recent thymic emigrants.

diagnosis of RNU4ATAC-opathy. Following the genetic diagnosis, the mitochondrial cocktail was discontinued.

At present, the patient is 36 months old, and continues to require recurrent hospitalizations due to lower respiratory tract infections. However, no further infection-triggered neurological deterioration has been observed for more than one year, possibly reflecting a beneficial effect of ongoing IVIG therapy. Neurological developmental delay persists, accompanied by physical inactivity and excessive weight gain. The patient remains on levetiracetam and valproic acid for epilepsy, along with antibacterial and antiviral prophylaxis and IVIG.

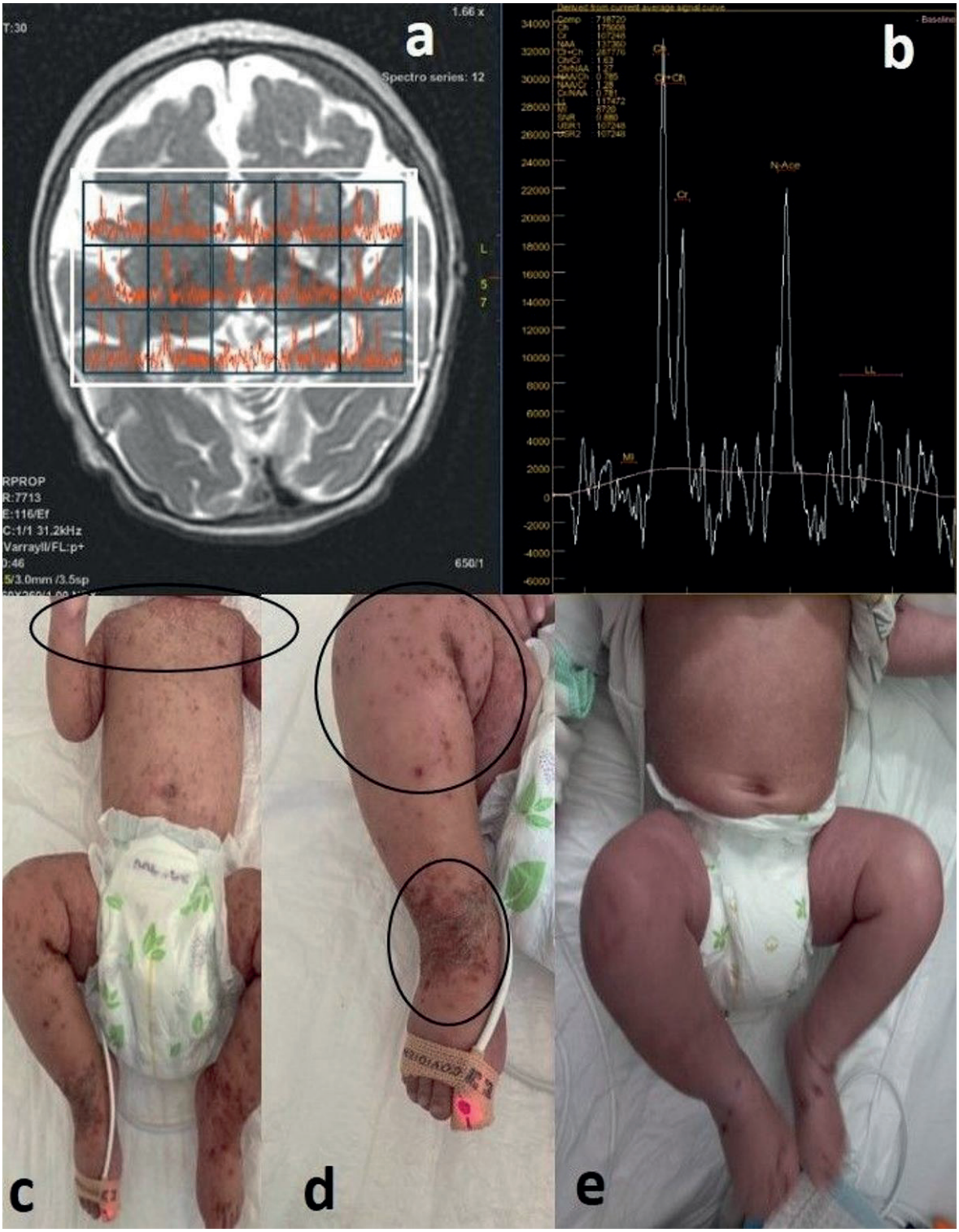

Fig. 2. a, b. Magnetic resonance spectroscopy (MRS) examination from the basal ganglia, an increase in the choline/creatine (Cho/Cr) ratio, a decrease in N-acetyl aspartate (NAA) values, and a lactate peak were observed. **c-e.** Eczematous lesions in the patient at 8 months. Before (c-d) and after treatment (e).

Genetic analysis

WES was performed at 10 months of age using DNA extracted from peripheral blood leukocytes with next-generation sequencing (NGS, Illumina) and the Illumina DNA Prep with Exome 2.0/2.5 Plus Enrichment Kit. The bioinformatic analysis of the raw data was performed and reported using the Varsome Clinical (Saphetor) software. The WES analysis revealed heterozygous n.55G>A and n.5A>C (RefSeq: NR_023343.1) variants in the 5′ stem-loop and Stem II structures of the *RNU4ATAC* gene, which is a non-coding spliceosomal gene. These variants were classified as "pathogenic" and as a "variant of uncertain significance" according to the American College of Medical Genetics and Genomics criteria, respectively. This biallelic configuration was validated by inspection of the NGS BAM file. Parental segregation analysis demonstrated that the n.5A>C variant (RefSeq: NR_023343.1) was inherited from the unaffected mother, while the father is wild type at both relevant nucleotide positions. The n.55G>A variant was absent in both parental samples and is therefore classified as *de novo*. Sanger sequencing confirmed both variants in the patient establishing the compound heterozygous state.

Written informed consent was obtained from the patient's parents.

