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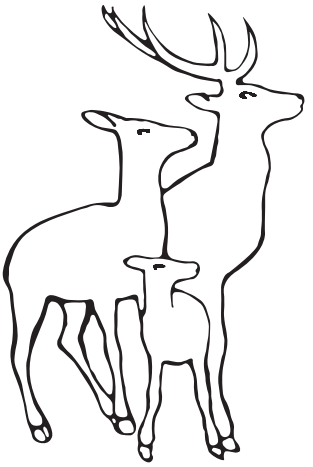

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Original Article

Functional gastrointestinal disorders in Turkish infants: impact of feeding practices, sleep quality, and maternal depression

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ABSTRACT

Background. Functional gastrointestinal disorders (FGIDs) significantly impact infant well- being and healthcare utilization, yet comprehensive data using updated Rome IV criteria in Turkish populations remains limited. Our objective was to determine the prevalence and characteristics of FGIDs in Turkish infants and examine associations with feeding patterns, sleep quality, and maternal depression.

Methods. A cross-sectional study was conducted in a tertiary hospital between February and August 2020. A total of 459 infants aged 1–12 months were enrolled. FGIDs were diagnosed according to Rome IV criteria. Feeding characteristics, sleep quality assessed by the Brief Infant Sleep Questionnaire, and maternal depression measured using the Edinburgh Postnatal Depression Scale were recorded through face-to-face interviews. Comparisons were primarily performed between infants with and without FGIDs. Multivariable logistic regression adjusted for infant age was used to evaluate the association between feeding type and FGIDs.

Results. At least one FGID was identified in 53.2% of infants (n=244). Co-occurrence of multiple FGIDs was observed in 92 infants. Infants with FGIDs were significantly younger than those without FGIDs with a median age of 3 months (interquartile range [IQR]: 2–5) vs 6 months (IQR: 3–9) ($p<0.001$). Poor sleep was markedly more prevalent among infants with FGIDs compared to those without (45.1% vs 22.3%, $p<0.001$). Mothers of infants with FGIDs had higher depression scores than mothers of infants without FGIDs (median: 7.0 [IQR: 4–11] vs 5.0 [3–10], $p=0.030$). In multivariable logistic regression analysis adjusted for infant age, the overall feeding model was not statistically significant ($p=0.240$); however, mixed breast milk and formula feeding was associated with increased FGID risk compared to exclusive breastfeeding (adjusted odds ratio: 2.16, 95% confidence interval: 1.17-3.98, $p=0.014$).

Conclusions. FGIDs affect over half of Turkish infants and are associated with sleep disturbances and maternal depressive symptoms. Mixed breast-formula feeding independently increased FGID risk after age adjustment. Integrated care approaches addressing feeding practices, sleep quality, and maternal mental health are warranted.

Key words: gastrointestinal diseases, postpartum depression, infant, newborn, sleep, breast feeding.

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This study was derived from the medical residency thesis of Betül Yıldırım, entitled "Functional Gastrointestinal Disorders in Infants and Associated Factors", prepared under the supervision of Dr. Özlem Erdede and co-supervision of Dr. Nevzat Aykut Bayrak at the Department of Pediatrics, University of Health Sciences, Zeynep Kamil Women and Children's Diseases Training and Research Hospital, in 2021.

Functional gastrointestinal disorders (FGIDs) are a major group of conditions that cause ongoing symptoms related to gut-brain axis development, which cannot be explained by any biochemical or structural abnormalities.[1,2] In young children, limited ability to express discomfort results in symptoms such as recurrent crying, irritability, and vomiting, causing substantial concern among caregivers.[3] Although FGIDs in childhood are not life threatening, delayed diagnosis and treatment may lead to physical and emotional stress.[2] Studies have shown that infants with FGIDs have a lower quality of life and increased rates of hospital visits.[4] Additionally, the unnecessary utilization of healthcare services and the use of inappropriate treatments during the diagnostic process represent significant challenges.[5]

FGID diagnoses rely on symptom-based Rome IV criteria, with infant regurgitation (IR), infantile colic (IC), and functional constipation (FC) as the most frequently observed conditions in neonates and infants.[3,6,7] Knowledge concerning dyschesia (ID) is notably limited, leading to potential misdiagnosis as IC or FC.[7] Although the pathogenesis of FGIDs is not fully understood, genetics, sociocultural effects, and the microbiome are all thought to have a role.[6] Furthermore, FGIDs have been linked to sleep problems and maternal depression.[8-10] However, investigations on the aspects that contribute to the development of FGIDs are sparse and yield conflicting results.

Previous research has examined individual FGIDs and their associated factors; however, there is limited data on the prevalence and co-occurrence of multiple FGIDs in Turkish infants using the updated Rome IV criteria. The relationship between FGIDs and varying cultural factors such as feeding traditions, sleep patterns, and maternal mental health requires further investigation.[11]

The feeding methods for Turkish infants and the prevailing family structures may influence the prevalence of FGIDs and related factors in ways that differ from those observed in Western countries, where extensive research has been conducted. Understanding these interactions is essential for developing culturally relevant national preventative and management strategies.

The aim of this study was to determine the prevalence and characteristics of FGIDs in Turkish infants and to evaluate their associations with feeding practices, sleep quality, and maternal depression.

Materials and Methods

Study design and setting

This was a single-center cross-sectional study conducted at a tertiary center specializing in obstetrics, gynecology, newborn and pediatric care from February 2020 to August 2020. The study included children between the ages of 1 and 12 months who were admitted to the hospital during this timeframe.

Ethical approval

Ethical approval was obtained from the Ethics Committee of the University of Health Sciences, Zeynep Kamil Women and Children's Diseases Training and Research Hospital on January 20, 2020 (Decision No: 17). The study was conducted in accordance with the principles of the Declaration of Helsinki. Prior to data collection, all participating mothers provided written informed consent.

Data collection

Study data were collected using a structured questionnaire administered to mothers after consent was obtained. The questionnaire included information regarding sociodemographic characteristics, medical history, and relevant clinical factors.

Study population and exclusion criteria

As a tertiary care institution with an average annual birth volume of approximately 3,500, the hospital routinely conducts longitudinal

follow-up of healthy infants up to 12 months of age through its well-baby outpatient clinic if preferred by the parents. Within the scope of this follow-up, infants presenting with various complaints are also systematically evaluated as part of standard pediatric surveillance. Infants were enrolled consecutively; those with known chronic illnesses, a history of extreme or very preterm birth, a confirmed diagnosis of cow's milk protein allergy, or failure to pass meconium within the first 48 hours of life were excluded from the study.

Data collection and group classification

The questionnaire used in the study included items on the child's feeding method, feeding frequency and duration, defecation characteristics, and gastrointestinal symptoms if present. Additionally, demographic characteristics, the infant's sleep patterns, and maternal depression assessment were recorded. Assessments were performed during routine visits, with evaluation timing documented in relation to the infant's age. Mothers were instructed to report symptoms and behaviors from the previous two weeks to reduce recall bias. Interviews were carried out in a private setting to promote open dialogue regarding sensitive subjects, including maternal mood and infant behavior.

Data were gathered on breastfeeding, formula feeding, and the utilization of complementary foods; the duration of exclusive breastfeeding; the timing of the introduction of complementary foods and wheat-containing products; the consumption of milk beyond breast milk or formula; feeding frequency; and the methods of feeding employed.

Maternal depression was assessed using the Edinburgh Postnatal Depression Scale (EPDS), which has been validated and shown to be reliable in the Turkish population by Aydın et al., with a cut-off score of ≥13 indicating probable depression.[12,13] To evaluate the children's sleep quality, the "Brief Infant Sleep Questionnaire (BISQ)" validated for Turkish children was utilized. Infants who woke more than three times during the night, had a total sleep duration of less than 9 hours, or experienced night awakenings lasting longer than 1 hour were classified as poor sleepers according to established criteria.[14,15]

Participants were categorized into two mutually exclusive groups: infants with at least one FGID and infants without FGIDs. All primary analyses were conducted based on this dichotomous classification. The two groups were compared with respect to the variables that were available in the dataset and presented in the results: infant age, sex, birth weight, current weight SDS, feeding interval, duration of exclusive breastfeeding, overall feeding type, infant sleep characteristics, and maternal depression scores.

Statistical analysis

The calculation of sample size was predicted on an anticipated FGID prevalence of 30%[5,6], with a precision of ±4% and a confidence level of 95%, necessitating a minimum of 504 participants. Data were analyzed using IBM SPSS Statistics for Windows version 21.0 (IBM Corp., Armonk, NY, USA). The normality of data distribution was assessed by the Kolmogorov-Smirnov test. Continuous variables were presented as mean ± standard deviation when normally distributed, and as median and interquartile range (IQR: Q1–Q3) when not normally distributed. Categorical variables were expressed as frequencies and percentages (%).

Continuous variables were summarized as median and interquartile range and compared between two independent groups (FGID vs No-FGID) using the Mann–Whitney U test. Categorical variables were expressed as frequencies and percentages and analyzed using the chi-square test; when chi-square test assumptions were not met, Fisher's exact test was applied. The association between feeding type and the presence of any FGID was evaluated using multivariable logistic regression analysis adjusted for infant age. Feeding type was included as a categorical independent variable

with exclusive breastfeeding as the reference category. Results of logistic regression analyses were reported as odds ratios (OR) with 95% confidence intervals (CI). A two-sided p-value <0.05 was considered statistically significant.

Results

Of 557 consecutive infants aged 1-12 months presenting during the study period, 98 were excluded for the following reasons: chronic diseases (n=23), extreme or very preterm birth <32 weeks (n=18), confirmed cow's milk protein allergy (n=31), failure to pass meconium within 48 hours (n=12), and parental refusal to participate (n=14). The final analysis included 459 infants (mean age: 5 ± 3.1 months, mean birth weight: 3.3 ± 0.5 kg, 46.2% female). The sample size of 459 yields 80% power to identify odds ratios of 1.8 or higher for binary exposures with a prevalence of 30%.

Vaginal delivery accounted for 42.3% (n = 194) of births, while cesarean section accounted for 57.7% (n = 265). The mean age of the mothers was 29.0 ± 5.0 years. Regarding hospital visit reasons, 30.5% (n = 140) of participants presented with complaints related to FGIDs, whereas 69.5% (n = 319) presented for other reasons.

Age-stratified analysis revealed that FGID prevalence was highest in infants aged 1-3 months (68.2%, n=156/229), decreased in those aged 4-6 months (45.3%, n=72/159), and was lowest in infants aged 7-12 months (22.5%, n=16/71) (p<0.001 for trend). Co-occurrence of multiple FGIDs was observed in 92 infants, corresponding to approximately 37.7% of those with any FGID. The most common co-occurring FGIDs were combinations of infant regurgitation with infantile colic and infant regurgitation with infant dyschezia. The prevalence of FGIDs and their co-occurrence frequencies are presented in Table I.

Feeding patterns showed that 45.3% (n=208) of infants were exclusively breastfed, 16.1% (n=74) received both breast milk and formula, 2.6% (n=12) were exclusively formula-fed, 29.2% (n=134) received breast milk and complementary foods, and 6.8% (n=31) consumed formula and complementary foods. Additionally, 42.3% (n=194) of the infants used pacifiers. Comparison of participants' demographic characteristics and feeding features is presented in Table II.

Table I. Frequency and co-occurrence of functional gastrointestinal disorders

	n	%
Functional gastrointestinal disorders		
Infant regurgitation	161	35.1
Infantile colic	97	21.1
Infant dyschezia	91	19.8
Rumination	18	3.9
Functional constipation	8	1.7
Functional diarrhea	2	0.4
Cyclic vomiting	0	0.0
Co-occurrence of functional gastrointestinal disorders		
Infantile colic + Infant dyschezia	11	2.3
Infant regurgitation + Infantile colic	36	7.8
Infant regurgitation + Infant dyschezia	24	5.2
Infant regurgitation + Infantile colic + Infant dyschezia	21	4.6

The total number of infants with any FGID was 244. Individual FGID subtypes are not mutually exclusive, as some infants met criteria for more than one FGID. Therefore, the sum of subtype frequencies exceeds the total number of affected infants. FGID: Functional gastrointestinal disorder.

Table II. Demographic and feeding characteristics of the participants

Characteristics	FGID (n=244)	No FGID (n=215)	p
Age (months), median (IQR)	3.0 (2-5)	6.0 (3-9)	<0.001[z]
Birth weight (kg), median (IQR)	3.3 (2.9-3.6)	3.4 (3.0-3.6)	0.062[z]
Current weight SDS, median (IQR)	0.07 (-0.8-0.7)	0.05 (-0.6-0.8)	0.469[z]
Sex, n (%)			0.149[c]
Male	139 (57.0)	108 (50.2)	
Female	105 (43.0)	107 (49.8)	
Birth weight category, n (%)			0.760[c]
Normal	216 (88.5)	187 (87.0)	
Low birth weight	17 (7.0)	15 (7.0)	
Macrosomia	11 (4.5)	13 (6.0)	
Feeding interval, n (%)			0.037[c]
Every hour	33 (13.5)	15 (7.0)	
Every 2–3 hours	103 (42.2)	84 (39.0)	
More than 3 hours	21 (8.6)	30 (14.0)	
On demand	87 (35.7)	86 (40.0)	
Duration of exclusive breastfeeding, n (%)			<0.001[c]
6 months	18 (7.4)	53 (24.7)	
4-6 months	49 (20.1)	68 (31.6)	
<4 months	132 (54.1)	68 (31.6)	
>6 months	12 (4.9)	16 (7.4)	
Never breastfed	33 (13.5)	10 (4.7)	

[z]: Mann-Whitney U test; [c]: Chi-square test.
FGID: Functional gastrointestinal disorder; IQR: Interquartile range (Q1–Q3)

Crude analyses suggested associations between certain feeding patterns and the presence of FGIDs; however, most of these associations attenuated after adjustment for infant age. In multivariable logistic regression analysis adjusted for age, the overall feeding model was not statistically significant (p=0.240). Nevertheless, examination of individual feeding categories revealed that mixed breast milk and formula feeding remained significantly associated with increased FGID risk compared to exclusive breastfeeding (adjusted OR: 2.16, 95% CI: 1.17–3.98, p=0.014). Other feeding patterns showed no significant associations after age adjustment. Estimates for the "formula only" group (n=12) were unstable due to sparse data and are not reported (Table III).

A statistically significant difference was observed between the groups regarding mothers' perception of their infant's sleep (p=0.022), with mothers of infants with FGIDs more likely to perceive their infant's sleep as a serious or minor problem compared to those without FGIDs. Similarly, infants with FGIDs were significantly more likely to meet the criteria for poor sleep (p<0.001).

In addition, maternal depression scores differed significantly between the groups (p=0.030), with higher median scores observed among mothers of infants with FGIDs. Detailed sleep characteristics and maternal depression scores are presented in Table IV.

Table III. Logistic regression analysis: effect of feeding type on risk of functional gastrointestinal disorders

Feeding type	Crude OR (95% CI)	p	Adjusted OR[#] (95% CI)	p
Exclusive breastfeeding (reference)	1.00	–	1.00	–
Breast milk + Formula	2.07 (1.14–3.76)	0.018	2.16 (1.17–3.98)	0.014
Formula only*	–	0.999	–	0.999
Breast milk + Complementary food	0.33 (0.19–0.56)	<0.001	1.32 (0.58–2.97)	0.506
Breast milk + Complementary food + Formula	0.32 (0.17–0.62)	0.001	1.35 (0.54–3.38)	0.523
Formula + Complementary food	0.19 (0.08–0.47)	<0.001	0.91 (0.30–2.78)	0.864

While the overall model was not statistically significant (p=0.240), indicating limited overall explanatory power of feeding type after age adjustment, individual comparison revealed that mixed breast milk and formula feeding was significantly associated with increased functional gastrointestinal disorder risk (p=0.014) compared to exclusive breastfeeding. Crude model: p<0.001, Adjusted model: p=0.240

[#] Adjusted for infant age (months)

*Estimates for the "formula only" group (n = 12) were unstable due to sparse data and are therefore not interpretable.