Discussion

This report describes a patient who was diagnosed with RNU4ATAC-opathy. MOPD1, LWS, and RFMN are overlapping syndromes associated with mutations in the *RNU4ATAC* gene.[1] The clinical phenotype varies, but typically includes growth failure, microcephaly, skeletal dysplasia, and cognitive impairment.[1,4] In our patient, the initial signs were microcephaly and growth failure, accompanied by combined immunodeficiency, eczematous lesions, and recurrent viral infections that triggered episodes of encephalopathy.

The n.55G>A variant, detected heterozygously in the patient, disrupts ncRNA function.[4] It is rare (gnomAD: 0.0000885), is classified as pathogenic in ClinVar (ID: 30179), and has been reported in multiple affected cases in the homozygous state.[6-8] These patients presented with the classical clinical spectrum of MOPD1, including severe microcephaly, growth restriction, skeletal dysplasia, neurodevelopmental impairment, and, in some cases, immunodeficiency and infection-triggered neurological deterioration.[4,6,8] The patient's other heterozygous variant, n.5A>C, is located within Stem II of *RNU4ATAC*. It is also rare (gnomAD: 0.00001), classified in ClinVar as a "variant of uncertain significance" (ID: 932367), and reported in one affected individual in the literature in a compound heterozygous state.[9]

Across RNU4ATAC-opathies, common immunological abnormalities include hypogammaglobulinemia, reduced memory B cells, recurrent infections, and variable T-cell defects, while NK cell counts ($CD16^+/CD56^+$) are usually within the normal range and functional NK assays were rarely performed.[9-16] Reported cases of RNU4ATAC-opathy presenting with immunological involvement are summarized in Table II. MOPD1 is frequently associated with significant humoral defects, such as reduced B-cell subsets, impaired antibody production, poor vaccine responses, and in some cases, $CD4^+$ T-cell lymphopenia, contributing to early mortality often secondary to infections.[11,13-15] RFMN is characterized by a more consistent immunodeficiency phenotype, including profound hypogammaglobulinemia, reduced B-cell numbers, impaired specific antibody responses, and occasional NK cell reduction, frequently necessitating long-term immunoglobulin replacement therapy.[10,12,16] Although described less often, LWS can also involve hypogammaglobulinemia and immune dysfunction.[9] These overlapping findings support the concept of a shared immunological phenotype across the RNU4ATAC-opathies.

Table II. Reported immunological findings in RNU4ATAC-opathy.

Patient and syndrome	T-cells	B-cells	NK Cells	Immunoglobulin levels	Clinical immunological features
Merico et al.[10], (2015) (P6) - Roifman	Normal T cells	↓ Circulating B-cell, normal mature and memory B cells	Normal	Variable immunoglobulin level	Poor vaccine response
Kılıç et al.[11], 2015 (P1) – MOPD1	Not reported	B-cell related anomalies	Not reported	Hypogammaglobulinemia	Recurrent infections (pneumonia, diarrhea) IVIG theraphy
Dinur Schejter et al.[12], 2017 (P2) - Roifman	↓ CD8+ T cells, Poor antigen response	↓ CD19+ B cells	Normal	Hypogammaglobulinemia	Recurrent pneumonia, ear infections, atopy (asthma, eczema); improved with IVIG, Absent responses to tetanus, MMR, VZV, pneumococcus vaccines
Farach et al.[9], 2018 (P3) - LWS	Not reported	B-cell related anomalies (one patient)	Not reported	Hypogammaglobulinemia (one patient)	Not detailed in 2 patients, Subclinical in one patient
Heremans et al.[16], 2018 (P3) - Roifman	↓ CD4+ T cells (in one patient), ↓ Total CD3+ T cells (one patient)	↓ B cells	Normal	Hypogammaglobulinemia	All patients experience recurrent viral infections, necessitating IVIG therapy. Herpes simplex infection (one patient), pneumococcal sepsis (one patient
Hagiwara et al.[13], 2021 (P1)-MOPDI	Decreases in total lymphocytes, CD4+ T cells, and T cell regenerative activity.	↓ B cells	Normal	Hypogammaglobulinemia	Recurrent infections (respiratory and URTI), ARDS and DIC with MRSA infection. ANE with HHV-6 Poor vaccine response to varicella-zoster, MMR and influenza
Sirohi et al.[14], 2023 (P2) – MOPDI-III	↓ CD8+ T cells	↓ CD19+ B cells	Normal	Hypogammaglobulinemia (one patient)	Recurrent infection, paucity of plasma cells in gastrointestinal biopsies Impaired antibody response to PCV13/PPV23; protective diphtheria/tetanus titers

AHEM: Acute Hemorrhagic Encephalomyelitis, ANE: Acute Necrotizing Encephalopathy, ARDS: Acute Respiratory Distress Syndrome, DIC: Disseminated Intravascular Coagulation, HHV-6: Human Herpesvirus 6, IVIG: Intravenous Immunoglobulin, LWS: Lowry Wood syndrome, MMR: Measles, Mumps, Rubella; MOPD1: Microcephalic Osteodysplastic Primordial Dwarfism Type I, MRSA: Methicillin-Resistant Staphylococcus aureus, P: number of patients, PCV13/PPV23: Pneumococcal Vaccines (13-valent conjugate / 23-valent polysaccharide), URTI: Upper Respiratory Tract Infection, VZV: Varicella Zoster Virus.

Table II. Continued.