CI: confidence interval, OR: odds ratio.

Table IV. Sleep characteristics of participants and comparison of maternal depression scores

Characteristics	FGID (n = 244)	No FGID (n = 215)	p
Mother's perception of infant's sleep, n (%)			0.022[c]
A very serious problem	28 (11.5)	15 (7.0)	
A minor problem	86 (35.2)	59 (27.4)	
Not a problem at all	130 (53.3)	141 (65.6)	
Meets poor sleep criteria, n (%)			<0.001[c]
Yes	110 (45.1)	48 (22.3)	
No	134 (54.9)	167 (77.7)	
Maternal depression score, median (IQR)	7.0 (4-11)	5.0 (3-10)	0.030[z]

[c] Chi-square test. [z]: Mann-Whitney U test

FGID: Functional gastrointestinal disorder; IQR: Interquartile range (Q1–Q3).

Discussion

In our study, at least one FGID was identified in 53.2% (n = 244) of the 459 children included. Among the evaluated children, 161 (35.1%) had IR, 97 (21.1%) had IC, and 91 (19.8%) had ID. FGIDs are known to be influenced by biological, psychosocial, and social factors: cultural practices, dietary and bowel habits, and perceptions of symptoms vary across cultures.[11] Differences in geography and cultural background may therefore contribute to variations in the distribution of FGID. Additionally, the higher prevalence observed in our study may be due to the younger age group of our study population and the fact that our hospital serves as a referral center in the region with a pediatric gastroenterology specialist, potentially leading to a higher concentration of children presenting with FGID symptoms. Multivariable analysis adjusted for infant age revealed important nuances in the feeding-FGID relationship. While the overall feeding model was not statistically significant (p=0.240), mixed breast milk and formula feeding emerged as a specific risk factor for FGIDs (adjusted OR: 2.16, p=0.014), independent of infant age. In contrast, the apparent protective associations observed with complementary food introduction in crude analyses became non-significant after age adjustment, suggesting these associations were largely confounded by infant maturation rather than reflecting direct effects of solid food introduction. The persistent significant association between mixed feeding and FGIDs may reflect gut microbiome instability from

alternating between breast milk and formula, incomplete enzymatic adaptation to formula proteins, or disruption of immune tolerance mechanisms.

In a study by van Tilburg et al., which included 264 children aged 0–3 years and utilized the Rome III criteria, at least one FGID was identified in 27.1% of children and at least two FGIDs in 3.4%.[4] In a 2016 review by Ferreira-Maia et al., the reported prevalence of at least one FGID ranged from 27.1% to 38%, while the prevalence of at least two FGIDs was reported as 20.8%.[5] In our study, co-occurrence of multiple FGIDs was observed in 92 infants, corresponding to 37.7% of those with any FGID. This substantial overlap suggests that FGIDs may share common underlying mechanisms and that these conditions should be evaluated within a broader, integrated clinical framework rather than as entirely separate entities.

The higher prevalence of FGID in our study population compared to Western cultures could be attributed to cultural differences in baby care methods, dietary patterns, and symptom interpretation. Turkish families generally have close physical touch with their infants and may be more inclined to identify subtle behavioral changes as worrisome symptoms. Furthermore, extended family involvement in newborn care may affect feeding habits and symptom identification. These cultural characteristics should be taken into account when translating our findings to other populations and devising culturally relevant intervention options. Future studies should look explicitly at how cultural practices affect FGID prevalence and outcomes.

When examining the mean age of participants, the median age of infants with FGIDs was significantly lower than that of those without FGIDs. Previous studies have also shown that the prevalence of FGIDs is inversely proportional to age.[16,17]The relationship between age distribution and FGIDs in our study is consistent with findings in the literature. In summary, the frequency of FGIDs decreases as age increases in children under 1 year of age.

Similarly, in studies conducted by van Tilburg et al. and Steutel et al., no significant difference was found between male and female infants regarding the presence of FGIDs, consistent with our findings.[4,16] In contrast, a 2015 review by Korterink et al., which included children aged 4–18 years, found that functional abdominal pain was significantly more common in girls. This finding was attributed to depression, anxiety, and stressful life events.[18] The absence of sex-related differences in FGID prevalence in our study and in two other studies involving children aged 0–1 year may be explained by the younger age of the population and the fact that these children are less likely to have been exposed to psychosocial stressors.

The relationship between breastfeeding and FGIDs has been investigated in several studies. Steutel et al. compared formula feeding and formula plus complementary feeding to exclusive breastfeeding and found a higher risk of FGIDs among infants fed with formula or formula plus complementary foods.[16] Chew et al., in a study conducted in Malaysia, reported a significantly lower incidence of IR in breastfed infants.[19] Kramer et al. observed that breastfed infants at 1 and 3 months of age experienced significantly less ID, although this difference was no longer apparent at 9 months.[20] Cohen Engler et al. noted fewer episodes of crying in breastfed infants compared to those fed formula.[21]

The non-significant overall feeding model ($p=0.240$) indicates that, when age is properly accounted for, feeding patterns as a whole explain limited variance in FGID occurrence compared to developmental maturation. However, the identification of mixed breast-formula feeding as an independent risk factor has important clinical implications: while exclusive breastfeeding or consistent formula feeding allows the infant's gut to adapt to a single feeding source, alternating between the two may prevent the establishment of a stable intestinal microbiome and enzymatic systems. Healthcare providers should be aware that infants on mixed feeding regimens

may be at higher risk for FGIDs, and when supplementation is necessary, consistent feeding patterns may be preferable to frequent alternation.

Although several biological mechanisms have been proposed to explain how breastfeeding might influence gastrointestinal function, human milk oligosaccharides exert prebiotic effects, and fermentation of breast milk produces short-chain fatty acids, which are thought to enhance gastrointestinal motility and may be linked to these disorders.[22] Additionally, increased melatonin levels transmitted through breastfeeding help regulate circadian rhythms, which may modulate FGID symptoms such as infantile colic.[23] However, in our study, these potential mechanisms were not supported by the adjusted analyses, as feeding type was not independently associated with FGIDs after controlling for infant age. Therefore, while the biological plausibility remains, our findings suggest that developmental and age-related factors may play a more dominant role in the occurrence of FGIDs during early infancy.

Previous studies have suggested that feeding practices and patterns may influence gastrointestinal symptoms in early infancy. Proposed mechanisms include increased air swallowing during frequent feeding, rapid gastric emptying related to high foremilk intake, and physiological immaturity of intestinal regulation during the first months of life.[24,25] These mechanisms remain biologically plausible and may contribute to symptom perception in individual infants.

However, in our study, after restructuring the analyses to focus on the comparison of infants with and without FGIDs and adjusting for infant age, feeding-related variables were not found to be independently associated with FGIDs. Therefore, although feeding counseling remains an important component of routine pediatric care, our findings do not support recommending specific feeding patterns solely for the prevention of FGIDs. Instead, clinical management should consider the multifactorial nature of FGIDs, including developmental factors, sleep quality, and maternal well-being.

FGIDs are frequently observed in conjunction with sleep disturbances.[26] A 2012 study conducted on children aged 8 to 17 years with FGIDs reported that 45% of these children experienced difficulties initiating or maintaining sleep.[27] One of the key components of the circadian rhythm is the sleep-wake cycle, which can be disrupted by environmental factors that obscure the distinction between day and night, thereby affecting sleep quality.[28] Additionally, studies have demonstrated that biological rhythms influence colonic motility.[29] The natural decline in FGID symptoms during early infancy, particularly after the first months of life when circadian rhythms become more established, has led to the hypothesis that circadian rhythm desynchronization may contribute to the pathophysiology of early-life FGIDs.[23] Supporting this view, İnce et al. demonstrated that morning melatonin levels were significantly higher in healthy controls compared to infants with colic symptoms.[23]

Regarding the relationship between sleep and FGIDs, our study demonstrated significant differences between infants with and without FGIDs. Mothers of infants with FGIDs were more likely to perceive their infant's sleep as a serious or minor problem compared to mothers of infants without FGIDs. According to the BISQ used in our study, infants who woke more than three times per night, had more than one hour of nighttime wakefulness, or slept less than nine hours per day were classified as having poor sleep.[14] The proportion of infants meeting these poor sleep criteria was significantly higher among infants with FGIDs compared to those without FGIDs.

Previous studies examining the relationship between sleep and FGIDs have reported mixed results. James-Roberts et al. reported that infants with gastrointestinal complaints slept significantly less than healthy controls, supporting an association between sleep problems and FGIDs.[30] In contrast, Brand et al.,

in a smaller cohort, did not observe a significant relationship between sleep patterns and colic symptoms.[31] While further research is needed in this area, it is believed that sleep disturbances may exacerbate FGID symptoms. Therefore, the relationship between poor sleep and FGIDs suggests that sleep assessment should be routine in infants presenting with gastrointestinal symptoms. Simple interventions to improve infant sleep hygiene may have dual benefits for both sleep quality and FGID symptoms.

Maxted et al., in interviews with 93 mothers attending a Colic Clinic, observed depressive symptoms in 45.2% of the mothers.[32] In another study involving 1,015 mothers, both infants and mothers were evaluated at 2 and 6 months postpartum. It was found that mothers of infants with colic had significantly higher EPDS scores at 2 months and at 6 months—when colic symptoms had resolved—compared to the control group.[10] In our study, mothers of infants with FGIDs had significantly higher depression scores compared to mothers of infants without FGIDs. These findings support the growing evidence that infant gastrointestinal problems and maternal mental health are closely interrelated, emphasizing the importance of considering maternal well-being in the comprehensive management of FGIDs.

Maternal postpartum depression is often overlooked. Considering the relationship between maternal postpartum depression and FGIDs, a thorough assessment of maternal mood, especially in the early months of life, would be beneficial for both infant and maternal health. Most importantly, our findings on maternal depression highlight the need for integrated care approaches. Pediatric practitioners should consider screening for maternal mental health issues, as addressing maternal depression may improve both maternal well-being and infant outcomes.

Our findings are consistent with those of the large-scale, multicenter study conducted in Turkey by Beser et al., which reported a high prevalence of FGIDs during the first six months of life.[33] However, our study extends the existing literature by incorporating psychosocial variables that were not evaluated in that previous investigation. In particular, we demonstrated that mothers of infants with FGIDs had significantly higher depression scores compared to mothers of infants without FGIDs, underscoring the potential psychological impact of infant gastrointestinal symptoms on caregivers. Furthermore, our results revealed a significant association between FGIDs and poor sleep quality, highlighting the importance of considering sleep disturbances in the clinical evaluation of these conditions. Unlike the earlier study, which primarily focused on prevalence and feeding patterns[33], our investigation provides a more comprehensive assessment that includes behavioral and psychosocial dimensions. Therefore, our study contributes novel and clinically relevant data to the understanding of FGIDs in Turkish infants and supports the need for a holistic approach in their diagnosis and management.

Limitations include the single-center design, the hospital's status as a referral center for pediatric gastroenterology which may have led to a higher proportion of patients with gastroenterological complaints, reliance on maternal self-reporting, and the subjective nature of maternal perceptions of time and infant discomfort. To our knowledge, this study is among the few in the literature to address these aspects comprehensively. The strengths of our study include the use of up-to-date Rome IV criteria, assessment of all FGIDs within the 1-12 month age range, face-to-face interviews with mothers, and evaluation of feeding, sleep, sociodemographic characteristics, and maternal depression as factors potentially related to FGIDs.

We believe our study raises awareness about FGIDs and provides guidance for larger-scale research on the prevalence of FGIDs in Turkish children, as well as on key related psychosocial factors such as infant sleep patterns and maternal mental health.

Conclusion

In conclusion, this study provides comprehensive information on the prevalence and clinical correlates of FGIDs in Turkish infants. Our findings demonstrate significant associations between FGIDs, poor infant sleep, and higher maternal depressive symptoms, highlighting the multifactorial nature of these disorders. Although crude analyses suggested associations between several feeding patterns and FGIDs, these relationships largely attenuated after adjustment for infant age. In age-adjusted multivariable analysis, feeding type as a whole was not independently associated with FGIDs. Nevertheless, category-level analysis indicated that mixed breast milk and formula feeding was associated with an increased risk of FGIDs compared to exclusive breastfeeding, suggesting that certain feeding patterns may still be relevant in specific contexts. The observed relationships with sleep disturbances and maternal mental health emphasize the importance of a holistic approach to the assessment and management of affected infants.

These results support the implementation of integrated care models in clinical practice that include routine evaluation of infant sleep patterns and screening for maternal mental health problems. Such approaches may help improve symptom management and overall family well- being during the crucial early months of infant development. Future research should prioritize longitudinal studies and intervention trials to clarify causal relationships and to evaluate the effectiveness of integrated prevention and management strategies. Understanding the mechanisms underlying these associations will be essential for developing evidence-based interventions adaptable to different cultural contexts.

Ethical approval

The study was approved by Ethics Committee of the University of Health Sciences, Zeynep Kamil Women and Children's Diseases Training and Research Hospital (date: January 20, 2020, number: 17).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: BY, ÖE, NAB; data collection: BY; analysis and interpretation of results: BY, NAB, ET; draft manuscript preparation: BY, ET, NAB, ÖE. Supervisor: NAB. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Maternal knowledge, attitudes, and practices regarding childhood fever: a cross-sectional study

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ABSTRACT

Background. Fever remains one of the most common reasons for pediatric visits and is a key issue in family health literacy. Misconceptions and fears often lead to inappropriate interventions or delayed medical care. Understanding mothers' perceptions of childhood fever is essential for effective health education. This study explored maternal attitudes and practices regarding fever to inform future health education strategies and guideline development.

Methods. A cross-sectional, descriptive study was conducted via face-to-face interviews with mothers of children attending a tertiary pediatric outpatient clinic for non-febrile complaints. Primary outcomes included knowledge of fever definition, medication use, and home remedies. Secondary outcomes assessed the impact of sociodemographic factors and reasons for seeking care. Incorrect antipyretic administration (inappropriate dose or dosing interval) was analyzed using multivariable logistic regression.

Results. Of 1000 participating mothers (aged 18–51, mostly high school graduates), 73.8% administered the correct antipyretic dose, while 15.7% used insufficient and 4.3% excessive doses. The main concern (93%) was preventing febrile convulsions. Traditional advice (45.4%) and online sources (32.4%) were frequently consulted. In infants under one year, mothers more often contacted a physician instead of using antipyretics at 38 °C. Tepid sponging with vinegar was less used in children under 1 and those aged 2–3 years at 40 °C. Multivariable analysis showed that lower maternal education, absence of a home thermometer, prematurity history, and absence of a family history of febrile seizures were independently associated with incorrect antipyretic administration; the strongest association was observed for absence of a home thermometer (adjusted odds ratio: 2.74, 95% confidence interval: 1.89–3.98). Mothers of adolescents (12–18 years) were less likely to use home-based interventions and showed a greater tendency toward seeking medical care at 38 °C. Families with one child were less likely to undress the child during a fever compared to those with multiple children.

Conclusions. Targeted education addressing misconceptions and inappropriate fever management practices could enhance outcomes and reduce unnecessary healthcare utilization.

Key words: childhood, fever, home remedies, mothers, health knowledge, attitudes, practices.

Childhood fevers represent a significant health literacy challenge for families and frequently lead to hospital visits.[1] In 44% to 66% of instances, a body temperature of at least 38 °C is reported as a fever, showing differences both between and within nations.[2-6] A fever is a natural reaction to infections that may indicate severe illness.[7] The fear of complications like febrile convulsions, brain damage, coma, dehydration, or even death leads many parents to treat even minor increases in their children's body temperature.[3,8]

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Parents' misconceptions and fears about childhood fever, often referred to as "fever phobia"[9], lead to inappropriate interventions and home remedies such as administering antipyretics even at normal body temperatures; waking the child for temperature checks; sponging with cold water, vinegar, or alcohol; wrapping the child in blankets; using antibiotics instead of antipyretics; and improper dosing and timing of antipyretic medications. The child's health can be negatively impacted by all these measures.[2,7,10] Child discomfort-related anxiety in families results in application delays and unnecessary medical visits, contributing to healthcare system strain.[11,12] The standard practice in medical facilities is for caregivers to expect a definitive fever diagnosis, antipyretics, and blood work.[13]

The goal of this study was to examine the knowledge and attitudes of Turkish mothers concerning childhood fever, focusing on its definition, appropriate medication, and home remedies. The secondary outcome focused on examining the impact of sociodemographic factors on maternal knowledge and fever management practices, as well as identifying the reasons for seeking medical care, and factors associated with incorrect antipyretic administration. This study sought to improve clinical reports used in educating mothers.

Materials and Methods

Study design and participants

Between March 2022 and March 2023, a descriptive, cross-sectional study was conducted using face-to-face interviews with mothers whose children were referred to the pediatric outpatient clinics of the University of Health Sciences, Zeynep Kamil Maternity and Children's Training and Research Hospital in İstanbul, Türkiye, for complaints other than fever. The study adopted a quantitative approach, focusing on measurable outcomes, despite incorporating face-to-face interviews and selected open-ended questions.

Ethical approval was obtained from the Hospital Ethics Committee (date: 23 February 2022; decision number: 26). Participation was voluntary, and all participants were informed about the study objectives and confidentiality measures. Verbal informed consent was obtained from each participating mother prior to enrollment.

A sample size of 1,000 mothers was calculated to provide generalizable results for Türkiye with a 95% confidence level and a 3.1% margin of error. Sample adequacy for multivariable analysis was assessed using G*Power (version 3.1.9.7), assuming a two-sided α of 0.05, 80% power, proportions of 0.20 and 0.28, and an allocation ratio of 1, which indicated a minimum required sample size of 894 participants. Eligible participants included mothers of children aged 1 month to 18 years who presented with non-febrile complaints. Mothers who were not the primary caregivers, whose children had an active fever at presentation, or who declined to participate were excluded.

Questionnaire and data collection

Data were collected using a structured questionnaire developed based on previous similar studies and reviewed for content validity by two pediatricians.[2,8] The questionnaire comprised 31-items organized into six thematic sections addressing demographic characteristics, fever history and equipment, knowledge about childhood fever, fever management practices, practices to specific fever thresholds (38 °C, 39 °C, and 40 °C), and sources of information. The full questionnaire and definitions of fever management practices are provided in Supplementary Table S1.

Fever management practices were defined in advance to ensure consistency in data interpretation. *Home observation* was defined as monitoring the child at home without immediate medical consultation while observing general condition and symptoms. *Reducing clothing layers* referred to removing excess clothing to facilitate heat loss and improve thermal comfort. *Excessive covering with blankets* was defined as covering the child with multiple or

thick blankets despite the presence of fever. *Tepid sponging* referred to wiping the child's body with lukewarm water (approximately 32–35 °C) to reduce discomfort associated with fever. *Application of alcohol* was defined as applying alcohol to the skin (e.g., rubbing or wiping) as a traditional method intended to reduce body temperature. *Application of a vinegar-soaked cloth* referred to placing cloths soaked in diluted vinegar on the child's body as a traditional fever-reducing practice. A *lukewarm shower or bath* was defined as bathing the child with lukewarm water to provide symptomatic relief during fever, whereas *cold bathing* referred to bathing the child with cold water in an attempt to rapidly reduce body temperature. *Oral antipyretic formulation* was defined as the administration of antipyretic medication via the oral route, including liquid or solid formulations.

The questionnaire included both closed-ended and open-ended questions, with selected items allowing multiple responses. Completion of the questionnaire required approximately 7–10 minutes and was conducted through face-to-face interviews by trained pediatricians. For questions permitting multiple responses, each option was analyzed independently; percentages may not total 100%. Frequencies represent the number of mothers selecting each option.

Caregiver-reported antipyretic doses were evaluated by recalculating weight-adjusted dosing according to the child's body weight and standard dosing recommendations. Recommended dosages were defined as 10–15 mg/kg per dose for paracetamol and 10 mg/kg per dose for ibuprofen, with administration intervals of 4–6 hours and 6–8 hours, respectively.[14] Administration was considered appropriate when the reported dose and interval were within these recommended ranges; otherwise, it was classified as inappropriate antipyretic administration.

Open-ended responses were analyzed using thematic content analysis. Responses were independently categorized by two researchers, and any discrepancies were resolved through consensus. All completed questionnaires were stored securely to ensure participant confidentiality until data analysis was initiated.

Statistical analysis

For statistical analysis, we used the NCSS 2007 Statistical Software (Number Cruncher Statistical System, Utah, USA). Categorical data are shown as frequencies and percentages; continuous data as means ± standard deviations. Normality of continuous variable distributions was evaluated via the Kolmogorov-Smirnov test. Depending on suitability, Pearson's chi-square or Fisher's exact test was used to compare categorical variables. Comparisons between groups of mothers, stratified by educational level, age, and number of children, were conducted using the chi-square test to assess differences in practices and attitudes. For repeated categorical responses across the three fever temperature scenarios (38 °C, 39 °C, and 40 °C), Cochran's Q test was used. Multivariable analysis was performed using binary logistic regression to identify factors independently associated with incorrect antipyretic administration. The variables entered into the model were maternal age, maternal educational level, child age, child sex, family history of febrile seizures, home thermometer availability, and history of prematurity; selected on the basis of clinical relevance and previous literature2,8, and our study population characteristics. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were calculated. A p-value of less than 0.05 was considered statistically significant.

Results

Demographic characteristics of the participants

The demographic and family characteristics of the 1,000 participants are summarized in Table I. Most parents (77.2%) reported having previous experience managing childhood fever.

Table I. Participant characteristics and their family histories

Variable	Value
Child's age, months	29 (1-204)
<1 year	439 (29.4%)
1–3 years	149 (23.2%)
4–5 years	111 (12.2%)
6–11 years	213 (24.3%)
12–18 years	88 (10.9%)
Male child	554 (55.4%)
Multiple pregnancy	39 (3.9%)
Number of children in the family	2 (1–7)
Single child	297 (29.7%)
Two children	473 (47.3%)
Three children	167 (16.7%)
≥4 children	63 (6.3%)
Mother's age, years	31.4 ± 6.1 (18–51)
≤24 years	137 (13.7%)
25–34 years	568 (56.8%)
35–44 years	273 (27.3%)
≥45 years	22 (2.2%)
Maternal education	
Illiterate	27 (2.7%)
Primary school	308 (30.8%)
Secondary school	105 (10.5%)
High school	413 (41.3%)
University	139 (13.9%)
Doctorate	8 (0.8%)
Family history	
Prematurity	230 (23.0%)
Epilepsy/seizures	114 (11.4%)
Febrile convulsions	167 (16.7%)
Chronic disease	154 (15.4%)

Continuous variables are presented as mean ± standard deviation for normally distributed data and as median (minimum–maximum) for non-normally distributed data. Categorical variables are presented as counts and percentages, n (%).

Fever history and equipment

Thermometer ownership was common, reported by 85.4% of families, predominantly digital thermometers (75.4%); 20.6% of households owned more than one thermometer. Antipyretics were available in 94% of households, most commonly paracetamol (59.9%) or a combination of paracetamol and ibuprofen (29.0%).

Fever definition and sources of information

Among 977 mothers, the mean axillary temperature threshold defining fever was 37.8 ± 1.3 °C. Correct identification of 35 °C as the hypothermia threshold was achieved by only 38.7% of respondents, while 49.6% were unable to provide a definition.

Healthcare professionals were reported as a source of fever-related information by 74.6% of respondents. Older family members (45.4%) and social media (32.4%) were also frequently cited, whereas formal education and books accounted for only 5.1%.

Regarding perceptions of fever, most mothers believed that fever could lead to febrile seizures (n = 920), brain damage (n = 567), or severe illness (n = 308).

Effects of maternal education level on fever management practices

Liquid antipyretic formulations, predominantly paracetamol, and inaccurate dosing were more frequently reported among mothers with lower levels of education (below high school level) (Table II). Lower maternal education was independently associated with incorrect antipyretic administration. Maternal education level was significantly associated with higher rates of thermometer ownership ($p<0.001$).

Waking children to assess body temperature showed no significant variation according to maternal education level ($p=0.123$). In contrast, education level significantly influenced information sources: mothers with lower education more frequently relied on older family members, whereas mothers with higher education levels more often consulted healthcare professionals, books, and social media ($p<0.001$).

Table II. Effects of maternal educational level on different parameters regarding fever management

Variable	Primary (n=308)	Secondary (n=105)	High school (n=413)	University (n=139)	p-value
Thermometer at home, present	238 (77.3)	88 (83.8)	370 (89.6)	130 (93.5)	**<0.001**
≥2 thermometers at home, present	17 (5.5)	18 (17.1)	107 (25.9)	49 (35.3)	**<0.001**
Waking a child for measurement	176 (57.1)	65 (61.9)	245 (59.3)	68 (48.9)	0.123
Antipyretic					
Paracetamol	221 (71.8)	51 (48.6)	242 (58.6)	61 (43.9)	**<0.001**
Ibuprofen	16 (5.2)	5 (4.8)	16 (3.9)	7 (5.0)	
Combination	71 (23.1)	49 (46.7)	155 (37.5)	71 (51.1)	
As syrup	200 (64.9)	62 (59.0)	263 (63.7)	108 (77.7)	**<0.001**
As suppository	41 (13.3)	8 (7.6)	50 (12.1)	6 (4.3)	
Combined use or tablet form	67 (21.8)	35 (33.3)	100 (24.2)	25 (18.0)	
Correct timing	201 (65.3)	73 (69.5)	318 (77.0)	121 (87.1)	**<0.001**
Incorrect usage	97 (31.5)	24 (22.9)	97 (23.5)	30 (21.6)	**0.032**
Source of information*					
Family elders' advice	144 (46.8)	34 (32.4)	218 (52.8)	43 (30.9)	**<0.001**
Neighbors	46 (14.9)	20 (19.0)	31 (7.5)	8 (5.8)	**<0.001**
Physician/healthcare worker	216 (70.1)	67 (63.8)	327 (79.2)	111 (79.9)	**<0.001**
Social media	41 (13.3)	24 (22.9)	197 (47.7)	55 (39.6)	**<0.001**
Books	5 (1.6)	1 (1.0)	18 (4.4)	19 (13.7)	**<0.001**
Degree of education	1 (0.3)	0 (0.0)	2 (0.5)	4 (2.9)	**0.015**
Reasons for preventing fever*					
To relieve child	113 (36.7)	29 (27.6)	245 (59.3)	60 (43.2)	**<0.001**
To prevent organ damage	101 (32.8)	28 (26.7)	206 (49.9)	42 (30.2)	**<0.001**
To prevent seizures	284 (92.2)	97 (92.4)	393 (95.2)	124 (89.2)	**<0.001**
To prevent disability	88 (28.6)	20 (19.0)	173 (41.9)	15 (10.8)	**<0.001**
To treat fever	126 (40.9)	26 (24.8)	225 (54.5)	56 (40.3)	**<0.001**
Fever may cause*					
Serious disease	91 (29.5)	20 (19.0)	156 (37.8)	31 (22.3)	**<0.001**
Brain damage	163 (52.9)	45 (42.9)	274 (66.3)	67 (48.2)	**<0.001**
Seizure	283 (91.9)	95 (90.5)	383 (92.7)	127 (91.4)	0.854
Coma	109 (35.4)	30 (28.6)	133 (32.2)	23 (16.5)	**<0.001**
Death	86 (27.9)	26 (24.8)	97 (23.5)	21 (15.1)	**0.026**

Values are presented as n (%) within each maternal education subgroup. Comparisons were performed using the chi-square test or Fisher's exact test.
*Column percentages may exceed 100% for multiple-response items.

Recognition of the role of education in fever management was significantly higher among university-educated mothers (p = 0.015). This group expressed lower concern regarding severe fever-related outcomes and was less likely to administer antipyretics to prevent seizures or disability.

Effect of previous fever experience on maternal practices

Mothers with prior fever management experience more frequently owned multiple thermometers and used a wider range of antipyretic formulations. This group also

demonstrated significantly greater knowledge of correct dosing and dosing intervals (p=0.001).

Effects of maternal age

Mothers aged ≥45 years were more likely to report the absence of antipyretics at home (22.7%) and were less likely to wake their child to measure body temperature (31.8%) compared with mothers younger than 45 years (both p<0.001). Concern about fever reduction for comfort (p=0.017), organ protection (p<0.001), and treatment purposes (p=0.002) was also significantly lower in this age group (Table III).

Reliance on older family members (p=0.018) and social media (p=0.008) was less frequent among older mothers (>45 years). Mothers younger than 24 years more often preferred rectal antipyretic formulations, predominantly paracetamol, and showed significantly lower adherence to recommended dosing intervals (p=0.001). Maternal age was not significantly associated with correct dosage (p=0.591). Concerns regarding fever-related coma, brain damage, and death were more prevalent among mothers younger than 45 years.

Table III. Effects of maternal age according to age groups

Variable	≤24 years (n=137)	25–34 years (n=568)	35–44 years (n=273)	≥45 years (n=22)	p-value
Thermometer at home, present	100 (73.0)	504 (88.7)	238 (87.2)	12 (54.5)	**<0.001**
≥2 thermometers at home, present	15 (10.9)	123 (21.7)	56 (20.5)	5 (22.7)	**0.043**
Antipyretic at home, present	118 (86.1)	545 (96.0)	260 (95.2)	17 (77.3)	**<0.001**
Time interval of antipyretics, appropriate	80 (58.4)	430 (75.7)	213 (78.0)	14 (63.6)	**<0.001**
Correct volume of antipyretics	96 (70.1)	424 (74.6)	206 (75.5)	15 (68.2)	0.591
Waking the child up for temperature measurement	99 (72.3)	339 (59.7)	128 (46.9)	7 (31.8)	**<0.001**
Source of fever information*					
Family elders	77 (56.2)	259 (45.6)	110 (40.3)	8 (36.4)	**0.018**
Neighbors	13 (9.5)	52 (9.2)	40 (14.7)	4 (18.2)	0.065
Physician, healthcare worker	95 (69.3)	433 (76.2)	203 (74.4)	15 (68.2)	0.350
Social media	42 (30.7)	205 (36.1)	72 (26.4)	3 (13.6)	**0.008**
Books	1 (0.7)	31 (5.5)	12 (4.4)	0 (0.0)	0.075
Degree of education	0 (0.0)	4 (0.7)	3 (1.1)	0 (0.0)	0.627
Reasons for preventing fever*					
To relieve the child	68 (49.6)	276 (48.6)	111 (40.7)	5 (22.7)	**0.017**
To prevent organ damage	70 (51.1)	240 (42.3)	77 (28.2)	3 (13.6)	**<0.001**
To prevent seizures	127 (92.7)	535 (94.2)	248 (90.8)	19 (86.4)	0.165
To prevent disability	65 (47.4)	185 (32.6)	52 (19.0)	3 (13.6)	**<0.001**
To treat fever	75 (54.7)	264 (46.5)	101 (37.0)	7 (31.8)	**0.002**
Fever may cause*					
Serious disease	66 (48.2)	183 (32.2)	58 (21.2)	1 (4.5)	**<0.001**
Brain damage	89 (65.0)	344 (60.6)	129 (47.3)	5 (22.7)	**<0.001**
Seizures	129 (94.2)	523 (92.1)	250 (91.6)	18 (81.8)	0.257
Coma	67 (48.9)	177 (31.2)	58 (21.2)	4 (18.2)	**<0.001**
Death	54 (39.4)	138 (24.3)	43 (15.8)	3 (13.6)	**<0.001**

Values are presented as n (%) within each maternal age subgroup. Group comparisons were performed using the chi-square test or Fisher's exact test.
*Column percentages may exceed 100% for multiple-response items.