Patient and syndrome	T-cells	B-cells	NK Cells	Immunoglobulin levels	Clinical immunological features
Gauthier et al.[15], 2024 (P2, twin) – MOPDI	Normal T cells	Low naïve B cells, ↓ memory B cells and plasmablasts	Normal	Normal	Mild B-cell deficiency, recurrent infections
The patient	↓ CD8 Naive T Cells, ↓ CD8 Central Memory T Cells, ↓ CD8 EffectorMemory T Cells, ↓ CD4 Central Memory T Cells	↓ Memory B Cells, ↓ Switched Memory B Cells, ↓ Marginal Zone B Cells	↓ CD16/56	Normal	ANE-AHEM with COVID-19, Recurrent infections (pneumonia), improved with IVIG

AHEM: Acute Hemorrhagic Encephalomyelitis, ANE: Acute Necrotizing Encephalopathy, ARDS: Acute Respiratory Distress Syndrome, DIC: Disseminated Intravascular Coagulation, HHV-6: Human Herpesvirus 6, IVIG: Intravenous Immunoglobulin, LWS: Lowry Wood syndrome, MMR: Measles, Mumps, Rubella; MOPD1: Microcephalic Osteodysplastic Primordial Dwarfism Type I, MRSA: Methicillin-Resistant Staphylococcus aureus, P: number of patients, PCV13/PPV23: Pneumococcal Vaccines (13-valent conjugate / 23-valent polysaccharide), URTI: Upper Respiratory Tract Infection, VZV: Varicella Zoster Virus.

Our patient demonstrated a broader and more complex immunological profile, with combined T- and B-cell abnormalities, normal immunoglobulin levels and reduced NK cells. The preserved serum Ig levels may reflect maternally transferred immunoglobulins. Decreased switched memory and memory B cells, along with impaired T-cell activation and reduced T-cell subpopulations, likely contributed to recurrent viral infections and infection-triggered neurological deterioration, as reported in similar cases.[8,13] These observations highlight that even in the presence of normal immunoglobulin levels, detailed immunological evaluation is essential for accurate diagnosis and management. In patients with T-cell defects and antibody deficiencies, early initiation of IVIG therapy may help prevent recurrent infections and improve prognosis.

RNU4ATAC-opathy is associated with various radiographic findings, including multiple epiphyseal dysplasia (MED), spondyloepiphyseal dysplasia (SED), and spondyloepimetaphyseal dysplasia (SEMD).[1,9] Historically, patients with MOPDI predominantly exhibit SEMD, while RFMN is characterized by SED, and LWS typically presents with MED.[1,9] However, these syndromes overlap, leading to the manifestation of features across these conditions. Our patient exhibited mild SED, reflecting this overlap.

Nearly all patients with MOPD1 have brain abnormalities such as a thin corpus callosum, and an abnormal gyral pattern.[17] Similarly, our case presented with these abnormalities during the initial admission. In the literature, a patient carrying the same n.55G>A variant as our patient presented with microcephaly, normal stature, and experienced status epilepticus and encephalitis triggered by infections. MRI findings, elevated serum and CSF lactate levels in this patient indicate the need for differential diagnosis of underlying mitochondrial disease.[8] However, further evaluation, including muscle and liver biopsies and OxPHOS enzymology testing, excluded this diagnosis. In our case,

when ANEC was diagnosed, MR spectroscopy raised suspicion of a metabolic disease. However, mitochondrial disease was definitively ruled out, as whole mitochondrial genome analysis yielded normal results. Encephalitis has also been reported in other MOPD1 cases carrying the n.55G>A variant.[13,18,19]

In the literature, RFMN and MOPD1 have been associated with dry skin and eczematous lesions.[12,20] Our patient was diagnosed with atopic dermatitis and exhibited refractory eczematous lesions over a short period. Cardiac abnormalities can be seen in the RNU4ATAC-opathy spectrum, though rhythm problems have not been reported.[1,17,18] Our patient's echocardiography was normal, but sinus bradycardia was observed and resolved in follow-up. In addition, neonatal cholestasis and hepatosplenomegaly have been reported in the literature.[21] Our case had mildly elevated transaminase levels that resolved with UDCA treatment.

A limitation of our report is the lack of functional assays to directly confirm the link between *RNU4ATAC* variants and immunodeficiency due to the patient's unstable clinical condition and limited access to advanced analyses. Nevertheless, the immunophenotyping findings presented here expand the current understanding of the immunological spectrum of RNU4ATAC-opathies and highlight the importance of comprehensive immune assessment in all affected patients.

In conclusion, patients with RNU4ATAC-opathy may present with T-cell immunodeficiency and progressive neurological regression, often triggered by various viral infections. Immunological evaluation of these patients is critically important, as cases with varying degrees of immunodeficiency have been reported. Reducing the frequency of attacks and effectively controlling infections may significantly improve the patient's prognosis. Further studies will be important to better explain the mechanisms of immune-mediated strokes and immunodeficiency in these patients.

Supplementary materials

Supplementary materials for this article are available online at https://doi.org/10.24953/turkjpediatr.2026.6568

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Ethical approval

Written informed consent was obtained from the patient and her legal guardians for publication of this case report and accompanying images. Ethical committee approval was not obtained, as it was not required for a single case report according to our institutional policy.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: DY, ESA; data collection: DY, MK, AK, AKB, OSN, BU, HY, ESA; analysis and interpretation of results: MK, AK, AKB, OSN, BU, HY, ESA; draft manuscript preparation: DY, ESA. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Case Report

Spontaneous renal pelvis perforation in an adolescent with a solitary kidney

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ABSTRACT

Background. Spontaneous renal pelvis perforation is a rare but serious condition, often associated with urinary obstruction, infection, or increased intrapelvic pressure. Here, we present a pediatric patient with a solitary kidney who developed this rare condition.

Case presentation. We report the case of a 14-year-old girl with a solitary kidney who presented with abdominal pain, vomiting, and anuria. Laboratory findings revealed acute kidney injury, requiring emergent hemodialysis. Imaging studies demonstrated a spontaneous perforation in the anteromedial renal pelvis. The patient was initially managed with antibiotics and a double-J (DJ) ureteral stent. However, persistent fever and worsening retroperitoneal fluid collection necessitated percutaneous abscess drainage. Despite initial clinical improvement, she later developed recurrent urine leakage due to DJ stent occlusion, which required percutaneous nephrostomy placement. At the three-month follow-up, spontaneous resolution of the perforation was confirmed, and the patient was diagnosed with stage 4 chronic kidney disease.

Conclusions. Spontaneous renal pelvis perforation remains a rare entity in the pediatric population, with limited cases documented in the literature. This case emphasizes the importance of early recognition, timely imaging, and appropriate urinary drainage to prevent long-term renal impairment. In pediatric patients with a solitary kidney, close monitoring and a multidisciplinary approach are crucial to optimizing outcomes.

Key words: acute kidney injury, children, solitary kidney, spontaneous renal pelvis perforation, urinary extravasation.

Spontaneous perforation of the renal pelvis is an exceptionally uncommon condition in the pediatric population, characterized by the extravasation of urine into the perinephric and retroperitoneal spaces. It is also rarely seen in the adult population and is often associated with underlying congenital anomalies of the kidneys and urinary tract and is typically caused by infection or urolithiasis, often in the setting of urinary obstruction.[1-4] Although the exact pathophysiology of perforation is not fully understood, increased intrapelvic pressure resulting from obstruction or infection is considered the primary mechanism.[3,5]

The clinical presentation is often nonspecific and can include symptoms such as abdominal pain, vomiting, oliguria, or anuria, which may

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delay diagnosis and increase the risk of serious complications such as sepsis, perirenal abscess formation, or acute kidney injury (AKI).[6,7]

Renal pelvis rupture is typically diagnosed through abdominopelvic computed tomography (CT) or retrograde pyelography.[2-4,6] Management strategies generally focus on ensuring adequate urinary drainage through ureteral stenting or percutaneous nephrostomy, while addressing any underlying pathology. In some cases, spontaneous healing of the perforation site may occur without the need for surgical intervention.[1-3,5,7]

Here, we present a rare case of spontaneous renal pelvis perforation in a pediatric patient with a solitary kidney, complicated by retroperitoneal abscess formation and AKI, which required interventional management.

Case Presentation

A 14-year-old girl was admitted to a local hospital with complaints of abdominal pain and vomiting for three days, along with anuria for one day. Her antenatal ultrasonography was reported as normal. She had no history of urinary tract infections or urinary incontinence. Additionally, there was no known history of chronic disease or prior trauma. She was referred to our hospital due to AKI, with laboratory findings showing elevated creatinine levels (8 mg/dL) and hyperkalemia (7 mEq/L). On admission, her vital signs, including temperature, pulse rate, and blood pressure, were within normal limits. Physical examination revealed a weak and pale appearance, right-sided costovertebral angle tenderness, and growth retardation, with a weight of 35 kg (SDS: -3.75) and a height of 132 cm (SDS: -5.02).

Laboratory tests showed: hemoglobin 9.3 g/dL, mean corpuscular volume 75 fL, leukocyte count 2,070 × 10^6/L, blood urea nitrogen 195 mg/dL, creatinine 8.5 mg/dL, potassium 7 mmol/L, and C-reactive protein levels exceeding 350 mg/L (0–5 mg/L), with arterial blood gas analysis revealing a pH of 7.40 and a bicarbonate level of 23.1 mEq/L. Emergent hemodialysis was initiated due to AKI and severe hyperkalemia. Abdominal ultrasonography and CT demonstrated a kidney size of 160×73×72 mm, grade 4 hydronephrosis, renal parenchymal thinning, and a perforation in the anteromedial renal pelvis of the right solitary kidney, accompanied by thickening of the proximal ureteral and bladder walls. A dense collection, appearing to be purulent and hemorrhagic, was observed in the perirenal and pararenal regions, extending into the pelvis along the retroperitoneal area (Fig. 1). The patient was started on intravenous meropenem (10 mg/kg per dose every 24 hours, adjusted for renal function) and was referred to pediatric urology. A DJ ureteral stent was inserted, and retrograde pyelography demonstrated a normal-appearing ureteropelvic junction, a narrow calyceal neck, and a markedly dilated upper calyceal system (Fig. 2). The patient started urinating immediately after the procedure. Urinalysis showed pyuria; however, urine culture was negative. Her kidney function gradually improved, allowing discontinuation of hemodialysis. Follow-up abdominopelvic magnetic resonance imaging (MRI) after DJ catheter insertion and medical treatment demonstrated the beginning resolution of the fluid collection.

One week after the insertion of the DJ ureteral stent, the patient developed persistent fever, severe abdominal tenderness, and recurrent vomiting. A follow-up abdominopelvic MRI

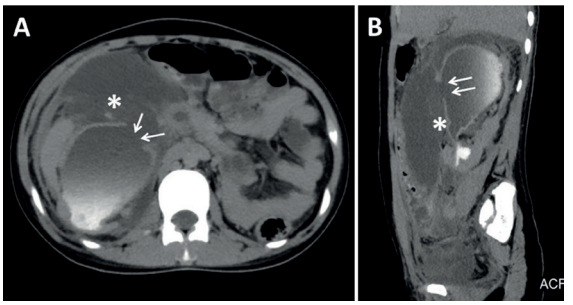

Fig. 1. Contrast-enhanced CT, axial (A) and sagittal reformatted (B) images show ruptured dilated renal pelvis (arrows indicate the defect) and retroperitoneal fluid collection (asterisk).

scan revealed a significant increase in the retroperitoneal fluid collection. In addition, the right renal parenchyma appeared thinned, particularly in the upper pole, with a heterogeneous parenchymal pattern. The ureteral wall surrounding the DJ stent was diffusely thickened and edematous along its entire course, and the bladder wall was also thickened (Fig. 3). Therefore, retroperitoneal abscess drainage was performed, and a drain was placed. Cultures for tuberculosis and other possible pathogens were negative. Following antibiotic revision and abscess drainage, the patient's fever subsided, her overall condition improved, and she was able to resume oral intake. The antibiotic regimens administered to the patient and their respective durations are shown in Fig. 4. Over the course of one month, her creatinine levels gradually decreased to 1.6 mg/dL. Given the presence of elevated parathyroid hormone levels, growth retardation and according to imaging findings, AKI was considered to have occurred on a background of chronic kidney disease (CKD). Due to occlusion of the DJ stent, the patient underwent DJ stent revision two more times. Seven weeks after the initial intervention, a percutaneous nephrostomy was placed due to recurrent occlusion of the DJ stent and persistent urine leakage from the perforated renal pelvis. After successful nephrostomy placement, hydronephrosis resolved, and the patient was discharged at the end of 2.5 months of follow-up, with a serum creatinine level of 1.95 mg/dL and estimated glomerular filtration rate (eGFR) of 29.2 mL/min/1.73 m^2.