Family practices at different degrees of fever and by child age

Fever management practices at different temperature levels are summarized in Table IV. Home-based interventions were more commonly reported at 38 °C, whereas seeking medical consultation and antipyretic use predominated at 39 °C and 40 °C ($p<0.05$).

Families with more than one child were more likely to remove clothing from their child at 39 °C ($p=0.001$), with lower rates among single-child families (28.78%) compared with families with two (37.12%) or more than three children (47.24%). The number of children did not significantly influence other practices.

Liquid antipyretic use at 38 °C was significantly lower among children aged <1 year ($p=0.042$) (Table V). Mothers of adolescents (12–18 years) showed a tendency toward seeking medical care and were less likely to use home-based

Table IV. Parents' practice at different axillary temperatures (38, 39, and 40 °C)

Variable	38 °C	39 °C	40 °C	p-value
Staying at home	373 (37.3)	64 (6.4)	4 (0.4)	**<0.001**
Taking off clothes	585 (58.5)	348 (34.8)	217 (21.7)	**<0.001**
Wrapping with blanket	6 (0.6)	5 (0.5)	1 (0.1)	0.172
Tepid sponging	368 (36.8)	152 (15.2)	69 (6.9)	**<0.001**
Sponging with alcohol	2 (0.2)	0 (0.0)	0 (0.0)	0.135
Sponging with vinegar	98 (9.8)	36 (3.6)	15 (1.5)	**<0.001**
Lukewarm shower	405 (40.5)	358 (35.8)	168 (16.8)	**<0.001**
Bath in cold water	24 (2.4)	25 (2.5)	18 (1.8)	0.581
Antipyretic syrup administration	701 (70.1)	672 (67.2)	539 (53.9)	**<0.001**
Antipyretic suppository application	124 (12.4)	110 (11.0)	82 (8.2)	**0.007**
Calling the doctor	74 (7.4)	68 (6.8)	33 (3.3)	**<0.001**
Hospital admission	440 (44.0)	868 (86.8)	988 (98.8)	**<0.001**
Antibiotic administration	6 (0.6)	6 (0.6)	4 (0.4)	0.778

Data are presented as n (%). As responses were obtained from the same individuals across the three temperature scenarios, differences in proportions were analyzed using Cochran's Q test. All observations were complete (n=1000).

Table V. Maternal fever practice with different age groups of children

		<1 years n=439	2–3 years n=149	4–5 years n=111	6–11 years n=213	12–18 years n=88	p-value
38° C	Staying at home	180 (41.0)	65 (43.6)	42 (37.8)	73 (34.3)	15 (17.0)	**<0.001**
	Take off clothes	283 (64.5)	87 (58.4)	72 (64.9)	111 (52.1)	30 (34.1)	**<0.001**
	Tepid sponging	180 (41.0)	53 (35.6)	40 (36.0)	73 (34.3)	21 (23.9)	**0.036**
	Syrup antipyretic use	286 (65.1)	115 (77.2)	80 (72.1)	158 (74.2)	64 (72.7)	**0.042**
39° C	Take off clothes	175 (39.9)	64 (43.0)	39 (35.1)	54 (25.4)	18 (20.5)	**<0.001**
	Calling the doctor	39 (8.9)	14 (9.4)	5 (4.5)	9 (4.2)	3 (3.4)	**0.047**
40° C	Take off clothes	110 (25.1)	39 (26.2)	19 (17.1)	42 (19.7)	10 (11.4)	**0.013**
	Sponging with vinegar	3 (0.7)	0 (0.0)	4 (3.6)	4 (1.9)	3 (3.4)	**0.041**
	Syrup antipyretic use	219 (49.9)	79 (53.0)	56 (50.5)	129 (60.6)	56 (63.6)	**0.027**
	Suppository antipyretic use	43 (9.8)	10 (6.7)	8 (7.2)	9 (4.2)	12 (13.6)	**0.042**

Data are presented as n (%) within each child age subgroup. Differences across age groups were analyzed using the chi-square test.

interventions such as undressing or sponging (p<0.05). At 39 °C, physician contact was more frequent among mothers of infants (p=0.047). At 40 °C, mothers of older children were less likely to remove clothing (p = 0.013). Across all age groups, antipyretic use increased significantly at 40 °C (p<0.05). Child age was not independently associated with incorrect antipyretic administration. Vinegar-soaked cloth application at 40 °C was less frequent among children aged <1 year and 2–3 years (p=0.041).

Multivariable analysis of factors associated with incorrect antipyretic administration

Multivariable logistic regression (Table VI) identified lower maternal education, absence of a home thermometer, lack of a family history of febrile seizures, and a history of prematurity as independent predictors of incorrect antipyretic administration. The absence of a home thermometer showed the strongest association with the outcome (aOR 2.74, 95% CI 1.89–3.98), while middle school education or lower remained associated with higher odds compared with university education or higher. A history of prematurity and lack of a family history of febrile seizures were also independently associated with incorrect administration. Maternal age showed a borderline association, whereas child age and sex were not independently associated with the outcome.

Discussion

Despite the availability of international guidelines and educational initiatives on childhood fever, parental misconceptions remain common and continue to influence fever management practices.[15] Consistent with the concept of "fever phobia," originally described by Schmitt[9] and subsequently confirmed in multiple populations, parental anxiety is often driven by fear of severe complications rather than clinical indicators. In this large cohort of 1,000 mothers, maternal knowledge, attitudes, and practices regarding childhood fever were systematically evaluated, allowing direct comparison with existing national and international data.

Although thermometers and antipyretics were widely available in households, substantial misconceptions regarding fever management persisted. Similar to previous studies from Türkiye and other countries, antipyretics were frequently administered to prevent febrile seizures, often with incorrect dosing.[2,8,16] Inconsistent definitions of fever and uncertainty regarding appropriate thresholds

Table VI. Multivariable logistic regression analysis of factors associated with incorrect antipyretic administration

Variable	Adjusted OR	95% CI	p-value
Child age (years)	1.03	0.99–1.07	0.210
Male sex	0.90	0.69–1.18	0.456
Maternal age (years)	0.98	0.95–1.00	0.068
Maternal education			**0.007**
Middle school or lower	1.91	1.24–2.95	**0.003**
High school	1.43	0.92–2.22	0.108
University or higher		Reference	
History of prematurity	1.43	1.04–1.96	**0.030**
No family history of febrile seizures	1.46	1.01–2.12	**0.044**
No thermometer at home	2.74	1.89–3.98	**<0.001**

n values are provided for subgroup categories.
CI: confidence interval; OR: odds ratio.

have been shown to increase reliance on informal information sources, including older family members and social media, rather than professional medical guidance.[6,10] Our findings further support evidence that prior experience with fever management improves adherence to recommended practices, while maternal age influences antipyretic use and perceptions of illness severity[17,18], and maternal age remained independently associated with differences in perceptions and behaviors. Multivariable analysis showed that incorrect antipyretic administration was independently associated with lower maternal education, absence of a home thermometer, absence of a family history of febrile seizures, and prematurity history. Collectively, these results underscore the need for targeted, evidence-based educational interventions addressing persistent knowledge gaps.

Fear of febrile seizures, brain damage, and severe illness represented the most prominent concerns among mothers in this study. Similar levels of anxiety have been reported globally, with systematic reviews demonstrating that exaggerated perceptions of fever-related harm remain widespread among caregivers.[17,19] Preventing febrile seizures and relieving discomfort were the primary motivations for antipyretic use, consistent with earlier reports.[16,18] Common home-based interventions included undressing, sponging, and increased fluid intake.[16] However, despite their widespread use, particularly in developing countries[19], many physical cooling methods lack robust evidence of benefit, and outdated practices such as cold applications or alcohol rubbing continue to be reported.[7]

In the present study, although over half of mothers reported removing their child's clothing, fewer than half used tepid sponging, and nearly 10% applied vinegar, a traditional practice that may provoke rebound fever and is currently discouraged.[20] Tepid sponging refers to wiping with lukewarm water (approximately 32–35 °C), whereas warm sponging uses slightly warmer water aimed primarily at comfort rather than rapid cooling. Randomized trials and comparative studies have demonstrated that tepid sponging does not confer additional benefit over warm sponging or antipyretic therapy alone and may increase discomfort in children.[20,21] These findings highlight a persistent discrepancy between evidence-based recommendations and real-world caregiver practices.

Encouragingly, antibiotic use for fever alone was reported by fewer than 1% of participants, reflecting the effectiveness of national antimicrobial stewardship and rational antibiotic use policies implemented in Türkiye.[2,8] This finding contrasts favorably with earlier reports from regions where inappropriate antibiotic use for febrile illnesses remains prevalent.[12]

Thermometer ownership in our cohort exceeded rates previously reported in both national and international studies[22,23], potentially reflecting improvements in socioeconomic conditions and access to medical devices. Notably, the absence of a home thermometer showed the strongest independent association with incorrect antipyretic administration. Consistent with existing literature, paracetamol remained the most frequently used antipyretic.[6,19,24] The marked decline in acetylsalicylic acid use aligns with safety concerns and public health messaging regarding its association with adverse outcomes.[19] Cultural factors appeared to influence medication administration routes; although suppository use has been reported in up to half of caregivers in earlier studies[3,6], its use was considerably lower in our cohort, particularly among younger mothers.

Alternating antipyretic therapy has not been shown to provide superior clinical benefit compared with monotherapy.[25] In line with this evidence, fewer than one-third of mothers in our study reported alternating paracetamol and ibuprofen, a proportion lower than previously reported in Türkiye.[2,8] This trend may reflect increased awareness of guideline-based recommendations or earlier healthcare consultation as fever severity increases.

Incorrect dosing of antipyretics remains a significant concern.[10] Comparable rates of dosing errors have been reported in previous Turkish cohorts[8], and our findings indicate that nearly one-quarter of mothers either administered incorrect doses or were uncertain about appropriate dosing. Given the well-documented risk of paracetamol toxicity associated with overdosing[13], these findings emphasize the importance of caregiver education regarding weight-based dosing and appropriate administration intervals.[11]

Previous regression-based studies have shown that the factors associated with fever-related outcomes may differ according to the outcome assessed, with some studies emphasizing caregiver characteristics and others highlighting the child's acute clinical condition.[10,24] In our cohort, absence of a family history of febrile seizures and a history of prematurity were associated with a higher likelihood of incorrect antipyretic administration. Although febrile seizure history has been linked to higher caregiver concern in previous work[13], greater familiarity with fever-related events may be associated with more cautious medication use. The association with prematurity may likewise reflect weight-based dosing challenges and the greater care burden of preterm-born children, although this interpretation requires confirmation in future studies. These findings also suggest that the source of information may influence how caregivers manage fever and administer medication at home.

Physicians were identified as the most trusted source of information, consistent with prior studies[26], although older family members and social media continued to play influential roles. While digital platforms can serve as effective tools for disseminating health information, misinformation has been shown to exacerbate parental anxiety and contribute to unsafe practices.[26,27] Structured, physician-guided digital education initiatives may therefore represent an opportunity to improve fever management literacy.

Consistent with previous research[18], nearly half of the participants reported seeking hospital care even for low-grade fever, reflecting anxiety-driven rather than clinically necessary healthcare utilization. Younger mothers expressed greater concern regarding fever-related complications and demonstrated lower adherence to recommended dosing intervals, whereas older mothers exhibited more conservative management strategies, likely reflecting greater experience and confidence.[17]

The association between maternal education and fever management remains controversial.[6] In agreement with earlier studies[18], university-educated mothers in our cohort were less likely to perceive fever as dangerous or to engage in aggressive fever reduction. However, educational attainment alone did not consistently translate into safer medication practices, reinforcing the need for practical, experience-based education rather than knowledge-focused interventions alone.

Key strengths of this study include its large and diverse sample size and the use of in-person surveys administered by pediatricians, minimizing response bias and enabling detailed data collection. By focusing on parents of children without active fever, the influence of acute anxiety on responses was reduced, allowing a more accurate assessment of baseline knowledge and attitudes.

This study has several limitations. Data were based on self-reported maternal practices rather than direct observation. The single-center design may limit generalizability, and selection bias is possible, as participating mothers may have had higher health literacy. The questionnaire was not formally pilot tested before implementation. Additionally, responses to open-ended questions may have been influenced by interviewer bias. The questionnaire was not psychometrically validated (e.g., reliability testing), which may limit measurement precision.

Conclusion

Misconceptions and anxiety-driven behaviors regarding childhood fever remain common among mothers, despite the availability of international guidelines. Consistent with previous studies, fever is frequently perceived as an immediate threat, leading to inappropriate practices such as incorrect antipyretic dosing, inappropriate antipyretic administration, non–evidence-based physical interventions, and unnecessary healthcare utilization for low-grade fever. Fever management behaviors were influenced by maternal age, prior experience, and sources of information, whereas higher educational attainment alone did not consistently translate into safer practices. The low rate of antibiotic use observed suggests that national antimicrobial stewardship efforts have been effective; however, persistent gaps in dosing accuracy and continued reliance on traditional practices underscore the need for targeted, evidence-based caregiver education. Integrating physician-led counseling into routine pediatric care and promoting reliable digital information sources may help reduce parental anxiety and improve home fever management.

Supplementary materials

Supplementary materials for this article are available online at https://doi.org/10.24953/turkjpediatr.2026.6662.

Ethical approval

This study received approval from the Zeynep Kamil Maternity and Children's Training and Research Hospital Ethics Committee (date: 23.02.2022, number: 26). Every participant received assurance regarding the privacy of their information and the voluntary nature of their involvement. All participating mothers were informed of the purpose of the study and provided their verbal consent.

Author contribution

Study conception and design: NUK, KG, ES; Data collection: KG, ÖE, ES; Analysis and interpretation of results: NUK, KG, ÖE; Draft manuscript preparation: NUK, KG, ES. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Factors affecting distal femoral cartilage in healthy adolescents: a cross-sectional ultrasonographic study

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ABSTRACT

Background. Distal femoral cartilage is the most commonly deteriorated articular cartilage during metabolic and inflammatory processes. Musculoskeletal ultrasound (MSUS) is a widely accessible imaging modality to assess distal femoral cartilage thickness (DFCT). This study aims to explore DFCT and associated factors in healthy adolescents.

Methods. Healthy adolescents aged between 12-18 years were eligible for the study. The central points of the medial and lateral femoral condyles and the intercondylar area were measured on bilateral knees by using B-mode MSUS according to a predefined scanning protocol. The average of DFCT measurements was evaluated according to age, sex, anthropometric measurements, exercise habits, and vitamin D levels.

Results. A total of 150 adolescents participated in the study, with a mean age of 15 year; 67% were female. Age and sex were two factors showing significant effects on mean DFCT ($p \leq 0.001$). A negative mild correlation was observed between age and mean DFCT ($r=-0.252$, $p=0.002$). Weight, height, body mass index, and exercise frequency were not related to DFCT. Participants with severe vitamin D deficiency had similar DFCT when compared with others, and no correlation was observed between their levels ($r=0.109$, $p=0.191$).

Conclusion. DFCT varies during adolescence, with age and sex identified as the primary associated factors. Anthropometric measurements, exercise frequency, and vitamin D levels did not show any effect on DFCT in healthy adolescents.

Key words: knee, cartilage, adolescence, musculoskeletal ultrasound, vitamin.

Articular cartilage is important for easy and compact movement of diarthrodial joints, ensuring optimal joint function and mobility. Various factors, including chronic diseases, mechanical overload, metabolic syndrome, aging, and genetic factors can significantly impact the structure, quantity, and quality of cartilage.[1] Notably, distal femoral cartilage (DFC) is one of the most commonly deteriorated articular cartilages during metabolic and inflammatory processes.[2]

Musculoskeletal ultrasound (MSUS) is increasingly used in imaging of joint structures in the pediatric population with rheumatic diseases.[3] Recent efforts have been made on normative data of the MSUS findings of joints in children and adolescents.[4,5] Most of these studies were mainly focused on cartilage thickness.[6,7] Yet, B-mode MSUS is an excellent, reliable, and feasible tool with a high level of agreement with magnetic resonance imaging to assess the DFC thickness (DFCT).[8,9] The studies in

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adults without chronic conditions reported that sex, height, vitamin D level, and professional sports are contributors to DFCT.[10-12] Despite the increased accessibility in the use of MSUS in the pediatric population, there remains a paucity of studies investigating DFCT and the associated factors to DFCT.

This study aims to explore DFCT according to age and sex and to examine its relationship with anthropometric measurements, exercise habits, and vitamin D levels during adolescence.

Materials and Methods

Study population and design

Adolescents aged between 12-18 years were included in this cross-sectional study between January-April 2023 in Tekirdağ City Hospital in the city of Tekirdağ located on the Northwestern coastline of Turkiye. Demographic and clinical characteristics, exercise routines, and routine laboratory data were noted. The participants were grouped according to their ages as follows: group 1: ≥12 and <14, group 2: ≥14 and <16, and group 3: ≥16 years. Standard deviation scores (SDS) of the anthropometric measurements (weight, height, and body mass index [BMI]) were calculated according to the growth charts of Turkish children.[13] Sex- and age-specific BMI ≥95th percentile defined obesity.[14] Serum 25-hydroxy-vitamin D (25-OH vitamin D) levels were considered deficient if <20 ng/mL and severely deficient if <10 ng/mL. Health-related quality of life (HRQoL) was evaluated using the Pediatric Quality of Life Inventory Generic Core Scales (PedsQL-GC) with young adult self- and parent proxy-reports[15], which have been translated and validated in the Turkish adolescent population.[16] The scale consists of 23 items encompassing four domains: physical, emotional, social, and school functioning. Domain scores were calculated as the mean of the transformed item scores within each domain. The Health Summary Score (HSS) in PedsQL is a composite measure that reflects a child's overall HRQoL by combining key functional domains. The Physical HSS was calculated by the physical functioning domain and the Psychosocial HSS by the emotional, social, and school functioning domains. Higher scores indicate better HRQoL.[15] Adolescents were excluded if they had a chronic disease, a history of knee trauma in the preceding six months or knee surgery. Adolescents with abnormal laboratory tests suggesting chronic diseases (e.g. hyperthyroidism) and those involved in professional sports were also excluded. The participants were recruited after their routine well-child visit for an ultrasonographic examination.

Ultrasonographic examination

A pediatric rheumatologist (POAA) and a physiatrist (EGK), blinded to the clinical/laboratory findings, measured DFCT by MSUS within 10 days of the clinical visit of the participants. Both clinicians had at least three years of experience in MSUS. A senior physiatrist (LO) technically controlled MSUS images and measurements.

During the measurements, the participants lay supine with their knees maximally flexed and the probe positioned just superior to the upper border of the patella in the transverse plane. The greatest DFCT (hyaline/articular cartilage) perpendicular to the bony surface was visualized.[17,18] The central points of the medial and lateral femoral condyles (right lateral condyle: RLC, left lateral condyle: LLC, right medial condyle: RMC, left medial condyle: LMC), and the intercondylar area (RICA and LICA) were measured bilaterally (Fig. 1). At least three consecutive measurements of each were taken and the average was noted. Likewise, the average of the measured RLC, LLC, RMC, LMC, RICA, and LICA was then defined as 'mean DFCT'. Intra- and inter-reader reliability of both physicians among the measurements taken from the same area on the same day were also assessed. All measurements were performed using either a 5-12 MHz linear transducer (Siemens Acuson S3000) or a 12-2 MHz linear transducer (Hitachi Arietta 65).

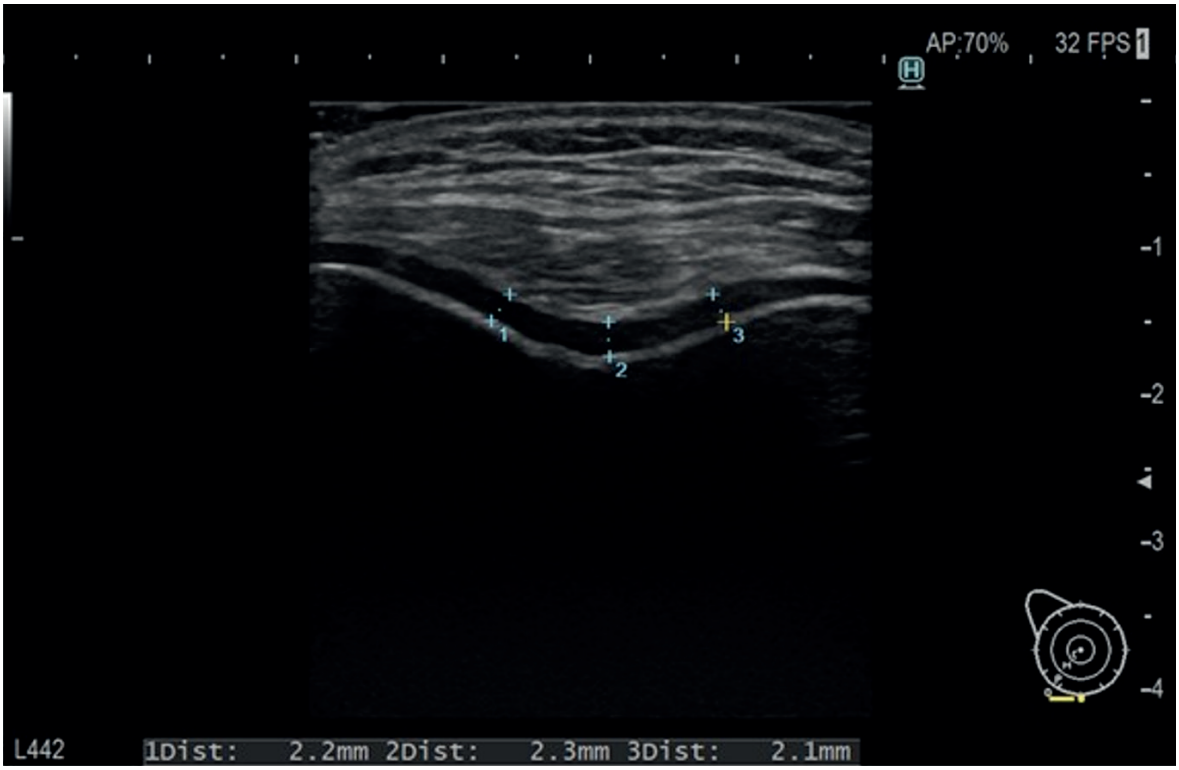

Fig. 1. Distal femoral cartilage thickness measurement at the lateral condyle (1), intercondylar area (2), and medial condyle (3)

The study complied with the Declaration of Helsinki and it was approved by the local Human Research Ethics Committee. Written parental permission and assent were obtained from all participants.

Statistical analysis

Descriptive statistics were defined by the frequency (n) and percentage (%) for categorical and mean ± standard deviation (SD) or median with interquartile range (IQR; 25th-75th percentile) for continuous variables. The Shapiro-Wilk test with distribution graphs was performed to demonstrate the normality of the data distribution. Categorical variables between groups were compared by the chi-square test while the Mann-Whitney U test was used for continuous variables. The effects of age group and sex on femoral cartilage thickness were evaluated using a two-way analysis of variance (two-way ANOVA) for each cartilage measurement (mean DFCT, RLC, RICA, RMC, LLC, LICA, and LMC). Age group (three levels: ≥12-14, ≥14-16, and ≥16-18 years) and sex (male, female) were entered as fixed factors, and each cartilage thickness parameter was analyzed as a separate dependent variable. For each model, main effects of age group and sex, as well as the interaction effect (age*sex), were examined. Assumptions of normality and homogeneity of variances across groups was assessed using the Shapiro-Wilk and Levene's test to ensure the validity of the model. Correlations between clinical, laboratory, and ultrasonographic measurements were evaluated by Pearson coefficients (r), whereby r ≥0.2 was considered significant, 0.4 - 0.6 as moderate, and r ≥0.6 as strong. Intra- and inter-reader reliability of two physicians was determined by intraclass correlation coefficient (ICC) with the 95% confidence interval (CI) and ICC ≥0.75 was considered an excellent level of reliability. All data were analyzed using SPSS version 21.0.0 and statistical significance was set at $p < 0.05$.

Results

A total of 150 adolescents between the ages of 12-18 years participated in the study. The characteristics of the participants are shown in Table I. DFCT measurements of the right and left knee were strongly correlated (r for RLC and LLC=0.862, p<0.001; r for RMC and LMC=0.861, p<0.001; r for RICA and LICA=0.854, p<0.001). Regarding MSUS measurements of the two physicians, the ICC for intra- and inter-reader reliability were 0.96 (0.95-0.97) and 0.86 (0.81-0.90), respectively.

Comparison of the DFCT according to the age groups and sex is given in Table II. Two-way ANOVA revealed significant main effects of age and sex on mean DFCT (p≤0.001 for age and sex). Overall, DFCT decreased with increasing age and was consistently thicker in males compared with females. The age*sex interaction was significant for mean DFCT (p=0.040), indicating that the age-related decrease in cartilage thickness differed between males and females. There was a negative mild correlation between age and mean DFCT (Table III). Weight, height, and BMI were not significantly correlated with DFCT measurements. Serum 25-OH vitamin D levels, weight, height, BMI, exercise habits, and HRQoL did not differ between the age groups (all p>0.05).

The participants with obesity had similar mean DFCT as those with normal weight (2.16 mm, IQR 1.97-2.43 vs. 2.04 mm, IQR 1.80-2.32, p=0.074). The mean DFCT of the participants doing exercise regularly did not differ from the others (2.10 mm, IQR 2.03-2.28 vs. 2.07 mm, IQR 1.87-2.37, p=0.673). The participants with severe vitamin D deficiency demonstrated similar mean DFCT when compared with others (1.96 mm, IQR 1.77-2.37 vs. 2.10 mm, IQR 1.88-2.34, p=0.111) and there were no correlations between vitamin D levels and mean DFCT (r=0.109, p=0.191).

Table I. Characteristics of the study population (N=150).

Age, years, mean ±SD	14.95 ± 1.74
Age groups, n (%)	
Group 1: ≥12-14	47 (31.3)
Group 2: ≥14-16	57 (38.0)
Group 3: ≥16-18	46 (30.7)
Female sex, n (%)	100 (66.7)
Weight, SDS, mean ±SD	0.45 ± 1.63
Height, SDS, mean ±SD	0.19 ± 1.03
BMI, SDS, mean ±SD	0.30 ± 1.57
Obesity, n (%)	30 (20.0)
25-OH vitamin D level, ng/mL, mean ±SD	13.53 ± 5.97
25-OH vitamin D status, n (%)	
Deficiency group: <20	132 (88.0)
Severe deficiency group: <10	44 (29.3)
Regular exercise, n (%)	11 (7.3)
PedsQL-GC, median (IQR)	
Physical HSS, self-report	84.38 (71.88-93.75)
Physical HSS, parent proxy-report	87.50 (69.53-93.75)
Psychosocial HSS, self-report	75.00 (63.33-86.67)
Psychosocial HSS, parent proxy-report	79.17 (61.67-86.67)

BMI: body mass index, HSS: Health Summary Score, IQR: interquartile range, PedsQL-GC: Pediatric Quality of Life Inventory-Generic Core, SD: standard deviation, SDS: standard deviation score.

Table II. Comparison of distal femoral cartilage thickness measurements according to age groups and sex.*

	Age Group	All participants mean ± SD (n)	Female mean ± SD (n)	Male mean ± SD (n)	Main Effect: Age (p-value)	Main Effect: Sex (p-value)	Interaction: Age*Sex (p-value)
Mean DFCT	≥12-14	2.29 ± 0.39 (47)	2.07 ± 0.29 (24)	2.52 ± 0.35 (23)	0.001	<0.001	0.040
	≥14-16	2.03 ± 0.32 (57)	2.02 ± 0.33 (47)	2.11 ± 0.26 (10)			
	≥16-18	2.04 ± 0.31 (46)	1.92 ± 0.25 (29)	2.24 ± 0.29 (17)			
RLC	≥12-14	2.36 ± 0.42 (47)	2.12 ± 0.27 (24)	2.60 ± 0.40 (23)	0.001	<0.001	0.027
	≥14-16	2.09 ± 0.33 (57)	2.07 ± 0.33 (47)	2.17 ± 0.35 (10)			
	≥16-18	2.12 ± 0.31 (46)	2.03 ± 0.31 (29)	2.27 ± 0.24 (17)			
RICA	≥12-14	2.23 ± 0.43 (47)	2.04 ± 0.35 (24)	2.43 ± 0.42 (23)	0.076	<0.001	0.176
	≥14-16	2.04 ± 0.39 (57)	2.02 ± 0.39 (47)	2.13 ± 0.37 (10)			
	≥16-18	2.03 ± 0.36 (46)	1.88 ± 0.26 (29)	2.28 ± 0.38 (17)			
RMC	≥12-14	2.31 ± 0.42 (47)	2.10 ± 0.63 (24)	2.53 ± 0.41 (23)	0.002	<0.001	0.099
	≥14-16	2.04 ± 0.35 (57)	2.03 ± 0.37 (47)	2.12 ± 0.21 (10)			
	≥16-18	2.03 ± 0.36 (46)	1.91 ± 0.30 (29)	2.24 ± 0.36 (17)			
LLC	≥12-14	2.36 ± 0.40 (47)	2.13 ± 0.67 (24)	2.60 ± 0.32 (23)	<0.001	<0.001	0.035
	≥14-16	2.07 ± 0.34 (57)	2.05 ± 0.34 (47)	2.14 ± 0.30 (10)			
	≥16-18	2.05 ± 0.33 (46)	1.92 ± 0.28 (29)	2.26 ± 0.30 (17)			
LICA	≥12-14	2.22 ± 0.40 (47)	2.01 ± 0.65 (24)	2.44 ± 0.36 (23)	0.008	<0.001	0.032
	≥14-16	1.98 ± 0.36 (57)	1.98 ± 0.38 (47)	2.01 ± 0.23 (10)			
	≥16-18	2.02 ± 0.35 (46)	1.89 ± 0.27 (29)	2.25 ± 0.35 (17)			
LMC	≥12-14	2.27 ± 0.41 (47)	2.04 ± 0.62 (24)	2.50 ± 0.36 (23)	<0.001	<0.001	0.071
	≥14-16	1.99 ± 0.33 (57)	1.97 ± 0.34 (47)	2.09 ± 0.31 (10)			
	≥16-18	1.97 ± 0.34 (46)	1.86 ± 0.30 (29)	2.16 ± 0.32 (17)			

*Two-way ANOVA; values are presented as mean ± SD (mm).
DFCT: distal femoral cartilage thickness, LICA: left intercondylar area, LLC: left lateral condyle, LMC: left medial condyle, RICA: right intercondylar area, RLC: right lateral condyle, RMC: right medial condyle, SD: standard deviation.