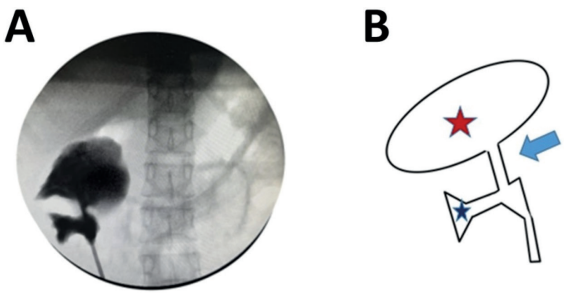

Fig. 2. Retrograde pyelography showing a normal-appearing ureteropelvic junction, a narrow calyceal neck, and a markedly dilated upper calyceal system (A). Schematic illustration of the same findings; the red star indicates the markedly dilated upper calyceal system, the blue arrow indicates the narrowed calyceal neck, and the blue star indicates the lower calyceal system (B).

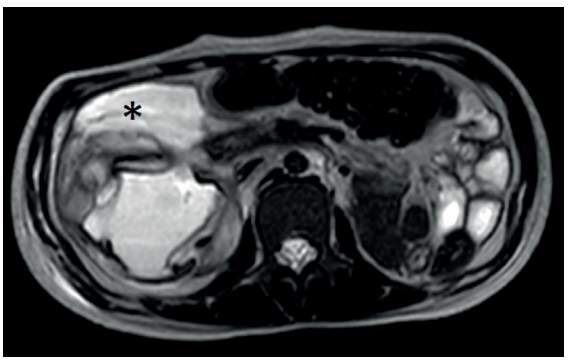

Fig. 3. Follow-up abdominopelvic magnetic resonance imaging demonstrating a significant increase in the retroperitoneal fluid collection (asterisk).

At the three-month follow-up, the nephrostomy catheter spontaneously dislodged. Urinary ultrasonography (US) did not reveal any evidence of a persistent perforation, and no further urine extravasation into the retroperitoneal area was observed. The patient has been under follow-up in our clinic for 17 months with a diagnosis of stage 4 CKD, with a current eGFR of 32.9 mL/min/1.73 m^2 and a serum creatinine level of 1.73 mg/dL.

Discussion

Spontaneous renal pelvis rupture is characterized by extravasation of urine into the perinephric, paranephric, or retroperitoneal spaces without a history of trauma or recent surgery. The underlying pathophysiology is primarily linked to increased intraluminal pressure, which may result from urinary obstruction, urolithiasis, or infection. However, cases without a clear underlying etiology have also been reported.[1-4] Gulati et al.[2] reported three adult cases associated with conditions such as emphysematous pyelonephritis, ureteral stones, and malignancy. Tylski et al.[7] described a case of idiopathic renal pelvis rupture in a 73-year-

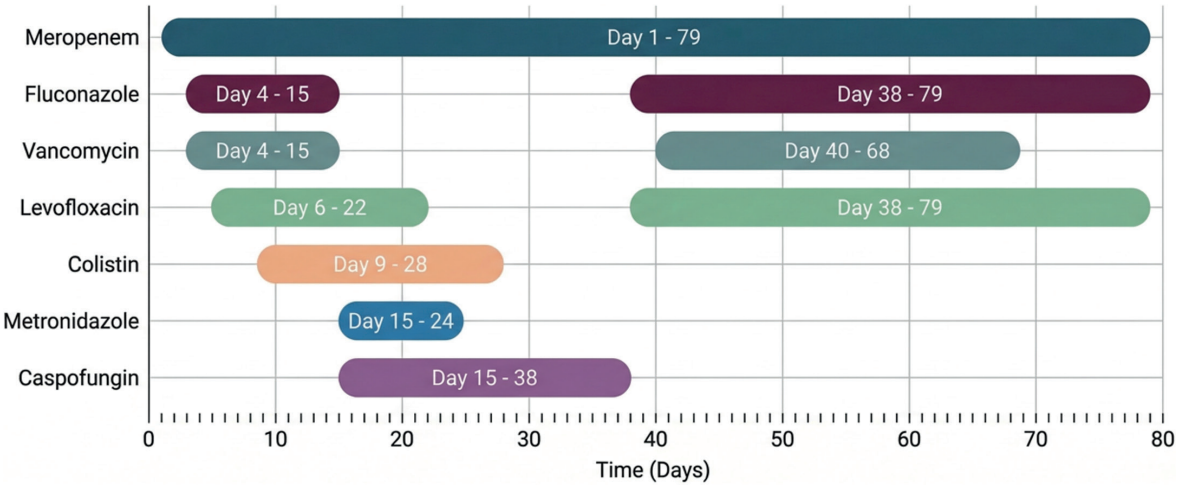

Fig. 4. Timeline of antibiotic regimens and corresponding treatment durations.
All antibiotic dosages were adjusted based on the patient's serial estimated glomerular filtration rate (eGFR) measurements.

old patient with a solitary functioning kidney, requiring hemodialysis—a presentation similar to that of our patient.

Spontaneous renal pelvis perforation is a rare but clinically significant condition that can lead to severe complications, including retroperitoneal abscess formation and AKI. Given its nonspecific clinical presentation, which often includes abdominal or flank pain, vomiting, and costovertebral angle tenderness, the condition closely mimics renal colic. Although rare, it should be considered in the differential diagnosis, particularly in patients exhibiting signs of peritoneal irritation.[1,5,8]

Spontaneous renal pelvis perforation is more frequently observed in adults, whereas pediatric cases remain extremely rare. Taşkınlar et al.[9] reported a case of an 18-month-old girl who developed spontaneous rupture of the renal pelvis due to an extruded kidney stone, a phenomenon rarely documented in the pediatric population. Similarly, Jiang et al.[10] described a case of spontaneous kidney rupture in a 9-month-old boy, associated with urinary obstruction and infection, further highlighting the rarity of this condition in children. These cases underscore the importance of considering spontaneous renal pelvis perforation in the differential diagnosis of pediatric patients presenting with acute abdominal pain and urinary abnormalities, particularly in those with predisposing factors such as urinary obstruction or congenital anomalies.

In the present case, a 14-year-old girl with a solitary functioning kidney developed spontaneous renal pelvis perforation, complicated by AKI and a retroperitoneal abscess. Although the exact type of anomaly could not be clearly identified, the solitary kidney was considered to be dysplastic. It is hypothesized that the renal pelvis perforation occurred secondary to infection in this structurally abnormal kidney. Notably, despite the absence of an apparent obstructive etiology, the patient presented with severe renal dysfunction requiring hemodialysis. An increase in the retroperitoneal fluid collection, which initially regressed with stent placement, eventually required percutaneous drainage. This case highlights the importance of close monitoring and early interventional management in pediatric patients with renal pelvis perforation, particularly in those with a solitary kidney, where renal function is already compromised.

Management of renal pelvis perforation is primarily aimed at relieving urinary obstruction and promoting drainage. In most cases, DJ ureteral stent placement is the first-line intervention, facilitating spontaneous

healing of the perforation.[1,2,8] However, in cases with persistent urine leakage, recurrent stent occlusion, or large fluid collections, percutaneous nephrostomy may be necessary, as demonstrated in our case. While conservative treatment is often effective, surgical intervention may be warranted in cases of extensive rupture or failed drainage.[1,8] However, it should be emphasized that renoprotective approaches are of great importance, especially in patients with a solitary kidney, as in our case.

Conclusion

Spontaneous renal pelvis perforation is a rare but clinically significant condition, particularly in pediatric patients. Given the limited number of cases reported in the literature, the optimal management strategy remains unclear. To our knowledge, none of the previous publications have reported spontaneous renal pelvis perforation in an adolescent with a solitary kidney. Early imaging, timely urinary drainage, and close follow-up are essential to prevent long-term renal impairment. This case highlights the importance of individualized management approaches and underscores the potential for healing in pediatric patients, even in the presence of severe complications.

Ethical approval

Informed consent was obtained from the patient's parents for the publication.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: SY, ZBÖ; data collection: DBÇ, BB, ÖSF, SKŞ; analysis and interpretation of results: DBÇ, SY; draft manuscript preparation: DBÇ, SY, BB, ÖSF, SKŞ, ZBÖ. All authors reviewed the results and approved the final version of the manuscript.

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When non-specific effects matter: methodological considerations in a randomized controlled trial of abdominal massage for pediatric functional constipation

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Dear Editor,

We thank Malekiantaghi et al. for conducting a randomized controlled trial (RCT) evaluating abdominal massage as an adjunctive therapy for functional constipation.[1] While the study offers valuable clinical perspectives on non-pharmacological management, several methodological issues merit further consideration.

First, although food diaries were collected and uniform dietary recommendations were provided, no between-group comparisons of actual dietary fiber or fluid intake were reported. Dietary factors are key modifiable determinants of functional constipation; fiber and fluid intake may influence gastrointestinal transit and stool characteristics.[2,3] Should dietary composition or consumption patterns differ between groups during the intervention period, the observed differences may partly reflect dietary variation rather than massage effects. Future studies should therefore employ standardized dietary assessment tools, such as three-day dietary records or food-frequency questionnaires[4], and incorporate dietary intake variables and measures of dietary adherence as covariates in analysis of covariance (ANCOVA) or multivariate regression models to minimize potential confounding.

Second, both groups received polyethylene glycol at 0.5 g/kg, with doses adjusted according to individual needs. While such flexibility reflects routine clinical practice, it may compromise internal validity and complicate the interpretation of treatment effects in an RCT context. Specifically, laxative dosing in both groups may have varied due to clinical judgment; however, the study did not report actual dosages administered, criteria or frequency of dose adjustments, or between-group comparisons of medication use. This introduces substantial bias risk, as differential dosing patterns—arising from clinician decision-making or varying responses to the intervention—may exist between groups. Consequently, observed outcome differences may partly reflect disparities in medication exposure rather than the effect of abdominal massage itself, with the direction of bias (overestimation or underestimation of the massage effects) remaining difficult to ascertain. A more rigorous approach would involve predefined dosing protocols, such as fixed-dose regimens where clinically appropriate or standardized titration algorithms. Additionally,

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detailed documentation of baseline dosages and subsequent modifications, along with analytical strategies that account for medication exposure (e.g., covariate adjustment or dose-stratified analyses), would improve comparability between groups.

Third, twelve massage sessions involved frequent interaction with therapists, whereas the medication-only control group had limited contact. This imbalance may bias outcomes through the Hawthorne effect[5], leading to enhanced adherence in the intervention group. Furthermore, children with functional constipation often develop defecation anxiety due to prior painful defecation experiences, resulting in stool-withholding behaviors.[6] Regular, non-threatening physical contact may foster a trusting clinician-patient relationship and alleviate children's apprehension. Verbal reassurance during massage may also facilitate relaxation of pelvic floor muscles and reduce stool-withholding behaviors. These relational and behavioral mechanisms, prompted by the additional attention and contact provided by therapists, may contribute to symptom improvement independently of the physiological effects of massage. Incorporating attention-matched control conditions (e.g., sham-massage, light touch, or structured interaction) and standardizing therapist–participant interactions in future studies would ensure equivalence in attention, contact intensity, and communication across groups, thereby strengthening causal inference.