Table III. Correlation of distal femoral cartilage thickness with age and anthropometric measurements according to sex.*

	Mean DFCT, mm		
	All participants (n=150)	Female (n=100)	Male (n=50)
Age, years	-0.252 (0.002)	-0.163 (0.105)	-0.315 (0.026)
Weight, SDS	0.149 (0.069)	0.208 (0.038)	0.006 (0.968)
Height, SDS	0.098 (0.232)	0.104 (0.301)	-0.026 (0.858)
BMI, SDS	0.140 (0.087)	0.194 (0.053)	0.016 (0.912)
25-OH vitamin D, ng/mL	0.109 (0.191)	0.044 (0.667)	-0.099 (0.507)

*Pearson correlation coefficients [r (p-value)]; mild: 0.2–0.39, moderate: 0.4–0.59, strong: ≥ 0.6; p-value <0.05
BMI: body mass index, DFCT: distal femoral cartilage thickness, SDS: standard deviation score.

Discussion

This cross-sectional study demonstrated that age and sex were the major associated factors of DFCT in healthy adolescents. On the other hand, anthropometric measurements, exercise, and vitamin D levels did not show any relation with DFCT during adolescence.

Cartilage thickness has been reported to be thicker during early childhood, decreasing till the ages of 13-15 years, and almost stabilizing thereafter.[4,19] In line with this finding reported by a few studies available in the literature, we found that DFC was thicker in participants below 14 years of age. Furthermore, we showed that an inverse correlation was present between age and DFCT during adolescence. The second significant factor affecting DFCT was found to be sex in our study, i.e., males had significantly thicker DFC than females. The observed interaction patterns suggest that the decrease in DFCT with age during adolescence does not progress uniformly between sexes. This result is not only consistent with postpubertal and adult reports but also with those of prepubertal children, which suggests factors other than sex hormones affect cartilage thickness.[5,7,11] Of note, the reason for different cartilage volumes between males and females even in the prepubertal period remains unexplained in the current literature.

A recent study reported that height, weight, and BMI were not effectors of cartilage thickness in school-aged children.[7] Another study found that thinner cartilage was observed with increasing height and weight in healthy children. Notably, height was suggested to be the best predictor of cartilage thickness with age.[5] Moreover, a longitudinal study demonstrated a significant positive correlation between the cartilage volume accrual with changes in height but not with weight. Indeed, children who were overweight had similar cartilage volume as children with normal weight.[20] We found no relationship between DFCT and height, weight, and BMI. Also, obesity appeared not to affect DFCT. Although obesity is a well-known risk factor for osteoarthritis, it seems that its effect on cartilage becomes apparent in older ages.[1] Lastly, we did not observe any impact of regular exercise on DFCT. However, the number of children doing regular exercise was limited in our study and we excluded those performing professional sports to homogenize our sample. A study in healthy young university students showed that cartilage thickness was higher in sportsmen and there was a direct relationship between the muscle percentage and cartilage thickness.[21] Moreover, children undertaking more vigorous sports showed higher amounts of cartilage accrual.[20]

Vitamin D is an essential mediator in skeletal health and there is a very well-known association between vitamin D deficiency and rickets, osteomalacia, and osteoporosis, particularly in newborns, the elderly, and high-risk patient populations. Besides, diverse studies suggest that vitamin D has many extraskeletal functions and that its deficiency is related to several other diseases.[22] Despite its prevalent deficiency worldwide, there is no consensus on the routine measurement of its level and vitamin D supplementation in healthy children.[23] Strikingly, vitamin D deficiency was present in almost 90% of our study population and one-third had severe vitamin D deficiency despite living in a coastline city of Turkiye with high numbers of sunny days. We showed that the DFCT was not affected by severe vitamin D deficiency. Fortunately, its potential detrimental effects on cartilage are not clearly evident during adolescence; however, opposite reports in adults and the elderly delineate further attention to implementing guidelines on screening and supplementation of vitamin D deficiency in this critical period of life.[10,24,25]

This study has several limitations, including its cross-sectional design and single-center setting. It investigated only DFC, although it is one of the most commonly deteriorated articular cartilages that is easily measured. Other cartilages can also be evaluated in the future. Unfortunately, the majority of the study population had low vitamin D levels and they mostly demonstrated

a sedentary lifestyle. Other environmental and hormonal factors that might affect cartilage thickness might have been included. Further, it would be interesting to have follow-up visits with longitudinal ultrasonographic evaluations of cartilage thickness. Also, the structural features that can be observed during MSUS, such as surface irregularity or echogenicity, might be taken into consideration in future studies. Advanced methods for functional and biomechanical assessment can be used to support our findings. On the other hand, the use of a standardized approach with excellent reliability in MSUS examination represents an important strength of our study.

In conclusion, DFCT shows variations during adolescence, whereby age and sex are the main associated factors, while weight, height, BMI, and exercise seem to have no effects. Vitamin D deficiency does not seem to affect DFCT in adolescents; however, given its negative effect on cartilage health in adults, longitudinal data are needed.

Ethical approval

The study was approved by the Clinical Research Ethics Committee of Tekirdag City Hospital (date: 25.11.2022, number: TSH-2023-017).

Author contribution

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

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The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Bridging the gap: knowledge deficits and adherence challenges in adolescents with congenital heart disease

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ABSTRACT

Background. Although approximately 90% of children with congenital heart disease (CHD) survive into adulthood, many lack sufficient knowledge about their condition and the need for life-long care. This leads to gaps in follow-up, especially during transition to adulthood, nonadherence to treatment, and increased risk of complications. This study aimed to assess CHD-related knowledge and adherence among adolescents.

Method. The Leuven Knowledge Questionnaire for Congenital Heart Disease (LKQCHD) was translated and validated into Turkish to evaluate CHD-related knowledge, including treatments, endocarditis, pregnancy risks, appropriate contraceptive methods, and the risk of recurrence. Adequate disease knowledge was defined as answering ≥80% of questions correctly. The Medication Adherence Reporting Scale (MARS) was used to assess medication adherence.

Results. Among 118 adolescents, only two had adequate knowledge (≥80% correct), with a mean LKQCHD score of 51.09/100. Older adolescents and those with higher adherence had significantly better knowledge. The poorest knowledge areas were endocarditis and reproductive health.

Conclusion. The insufficient disease knowledge among CHD patients may lead to poor adherence and increased comorbidities, and higher mortality in adulthood. We recommend implementing a structured education and transition program focused on improving health literacy, adherence, and continuity of care, developed collaboratively by cardiologists and adolescent medicine specialists.

Key words: adolescent, congenital heart disease, disease knowledge, treatment adherence, transitional care.

Congenital heart disease (CHD) is the most common congenital defect, with an estimated prevalence of nearly 8 per 1000 live births.[1] Due to advances in diagnosis and treatment, around 90% of children with CHD now reach adulthood.[2] Lifelong follow-up of these patients are necessary due to long term complications of CHD such as heart failure, endocarditis, arrhythmia and pulmonary hypertension.[3] Despite its importance, many patients

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experience lapses in care—often around the age of 19-20 years, during the transition to adult services—largely due to a false sense of being "cured" or unawareness of the need for follow-up.[4-8] Many adolescents with CHD have a limited understanding of their condition, while greater knowledge is linked to better follow-up adherence and fewer risky health behaviors such as substance use, poor oral hygiene, and insufficient physical activity.[8-11] To address these gaps, transitional care programs have been developed to enhance disease knowledge, reinforce self-management skills, and emphasize the importance of lifelong care—ultimately improving adherence and reducing long-term health risks.[12-14]

Beginning in early adolescence, the programs gradually shift healthcare responsibilities from parents to adolescents, promoting a deeper understanding of their condition and encouraging greater self-management.[13,14] Current evidence indicates that participation in these programs not only enhances patient education and disease-related knowledge but also promotes autonomy, improves disease management, and fosters self-acceptance.[15-18] Research also demonstrates that greater disease knowledge is linked to engagement in positive health behaviors, and that integrated, clinic-based transition interventions can reduce loss to follow-up among adolescents and young adults with CHD.[19,20] However, the direct impact of disease knowledge on medication adherence remains unclear among adolescents with CHD. Existing data on disease knowledge among adolescents with CHD predominantly originates from studies conducted in high- and middle-income Western countries, whereas research from low-and middle-income countries remain limited in this area.

To the best of our knowledge, no Turkish studies have investigated disease knowledge or treatment adherence among adolescents with CHD, nor is there a validated tool available to assess CHD-related disease knowledge. With this study, we aimed to assess CHD-related knowledge and compliance among adolescents under our care.

Materials and Methods

Study population and design

This prospective, survey-based cohort study included adolescents and young adults with CHD and was conducted between April 2023 and May 2024 with the approval of local Ethics Committee. Youth with CHD (aged 14 to 24 years) who were followed up at our hospital and who attended at least one outpatient visit at our Pediatric Cardiology clinic or who were assessed by our Pediatric Cardiology team during inpatient admission were included in the study. Patients with known intellectual disability or with major congenital anomalies of other organ systems (apart from the existing congenital cardiac anomaly) were excluded from the study. For patient selection, the applications to the Pediatric Cardiology outpatient clinic were monitored daily, and patients with a diagnosis of CHD who met the inclusion criteria were identified and invited to participate in the study following their examinations at the pediatric cardiology outpatient clinic.

Informed consent was obtained from both adolescents and parents or guardians of the patients under 18 after introducing the study purpose and procedure. After obtaining the necessary consent, face-to-face interviews lasting around 12-15 minutes were conducted with the patients in the meeting room of the pediatric cardiology department. Patients were asked to fill out the Leuven Knowledge Questionnaire for Congenital Heart Disease (LKQCHD) along with the Medication Adherence Report Scale (MARS) if they were on any medication for their cardiac disease. All patients were also asked to fill out the "Demographic and Socioeconomic Assessment Form".

Information obtained from medical records

The cardiac diagnosis, the age at the time of diagnosis, history of any cardiac interventional procedures or surgeries, presence of bioprosthetic or mechanical valves, presence of an intracardiac defibrillator (ICD) or pacemaker, hospital admissions due to cardiac causes in the last 5 years, history of endocarditis, presence of accompanying pulmonary hypertension, and non-cardiac chronic diseases were queried through medical records obtained from the electronic records and patient files.

Participants were grouped based on the cardiac diagnoses, the anatomical complexity of their congenital cardiac defects using the Bethesda classification (simple, moderate and high complexity) and their functional limitations according to the New York Heart Association (NYHA) Functional Classification for Heart Failure. NYHA functional classification was determined based on the clinical complaints and physical limitation indicators assessed during the most recent Pediatric Cardiology outpatient visit. The scale responses, form answers, details of the individual's medical history, and NYHA classifications were processed into the study's database with a patient-specific assigned code.

Demographic and socioeconomic assessment form

This form was developed by the research team. The participant's age, the province they live in, their education level (the grade they are in if they are continuing their education, the last grade they attended if they took a break from their education, whether they took a break from their education due to heart disease, and the duration of the break), details about their parents (age, education, occupation, living status, and whether they live together), the number of people the participant shares their household with, and the presence of CHD or other chronic diseases among the household members were questioned.

Medication Adherence Reporting Scale (MARS)

Participants taking at least one medication for their heart disease were asked to complete the Medication Adherence Report Scale (MARS), a five-item tool developed by Horne and Hawkins to assess adherence in individuals with chronic diseases, and adapted into Turkish by Temeloğlu Şen et al. in 2019.[21,22] Participants with a MARS score of 23 and above were considered to have high adherence to their medication therapy.[23,24]

The Leuven Knowledge Questionnaire for Congenital Heart Disease (LKQCHD)

The Leuven Knowledge Questionnaire for Congenital Heart Disease was developed by Dr. Philip Moons and colleagues to measure disease-related-knowledge in patients with CHD.[25] This tool involves 25 questions for males and 27 questions for females, evaluating knowledge on various areas including physical limitations, used medications and potential side effects, endocarditis, healthy behaviors to maintain general well-being, pregnancy risks related to heart disease and risk or recurrence in the offspring. Since CHDs are a heterogeneous group with variable anatomical and physiological complexity, causing different degrees of physical limitation, the accuracy of responses was evaluated based on the patient-specific congenital heart anomaly, in-line with the coding manual of the LKQCHD 2009 UK version, item related guidelines and literature.[26-30] Participants' responses to each LKQCHD item were evaluated as correct, incomplete, incorrect or unknown. Patients who answered 80% or more of the items of the LKQCHD correctly were considered to have sufficient knowledge, those with 50–80% considered to have moderate knowledge, and those with less than 50% considered to have insufficient knowledge.[8,9,25]

Translation, content and construct validity study of the Turkish version of LKQCHD

Following the approval of Dr. Moons, the developer of the LKQCHD, the Turkish translation and validation study of the scale was initiated. A three-step linguistic validation method: (i) forward translation, (ii) backward translation, and (iii) patient testing was used for adapting The Leuven Knowledge Questionnaire for Congenital Heart Disease (LKQCHD) into Turkish. During the forward translation phase, the questionnaire was translated into Turkish by a pediatrician who was a native Turkish speaker and demonstrated proficiency in English at a C1 level. Subsequently, the Turkish translation of the scale and the original version in English were presented to a panel of experts consisting of a pediatric cardiologist, two adolescent health specialists, and a pediatrician actively working in the field of pediatric cardiology. Each expert was asked to rate the relevance and the clarity of the items in the scale as "appropriate," "item should be slightly revised," "item should be seriously revised," and "item is not appropriate".[31]

Items with a I-CVI of 0.78 and above were considered to demonstrate good content validity.[32] Among the 27 items in the scale, only the 24th item (inquiry about physical limitations regarding sexuality in patients with CHD) was rated as "item should be seriously revised" by all four experts. I-CVI was calculated as 0 for the 24th item, the item was revised to make it more understandable and clearer. The CVI for the rest of the 26 items were calculated as 1, S-CVI of the questionnaire was calculated as 0.96. To assess interrater reliability, kappa analysis was used, which was calculated to be 1, indicating perfect agreement among raters.[33]

The Turkish questionnaire was translated into English by a professional translator with expertise in medical translation, then back-translated and reviewed alongside the original by researchers and experts to ensure consistency. A pilot test with five eligible patients confirmed its clarity, after which it was administered to a larger group. Construct validity was assessed using the known-groups method by testing three hypotheses based on prior studies involving adolescents with CHDs and other chronic conditions.

Hypothesis 1: Older patients will have higher LKQCHD scores.[34,35]

Hypothesis 2: There will be no significant relationship between the level of anatomical complexity of cardiac disease and LKQCHD scores.[35]

Hypothesis 3: Patients with high medication adherence will have higher disease knowledge levels compared to those with lower adherence.[23,24]

For the third hypothesis, participants using at least one medication for cardiac diseases were evaluated within themselves. The results demonstrated statistical significance, supporting the tool's validity.

The validity and reliability assessment of the Turkish version of the questionnaire included 96 participants, with an average age of 17.01±2.08 years. The group consisted predominantly of male participants (59.4%, n=57), and the majority (41.7%, n=40) had moderately complex cardiac defects. Patients aged 18 and above scored, on average, 8.33±2.74 points higher on the LKQCHD compared to those under 18 (58.30 vs. 49.97, p=0.002). Among the 61 participants using at least one medication for cardiac diseases, those with high medication adherence had an average LKQCHD score 5.88±3.15 points higher than participants with lower adherence (53.33 vs. 47.45, p=0.034). No significant association was observed between the level of anatomical complexity of the cardiac defect and knowledge scale scores. The confirmation of all three hypotheses validated the Turkish version of the scale.

Statistical analysis

An online kappa calculator (http://justusrandolph.net/kappa/) was used to calculate the free marginal multirater kappa coefficient. For descriptive and inferential statistics, IBM SPSS software version 29 was used. Quantitative data were presented as mean ± standard deviation or median (minimum–maximum), while categorical data were reported as frequency and percentage. For inferential statistics, the independent samples t-test and two-way analysis of variance (ANOVA) were applied. The Type II Sum of Squares method was used to obtain a balanced ANOVA model and to independently assess the main effects in the analysis. The effects of the variables on the dependent variables were interpreted using F-values and corresponding p-values. A significance level of $p < 0.05$ was considered statistically significant.

Results

This study included 120 patients with CHD. Two patients were excluded for incomplete responses, resulting in a final sample of 118 patients. Demographic and clinical characteristics of the patients are shown in Table I. The vast majority were using medication for cardiac diseases (63.6%, n=75), the group with the highest incidence of using two or more medications consisted of patients with severely complex cardiac anatomy.

The mean age of the mothers was 44.90 ± 6.02 years, whereas the mean age of the fathers was 47.58 ± 5.73 years. The majority of parents were primary school graduates (60.3% of mothers and 43.5% of fathers), while a smaller proportion were university graduates (13% of mothers and 15.6% of fathers).

Regarding employment status, 67.2% of mothers were unemployed, whereas the vast majority of fathers were employed (93.9%). Most participants lived in bi-parental households (89.8%). The presence of congenital heart disease (CHD) in other individuals sharing the same household was reported by 5.1%. Additionally, 43.2% of participants reported the presence of other chronic diseases among individuals sharing the same household.

Leuven Knowledge Questionnaire for Congenital Heart Disease scores

When evaluated on a scale of 100, the LKQCHD scores applied to assess the patients' disease knowledge indicated an average LKQCHD score of 51.09 ± 13.28 for all participants. Only two patients (1.7%) demonstrated sufficient knowledge (LKQCHD score ≥80), while 38.9% (n=46) answered fewer than half of the scale items correctly. Questionnaire items and distribution of correct responses among participants are given in Table II.

Disease knowledge and clinical symptom awareness

Only 37.3% (n=44) of patients correctly named their structural heart disorder, and 15.3% (n=18) could describe its location. 45.8% of patients identified all seven symptoms of heart failure progression, with palpitations most frequently recognized (71.2%, n=84) and swelling in the feet and legs was the least recognized (25.4%, n=30).

Knowledge about treatment and medications

While 85.6% of patients (n=101) understood the recommended follow-up frequency, only 57.6% (n=68) recognized its purpose in detecting unexpected deterioration. Additionally, 39.8% answered incorrectly when asked if CHD requires lifelong follow-up. Most participants (84.7%, n=100) knew their past treatments; however, among those on medication, only 8% (n=6) could accurately state key details about their therapy, including name, dosage, timing, function, side effects, and interactions.

Table I. Demographic and clinical characteristics of the patients

Characteristics	Value (N = 118)
Sex, n (%)	
Female	51 (43.2)
Male	67 (56.8)
Age (years), M ± SD	17.05 ± 2.09
Educational background, n (%)	
High school student	83 (70.3)
High school drop-out	3 (2.5)
High school graduate	20 (16.9)
University student	12 (10.2)
Complexity level of CHD according to the Bethesda classification, n (%)	
Simple	42 (35.6)
Moderately Complex	50 (42.4)
Severely Complex	26 (22)
Primary cardiac diagnosis, n (%)	
Tetralogy of Fallot (TOF)	26 (22)
Atrial septal defect (ASD)	17 (14.4)
Ventricular septal defect (VSD)	12 (10.2)
Single ventricle palliation	12 (10.2)
Coarctation of the aorta	11 (9.3)
Congenital aortic valve anomalies	9 (7.6)
Congenital mitral valve anomalies	5 (4.2)
Atrioventricular septal defect (AVSD)	5 (4.2)
Dextro-transposition of the great arteries (D-TGA)	5 (4.2)
Anomalous pulmonary venous return	5 (4.2)
Pulmonary atresia	4 (3.4)
Congenitally corrected transposition of the great arteries (L-TGA)	3 (2.5)
Pulmonary stenosis	2 (1.7)
Ebstein's anomaly	1 (0.8)
Cor triatriatum	1 (0.8)
Number of medications used for cardiac disease, n (%)	
None	43 (36.4)
≥1 medication	75 (63.6)
New York Heart Association (NYHA) Heart Failure Functional Class, n (%)	
Class 1	81 (68.6)
Class 2	28 (23.7)
Class 3	7 (5.9)
Class 4	2 (1.7)
Medical history, devices and complications, n (%)	
Prior transcatheter intervention	86 (72.9)
≥1 prior cardiac surgery	84 (71.2)

%: patients as a percentage, CHD: congenital heart disease, M:mean, n: number of patients, SD: standart deviation.

Table I. Continued

Characteristics	Value (N = 118)
Prior admission to the hospital within last 5 years due to cardiac causes	28 (23.7)
Prosthetic valve (prosthetic or mechanical)	23 (19.5)
Pacemaker or implantable cardioverter defibrillator	7 (5.9)
Pulmonary hypertension or Eisenmenger syndrome	5 (4.2)
History of endocarditis	3 (2.5)
Additional chronic disease	23 (19.5)

%: patients as a percentage, CHD: congenital heart disease, M:mean, n: number of patients, SD: standart deviation.

Patients were most familiar with antiplatelets and anticoagulants, often described as "blood thinners," while other drugs like diuretics, antiarrhythmics, beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers were partially recognized by their general effects. Only those taking acetylsalicylic acid identified bleeding as a side effect, and all patients aware of food and drug interactions (n=3) were on warfarin.

Knowledge about endocarditis

Items 11-14, which assessed patients' knowledge about endocarditis (definition, clinical findings, recurrence risk, and risk factors), had the lowest percentage of correct responses on the scale. In item 14, the percentage of patients who correctly identified all the risk factors for endocarditis presented in the options (sharing dirty or contaminated needles, bacteria causing skin infections, dental abscesses, poor skin and nail care or hygiene, and piercing or tattoo procedures) was 1.7% (n=2). The least recognized risk factors were piercing and tattoo procedures (4.2%; n=5) and poor skin and nail hygiene (5.9%; n=7), while the most recognized risk factor was sharing dirty or contaminated needles (13.6%; n=16). The percentage of patients who were aware that dental abscesses or infections could cause endocarditis was 8.5% (n=10). When questioned about the healthy lifestyle habits they should adopt to protect their overall health, it was found that 44.9% of patients (n=53) believed they should use antibiotics before every visit to the dentist.

Knowledge about sports participation and physical limitations

Most participants (65.3%; n=77) correctly understood that licensed sports participation is deemed appropriate by cardiologists. However, it was found that even patients who are permitted to engage in licensed sports (a total of 16 patients, constituting 13.5% of the entire sample) believed that they could not participate in sports that require regular training.

Knowledge about sexual and reproductive health

The percentage of patients who answered incorrectly or indicated that they did not know the answer to item 24, which assessed their knowledge about physical limitations in sexuality, was 62.7% (n=74); the average age of these patients was 16.82 years. Only 36.4% (n=43) of patients accurately understood the risk of CHD recurrence in the next generation. Among those who answered incorrectly or chose "I don't know," the average age was 16.86 years, with 40% female and 60% male. Additionally, just 5.9% (n=3) of female patients had sufficient knowledge of contraceptive methods, while 37.3% (n=19) were aware of pregnancy-related risks associated with their heart condition.

Medication Adherence Report Scale scores

The average MARS score for patients using medication (n=75) was calculated to be 22.08 (min-max10-25). Sixty percent of the patients using medication (n=45) showed high adherence

Table II. Leuven Knowledge Questionnaire for Congenital Heart Disease questions and correct answer rates among participants

Questions	Correct Answer n (%)
Disorder and treatment	
What is the correct name of your heart defect?	44 (37.3)
Describe below or indicate on the diagram where your heart defect is located.	18 (15.3)
How often do you have to come to the clinic for follow-up of your heart disease?	101 (85.6)
What is the main purpose of this follow-up?	68 (57.6)
How has your heart condition been treated to date?	100 (84.7)
If you are on medication, give the name, dose, schedule, reason or function, most important side effects, and interactions with other medication or foods.	6 (8.0)
If you experience side effects of your medication, does this mean you should stop taking them?	28 (23.7)
Do you have to follow a diet? If you answer yes, please indicate the type of diet.	100 (84.7)
Mark all symptoms which may occur if your heart condition deteriorates and for which you have to contact your cardiologist.	54 (45.8)
If the cardiologist informs you that everything is alright, does that mean that you do not need further follow-up?	71 (60.2)
Prevention of complications	
What is endocarditis?	21 (17.8)
Indicate the most characteristic or typical sign of endocarditis.	11 (9.3)
Can you only get endocarditis once in your lifetime?	5 (4.2)
A number of risk factors for endocarditis are listed below. Do you think these factors contribute to the onset of endocarditis?	2 (1.7)
As you have a congenital heart disease, you should take antibiotics immediately if you have a temperature (without consulting a doctor).	86 (72.9)
You should have a dental check-up at least once a year.	84 (71.2)
You should take antibiotics before every visit to the dentist.	65 (55.1)
Bleeding gums need extra attention.	95 (80.5)
You should clean your teeth at least once a day.	105 (89.0)
Smoking is more harmful for someone with a congenital heart disease than for someone without such a disorder.	7 (5.9)
Consuming three or more alcoholic drinks per day is more harmful for someone with a congenital heart disease than for someone without such a disorder.	91 (77.1)
Physical activity	
You may take part in competitive sports (regional or national) requiring daily training?	77 (65.3)
You should choose an occupation that is not too physically demanding, as you should be careful not to over-exert yourself.	82 (69.5)
May you engage in all physical sexual activity of which you feel you are capable?	44 (37.3)
Sexuality and heredity	
What is the chance that your children will have a congenital heart disease?	43 (36.4)
Which contraceptives are the most advisable for you to use in the light of your congenital heart disease?	3 (5.9)
Do you run a risk for complications during pregnancy?	19 (37.3)

%: patients as a percentage, n: number of patients.

to their medication (MARS score ≥23). Neither the anatomical complexity level of the CHD nor the number of medications used had a significant impact on medication adherence ($p > 0.05$).

Factors associated with disease knowledge

When the patients were classified according to their anatomical complexity and the average LKQCHD scores for the three groups were analyzed using the Kruskal-Wallis test, no statistically significant difference was found (p=0.701).

In order to assess the overall impact of age and clinical characteristics on disease knowledge, a two-way analysis of variance (ANOVA) was conducted, using the LKQCHD score as the dependent variable and the following as independent variables: age, complexity level of CHD, NYHA functional class, number of medications used, history of hospitalization due to cardiac reasons in the past 5 years, history of cardiac catheterization, history of cardiac surgery, and the presence of additional chronic diseases (Table III). The age and history of cardiac catheterization were shown to have a significant impact on disease knowledge scores. Participants aged

Table III. Factors influencing leuven knowledge questionnaire for congenital heart disease scores

Variable	Category	n	LKQCHD score (M ± SD)	F	p
Age (years)	<18	83	49.03±13.13	9.367	0.004*
	≥ 18	35	55.97±12.49		
Complexity level of CHD	Simple	42	52.32±12.22	0.318	0.728
	Moderately complex	50	50.56±13.38		
	Severely complex	26	50.14±15.02		
New York Heart Association (NYHA) Functional Class	Class 1	81	50.72±13.55	0.497	0.610
	Class 2	28	51.99±12.32		
	Class 3 and 4	9	51.70±15.07		
Number of medications used for cardiac disease	0	43	53.39±13.46	1.313	0.274
	1	34	49.42±11.91		
	2	23	48.93±16.15		
	3 and more	18	51.52±11.29		
Prior admission to the hospital within last 5 years due to cardiac causes	No	90	50.32±12.00	3.647	0.059
	Yes	28	53.58±16.76		
Prior transcatheter intervention	No	32	55.33±10.13	5.528	0.021*
	Yes	86	49.52±14.00		
≥1 prior cardiac surgery	No	34	53.01±11.88	0.090	0.764
	Yes	84	50.32±13.80		
≥2 prior cardiac surgery	No	88	50.46±13.48	2.284	0.134
	Yes	30	52.97±12.71		
Presence of pacemaker or implantable cardioverter defibrillator	No	95	51.28±12.47	0.731	0.395
	Yes	23	50.33±16.52		
Additional chronic disease	No	95	50.93±13.26	0.025	0.875
	Yes	23	51.79±13.64		

CHD: congenital heart disease, LKQCHD: Leuven Knowledge Questionnaire for Congenital Heart Disease, M: mean, n: number of patients, SD: standart deviation.

18 and older exhibited a statistically significant higher average LKQCHD score compared to their younger counterparts (55.97 ± 12.49 vs. 49.04 ± 13.13, F = 9.367, p=0.004). Participants who had undergone cardiac catheterization previously demonstrated significantly lower knowledge scores compared to those who never had such procedures (49.52 ± 14.00 vs 55.33 ± 10.13, F = 5.528, p = 0.021). No statistically significant associations were identified between demographic or socioeconomic variables obtained from the Demographic and Socioeconomic Assessment Form, including parental education level, parental employment status, household income, and living conditions, and disease knowledge scores (all $p > 0.05$).

The average LKQCHD score of patients considered to have high medication adherence was significantly higher compared to those with lower medication adherence (One-way t-test; difference of 5.96 points, 52.16 vs. 46.20; p=0.026).

Discussion

Although CHDs require lifelong follow-up, patients often neglect appointments or drop out of care after transitioning from pediatric to adult services.[5,6,36,37] These lapses in care have been shown to result in increase in morbidity and mortality.[4,36,38] While educational transitional care programs exist globally to educate youth with CHD and prevent related morbidity and mortality due to lapses in care, no such program currently exists in Türkiye.[14,17] Our study highlights the need for a structured transitional care program. Despite most patients being at or beyond the usual age for transitioning from pediatric to adult care, they were only able to answer, on average, just over half of the questions correctly. Only 1.7% of participants had sufficient disease knowledge; many couldn't define their condition or recognize the warning signs of deterioration.