Fourth, "time until initiation of bowel movements" was prespecified but not reported; this is selective reporting that limits comprehensive assessment. Per "Consolidated Standards of Reporting Trials" (CONSORT)[7], all predefined outcomes should be reported or justified, thereby improving transparency.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: FYZ, LPY; analysis and interpretation of results: FYZ, LPY, QQF, JYZ; draft manuscript preparation: FYZ, JYZ; manuscript revision: FYZ, LPY, QQF, JYZ. All authors reviewed the results and approved the final version of the manuscript.

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Before attributing Guillain-Barré syndrome to an adenovirus infection, alternative causes must be thoroughly ruled out

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We read with interest the article by Tuychiboeva et al. about two pediatric patients (Patient-1, 4 years old, boy; Patient-2, 6.5 years old boy) who were both diagnosed with Guillain-Barré syndrome (GBS) of the acute inflammatory demyelinating polyneuropathy (AIPD) subtype, triggered by an adenovirus infection.[1] Patient-1 partially recovered after administration of intravenous immunoglobulins (IVIG), and Patient-2, who also required mechanical ventilation for 7 days, showed improvement after IVIG administration and plasmapheresis.[1] The study is interesting, but a couple of points require discussion.

First, alternative triggers of GBS were not considered and ruled out in the two patients.[1] Since adenoviruses rarely cause GBS[2] and the patients were recruited during the pandemic, testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) would have been essential. Because SARS-CoV-2 can be associated with superinfections[3] and is a common trigger of GBS, it is conceivable that the actual cause of GBS was a SARS-CoV-2 infection rather than the adenovirus infection. Furthermore, since patient-2 also presented with gastrointestinal symptoms, it would have been crucial to rule out a prior infection with *Campylobacter jejuni*, the most common cause of GBS.[4] Other rare GBS triggers that should have been excluded include infections with cytomegalovirus, hepatitis B and C viruses, Epstein-Barr virus, varicella zoster virus, Zika virus, dengue, and *Mycoplasma pneumoniae*. It should also be clarified whether the patient had received any vaccinations before the onset of GBS.

The second point concerns the fact that no contrast-enhanced magnetic resonance imaging of the lumbar spine was performed in Patient-1.[1] To document thickening and contrast enhancement of the lumbar nerve roots, it would have been helpful to confirm GBS imaging-based, as was done in Patient-2.

In conclusion, adenoviruses should not be considered as a cause of GBS as long as all other triggers have been thoroughly ruled out.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: JF; data collection: JF; analysis and interpretation of results: JF; draft manuscript preparation: JF. All authors reviewed the results and approved the final version of the manuscript.

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Adenovirus as a plausible trigger of Guillain-Barré syndrome: response to the letter to the editor

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Dear Editor,

We would like to thank the authors for their thoughtful and constructive comments regarding our manuscript.[1,2] We appreciate the opportunity to clarify several important points raised in their letter. We fully agree that establishing a causal relationship between a specific infectious agent and Guillain-Barré syndrome (GBS) is inherently challenging, particularly in the context of case-based observations.

We agree that GBS is most commonly associated with a range of infectious triggers, including *Campylobacter jejuni*, SARS-CoV-2, and other viral pathogens.[3] Adenovirus infections are known to have a broad clinical spectrum in children, ranging from mild disease to severe systemic involvement, particularly in the presence of comorbidities.[4] Due to the word limitations of the case report format, these detailed microbiological or virological evaluations were not fully elaborated in the original manuscript, although they were systematically performed. As outlined below, a comprehensive microbiological evaluation was undertaken in both cases. Blood and cerebrospinal fluid cultures were negative, and a respiratory viral panel including SARS-CoV-2, influenza viruses, respiratory syncytial virus, rhinovirus, enterovirus, metapneumovirus, parainfluenza viruses, and seasonal coronaviruses, detected only adenovirus. Stool cultures were also negative. Neither patient had a history of recent vaccination. Testing for Zika virus was performed in only Case 2 and was negative, while dengue testing was not performed due to the absence of epidemiological risk in our non-endemic setting. Cerebrospinal fluid testing was negative for varicella-zoster virus, herpes simplex virus, and cytomegalovirus, and TORCH panel testing showed no evidence of infection. Respiratory molecular testing was negative for *Mycoplasma pneumoniae* and other atypical bacterial pathogens. While we acknowledge that it is not possible to definitively exclude all potential infectious triggers, the temporal association and the absence of alternative identifiable causes support adenovirus as a plausible antecedent infection rather than a proven causal factor. In this regard, our intention was not to imply causality, but to report a clinically relevant temporal association observed after a reasonably comprehensive exclusion of common alternative triggers.

Cerebrospinal fluid analysis in our patients was consistent with the diagnosis of GBS. In Case 2, classical albuminocytologic dissociation was clearly demonstrated. In Case 1, although interpretation was limited due to a traumatic

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lumbar puncture, elevated protein levels in the absence of pleocytosis were supportive in the appropriate clinical context.[5]

Regarding imaging, although contrast-enhanced spinal magnetic resonance imaging could have provided additional supportive findings in Case 1, the examination was technically limited due to poor cooperation. In this context, the diagnosis was based on the clinical presentation and electrophysiological findings, which remain the cornerstone of GBS diagnosis in routine clinical practice, particularly when imaging is inconclusive or technically limited.

In conclusion, we fully agree that adenovirus should not be considered a definitive cause of GBS without careful exclusion of other triggers. Our aim was to highlight adenovirus as a plausible antecedent infection in the appropriate clinical context. Adenovirus infections are known to mimic immune-mediated conditions such as Kawasaki disease.[6] In addition, adenovirus has been associated with immune-mediated neurological complications such as acute disseminated encephalomyelitis, supporting a potential mechanistic basis for such associations.[7] We believe that our findings contribute to the limited literature on this association and underscore the need for further studies. Importantly, the accumulation of well-characterized case reports and case series remains essential to better define such rare associations and to generate hypotheses for future mechanistic and epidemiological studies.

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Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: GT, KA, IO, GCC; data collection: KA; analysis and interpretation of results: GT, KA, IO, GCC; draft manuscript preparation: GT, KA ABC. All authors reviewed the results and approved the final version of the manuscript.

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Neonatal bacterial meningitis

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Dear Editor,

We read with great interest the article by Shao et al.[1] examining predictors of poor outcomes in neonatal bacterial meningitis. Despite the improvements in surveillance, meningitis remains a significant contributor to infant morbidity and mortality, with the greatest risk of death occurring during the neonatal period.[2]

However, some methodological limitations should be noted in the article. The immature immune system of neonates, especially preterm, puts them at high risk for bacterial meningitis.[3] First, why were neonates with gestational age <34 weeks and birth weight <1500 g excluded, even though they are one of the highest risk groups for neonatal bacterial meningitis and poor neurodevelopmental outcomes? Secondly, limiting inclusion to only microbiologically confirmed infections may create selection bias because previous antibiotic use may result in sterile cultures regardless of strong clinical evidence of bacterial meningitis. Thirdly, acute neurological complications were major predictors of poor prognosis; however, it is unclear whether neuroimaging (computed tomography, magnetic resonance imaging, or transfontanelle ultrasonography) was performed in all neonates or only in severe cases. Standardized imaging protocols are important to ensure accurate detection of complications and reliable prognostic interpretation.

The primary reliance on the Gesell Developmental Diagnosis Scale may result in underestimating the presence of more subtle cognitive, language, and behavioral deficits. Were long-term developmental assessments conducted by evaluators who were blinded to clinical status and imaging results to reduce bias? Additional detail is also needed about the hearing evaluation, including whether otoacoustic emissions (OAE) or brainstem evoked response audiometry (BERA) were used, because adequate evaluations of hearing are critical to have in long-term follow-up assessments.

Finally, were the predictors identified applicable to the extremely preterm and very-low-birth-weight infants, who remain very vulnerable and were excluded from this investigation? Overall, this study underlines the importance of recognizing early neurological involvement in neonatal bacterial meningitis as a critical prognostic factor. These concerns related to the study's methods will improve the overall quality and applicability of the results.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: AT; data collection: AT; analysis and interpretation of results: AT; draft manuscript preparation: AT. All authors reviewed the results and approved the final version of the manuscript.

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Authors' reply: methodological considerations in evaluating outcomes of neonatal bacterial meningitis

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Dear Editor,

We thank the authors of the Letter to the Editor for their careful reading of our article, "Factors for poor outcomes of neonatal bacterial meningitis: a retrospective multicenter study,"[1] and for their valuable insights.[2] We appreciate the opportunity to clarify the methodological aspects of our research.

Regarding the exclusion of neonates with gestational age <34 weeks and birth weight <1500 g: We deliberately set the inclusion criteria to neonates with a gestational age greater than 34 weeks and birth weight above 1500 grams. Extremely preterm and very-low-birth-weight infants possess a significantly high baseline risk for neurodevelopmental delays and severe intracranial complications (such as intraventricular hemorrhage) that are independent of meningitis.[3] Including this highly vulnerable population would have introduced substantial confounding factors, making it difficult to definitively attribute poor outcomes to bacterial meningitis. Consequently, our findings cannot be directly extrapolated to extremely preterm infants, and we agree that this specific population warrants separate, dedicated investigations.

Regarding the reliance on microbiologically confirmed infections: The diagnosis in our cohort required confirmation by cerebrospinal fluid (CSF) Gram-stained smear or bacteriological culture. We acknowledge the concern that prior antibiotic use can yield sterile cultures, potentially introducing selection bias by excluding partially treated cases.[4] However, relying solely on clinical evidence and CSF pleocytosis in a retrospective multicenter study would inevitably introduce confounding conditions that mimic bacterial meningitis. For instance, without microbiological gold standards, it is notoriously difficult to differentiate partially treated bacterial meningitis from viral meningoencephalitis (such as enterovirus or herpes simplex virus infections). Furthermore, aseptic meningitis associated with systemic inflammatory conditions, such as Kawasaki disease, presents a significant diagnostic challenge when cultures are negative.[5] Therefore, applying these strict microbiological criteria was essential to ensure absolute diagnostic certainty and cohort homogeneity, avoiding the inclusion of these non-bacterial or sterile neuroinflammatory mimics.

Regarding neuroimaging: In our routine clinical practice, cranial magnetic resonance imaging (MRI) is systematically scheduled as a standard evaluation for every neonate suspected of having bacterial meningitis, rather than being restricted only to severe cases. Virtually all patients in our cohort underwent neuroimaging, with the only exceptions being the exceedingly

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rare instances where parents explicitly refused the examination. Thus, the detection of acute neurological complications in our study was both comprehensive and robust.

Regarding developmental assessments: As we noted in our limitations section, evaluating neurodevelopmental outcomes using the Gesell Developmental Diagnosis Scale (GDDS) rather than more comprehensive neuropsychological tools may have resulted in the underestimation of subtle cognitive or behavioral impairments. Furthermore, because follow-up data were retrospectively extracted from outpatient electronic medical records, the evaluating clinicians conducting routine follow-ups typically had access to the infants' medical histories, precluding strict blinding.

Regarding the hearing evaluation: In our clinical centers, brainstem auditory evoked potential (BAEP, equivalent to BERA as mentioned in your query) is a mandatory and routine examination for all neonates and infants diagnosed with bacterial meningitis. This standardized assessment is systematically performed both during the acute disease course and throughout the long-term follow-up. The unilateral hearing loss documented among the neurological sequelae in our study was exclusively based on these rigorous and comprehensive BAEP evaluations.

We thank the readers again for highlighting these important clinical considerations. We believe this discussion further contextualizes our findings and underscores the necessity of early neurological assessment and structured long-term follow-up in affected neonates.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: FL; data collection: FL; analysis and interpretation of results: FL; draft manuscript preparation: FL. All authors reviewed the results and approved the final version of the manuscript.

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CASE REPORTS

LETTERS TO THE EDITOR

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