Among patients on medication, most knew the name, dosage, and frequency, but lacked awareness of side effects and interactions. As in prior studies, those with higher adherence showed better disease knowledge.[23,24] Despite many participants' limited understanding of their cardiac condition, overall medication adherence in our cohort was acceptable. Medication adherence is known to be influenced by a variety of factors, including patient-related elements such as perceptions and beliefs about illness, health system factors like the availability and accessibility of medications, and broader socioeconomic and cultural influences.[39] The relatively high adherence rates observed in our cohort may be partly explained by the prevailing collectivist cultural background in Türkiye and the involvement of family members in patients' care.[40]

Factors such as functional impairment, invasive procedures, presence of prosthetic devices, recent hospitalizations, and a history of endocarditis were evaluated to assess disease severity. While some studies link severe cardiac disease to better adherence, only a history of cardiac catheterization showed a significant association in our cohort—and unexpectedly, those patients had lower disease knowledge scores.[41] This may be due to unequal group sizes or the heterogeneous nature of catheterization, which is often performed for both diagnostic and interventional purposes in CHD. These limitations highlight the need for further research with larger, more balanced samples.

Our patients particularly lacked knowledge in two areas; endocarditis and reproductive health. Incidence of infective endocarditis in individuals with CHD is twice as high as in the general population but most of our patients had a very little understanding of the disease.[42] In our study, 17.8% of patients were able to define endocarditis, while studies conducted with individuals aged 12 to 32 with CHD reported a varying percentage between 4% and 50%.[8,34,43]

The European Society of Cardiology recommends that all female patients diagnosed with CHD receive counseling on reproductive health starting from menarche.[27] While studies in the literature indicates that psychosocial maturation in young people with chronic illnesses may be somewhat delayed compared to healthy peers, other studies involving adolescents with CHD have shown that a portion of those aged 16 to 18—between 14% and 26%—are sexually active, and among those who are sexually active, 72% engage in risky sexual behaviors (such as having two or more sexual partners and not using protective methods to prevent unwanted pregnancies).[44-46] It is believed that providing comprehensive sexual health education to adolescent girls with CHDs, would be effective in preventing unwanted pregnancies that could pose medical risks for the patient, as well as adverse events arising from incorrect contraceptive use.[27,47] However, studies show that physicians often avoid these discussions related to sexuality and reproductive health, leaving many female CHD patients with inadequate knowledge.[48,49] Similarly, our study found that adolescent and young adult female patients have insufficient information about pregnancy risks and contraceptive methods. Patients' lack of knowledge on this topic may stem from physicians' assumptions about their sexual activity or readiness for parenthood. This issue is not unique to adolescents with CHD though; the 2023 Türkiye Youth Research report highlights major gaps in sexual and reproductive health knowledge among all youth aged 15–24, including poor understanding of anatomy, sexually transmitted infections, declining HIV/AIDS awareness, and persistent misconceptions about pregnancy and contraception.[50] A lack of training in reproductive counseling during cardiology subspecialty education and physicians' discomfort with the topic may further limit access to accurate information.[49] Collaborating with adolescent health specialists experienced in contraception counseling could enhance the quality of comprehensive sexuality education which lacks in this group.

A notable finding was participants' views on licensed sports participation. While 65.3% correctly understood it is generally permitted, 13.5% of patients unnecessarily restricted themselves despite having no medical limitations. Misconceptions, especially among those with simple defects such as isolated ASD or VSD, may lead to sedentary lifestyle, negatively impacting physical and mental health.[26,51,52] Families' overly protective approach, which does not even allow patients to participate in sports or games that do not physically strain them, may have led to this perception.[14,53]

Previous studies indicate that family structure and parental education significantly influence children's health literacy.[54] Higher parental education is also associated with a better understanding of a child's diagnosis and management.[55] Although we found no statistically significant association between parental or household characteristics—such as educational background, cohabitation status, or the presence of congenital heart disease (CHD) in another household member—and disease knowledge, this may be due to limited statistical power.

Our study findings point to our failure to inform our patients age appropriately. The high number of daily visits to our hospital's pediatric cardiology clinic, absence of specialist nurses and such supporting health professionals in our department restrict the time that can be dedicated to patient education. It can be suggested that physicians' failure to provide age-appropriate information without considering the patients' cognitive and psychosocial development may also have had an impact.[14] During adolescence, patients should gradually be encouraged to attend clinic appointments independently and assume greater responsibility for their health and treatment, such as taking their medications at the correct times and dosages without needing parental reminders.[14] While pediatric providers often focus on family involvement, adolescents should directly receive age-appropriate information from early adolescence on heart-healthy habits, substance risks, contraception,

pregnancy, recurrence risks, and long-term prognosis.[14,47,48] Vocational and employment guidance should extend into early adulthood.[14]

This study has several limitations. As a single center study, it relied on self-reported measures (LKQCHD and MARS), which may be affected by response bias. Objective adherence measures, such as parental reports or serum drug levels, were not included. The sample size may have been too small to detect significant effects of adolescent, family, and household factors, limiting generalizability. Additionally, the knowledge scale lacked questions specific to patients with pacemakers or ICDs, potentially missing important knowledge gaps. Future research should use larger samples and include device-specific questions for a more comprehensive assessment. In conclusion, our study shows the lack of adequate knowledge our patients have concerning their cardiac condition. A structured transition program involving collaboration between Pediatric Cardiology, Adolescent Medicine, Adult Cardiology, and Nursing Faculty has the potential to significantly improve outcomes for adolescents with CHD as they move from pediatric to adult care. By enhancing health literacy, promoting self-management skills, and supporting adherence to treatment, such a program could serve as a crucial intervention to ensure long-term health and well-being. Establishing a comprehensive educational transition framework would not only empower patients but also help prevent avoidable health complications and reduce mortality associated with a lack of knowledge. A multidisciplinary approach is essential to bridging this critical gap in care and securing a healthier future for adolescents with CHD.

Ethical approval

The study was approved by Hacettepe University Health Sciences Research Ethics Committee (date: 04.04.2023, number: GO 22/1324).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: EYK, SA, MPK, İE; data collection: EYK; analysis and interpretation of results: EYK, EK, SA, MPK, İE, OD; draft manuscript preparation: EYK, SA, MPK, İE, OD, TK, HHA. 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

Phenotypic spectrum in patients with 16p11.2 deletion: a single tertiary centre experience in Türkiye

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ABSTRACT

Background. The 16p11.2 deletion is one of the most frequent recurrent copy number variations associated with a broad neurodevelopmental and phenotypic spectrum. Despite its relatively well-characterized genomic region, clinical expressivity remains highly variable, posing challenges for diagnosis and management.

Methods. We conducted a retrospective single-centre study of 25 individuals with molecularly confirmed 16p11.2 deletions, including 13 males (52%), 12 females (48%), and 7 familial (28%). Both *de novo* and inherited cases were included. The main testing method was chromosomal microarray, although karyotyping and additional tests such as sequencing and trinucleotide repeat testing were also utilized. Comprehensive clinical data were collected from medical records, including neurodevelopmental, neuropsychiatric, metabolic, skeletal, and systemic features.

Results. The majority of the cases had the typical ~600 kilobase deletion while two had distal ~220kb deletion. One patient was found to have a double genetic diagnosis. Developmental delay was almost universal in the probands, with expressive language significantly more impaired than receptive language abilities. Intellectual disability / learning difficulties and language problems were observed in 18/25 (72%) cases. Around half of the probands showed obesity and related hyperphagia. Autism spectrum disorder, attention deficit hyperactivity disorder, stereotypic movements, and aggressive behaviour were frequently reported. Epilepsy was present in thirteen patients (52%), with electroencephalographic abnormalities supporting generalized or focal epileptiform activity. Dysmorphic facial features and skeletal anomalies such as pes equinovarus, syndactyly, and scoliosis were variably present. Brain magnetic resonance imaging revealed abnormalities in several patients, including hypoplasia of the corpus callosum and intracranial hypertension. Additional systemic findings included hepatic steatosis, constipation, and ophthalmologic anomalies. Parental testing revealed asymptomatic or mildly affected carriers in multiple cases.

Conclusion. Our findings emphasize the broad and heterogeneous clinical spectrum of 16p11.2 deletions in a Turkish cohort. Early recognition, multidisciplinary evaluation, and family-based genetic counselling are essential for timely diagnosis and optimal care of affected individuals.

Key words: 16p11.2 deletion, phenotypic variability, genotype-phenotype correlation, Turkish cohort.

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The 16p11.2 region of the human genome is enriched with low copy repeats, making it prone to misalignment during meiotic recombination. This susceptibility often results in non-allelic homologous recombination, leading to recurrent copy number variations (CNVs) at specific breakpoints. Among these, deletions and duplications of 16p11.2 are recognized as among the most frequently observed pathogenic CNVs associated with neurodevelopmental disorders.[1] Despite notable clinical variability, affected individuals often share overlapping features such as developmental delay (DD), intellectual disability (ID), neuropsychiatric symptoms, obesity or underweight, congenital anomalies, and epilepsy.[2]

The well-characterized "typical" 16p11.2 deletion spans the BP4–BP5 region (OMIM #611913), covering approximately 600 kilobases and 29 genes, 17 of which show neuronal expression, between 29.6 and 30.2 Mb on chromosome 16. In contrast, the "distal" CNVs involve the BP2–BP3 region (OMIM #613444), covering ~220 kb between 28.8 and 29 Mb (based on GRCh37/hg19) (Fig. 1). The estimated prevalence in the general population is 1 in 2000 for the typical deletion and 1 in 4100 for distal deletions. However, these figures are likely underestimated in clinical practice, partly due to limited awareness among clinicians regarding the variable expressivity and potential consequences of 16p11.2 CNVs. Notably, many parents carrying the same CNV as their affected child may show only mild or subclinical features. The majority of typical deletions are *de novo* (~93%), although there is evidence for dominant inheritance from an affected mother or father. Environmental and parental modifiers contributing to the wide phenotypic range remain poorly defined in the current literature.[3,4]

Although the 16p11.2 deletion has been extensively studied in various populations, data from Turkish cohorts remain limited. In this study, we present a single-centre retrospective analysis of 25 molecularly confirmed Turkish patients with 16p11.2 deletions. Our aim is to characterize the clinical and genetic spectrum

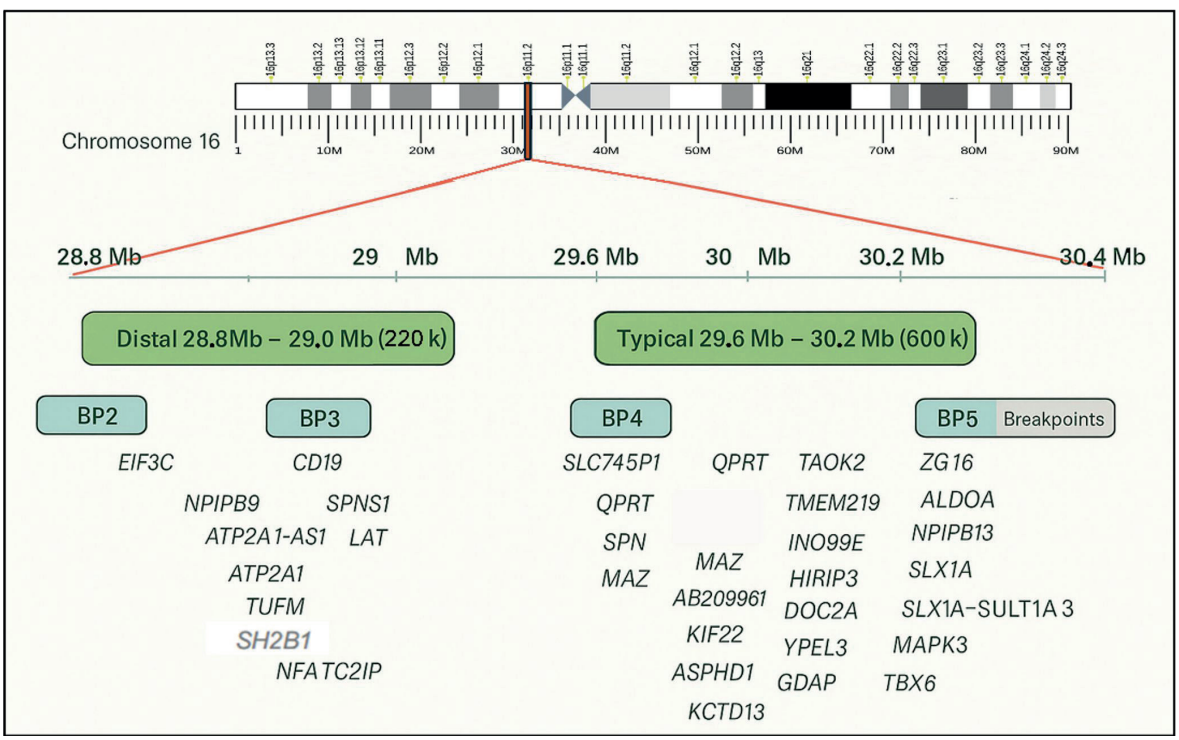

Fig. 1. Graphical display of the critical regions in 16p11.2 and the distribution of the genes.

observed in this cohort and contribute to the growing body of literature regarding genotype-phenotype correlations. Understanding these variations can ultimately guide earlier diagnosis and more tailored testing and management strategies.

Materials and Methods

Patient selection

We performed a retrospective analysis of the patients who were referred to our diagnostic centre for genetic diseases for molecular diagnosis between 2022 and 2025. All patients included in the study were referred for routine clinical indications, which included a wide variety of presenting features, such as neurological delay, speech delay, obesity, autism, dysmorphism or a combination of these symptoms. All routine clinical investigations and tests were performed in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from the patients or their legal guardians. This study was approved by the Ethics Committee of Ankara Etlik City Hospital (date: 16.07.2025, number: AEŞH-BADEK1-2025-280).

Generation and interpretation of the genetic data

All relevant genetic tests were performed in our genetic diagnosis centre using devices and kits provided by different manufacturers, following the manufacturer's instructions, with genetic material obtained from peripheral blood cells. For chromosomal microarray analysis we used two different platforms; Infinium Global Screening Array Cyto (GSA-Cyto) chips on the Illumina iScan platform-NxClinical (v.6.0) by using Biodiscovery- Human Genome Build GRCh37 (hg19) and, CytoScan HT-CMA chips on the GeneTitan MC Fast Scan platforms Chromosome Analysis Suite (ChAS) and Reproductive Health Research Analysis Software (RhAS) using the Human Genome Build GRCh38 (hg38) reference genome. Some patients also underwent clinical exome sequencing for additional symptoms, using the Clinical Exome Solution By Sophia Genetics kit, including mitochondrial DNA sequencing, on the NovaSeq Platform (Illumina, USA) for next-generation sequencing analysis (NGS). Additional tests included methylation multiplex ligation-dependent probe amplification (MLPA) for Prader-Willi / Angelman syndromes (SALSA® MLPA® Probemix ME028 Prader-Willi / Angelman; MRC Holland, Netherlands) and trinucleotide repeat analysis for *FMR1* gene repeat region. Potential causative variants that had <20X reads on NGS were confirmed with the Sanger sequencing before reporting. A lift-over process was applied for chromosome designations according to GrCh38 in tables. Patients who could not be evaluated for specific features were indicated as 'NE: Not Evaluated' or 'NA: Not available'. For the interpretation of percentile-based anthropometric measurements, we used the growth reference curves standardized for Turkish children by Neyzi et al. and applied the standard body mass index (BMI) classification for individuals aged 18 years and older.[5]

Statistical analysis

Descriptive statistics were used to summarize the clinical and demographic characteristics of the cohort. Categorical variables are presented as frequencies and percentages. For continuous variables, such as age at diagnosis, data are expressed as median values accompanied by the interquartile range (IQR, Q1–Q3) to describe the distribution.

Results

A total of 25 patients with molecularly confirmed 16p11.2 deletions were evaluated (13 [52%] males, 12 [48%] females, and 7 [28%] familial cases). The age of the probands at diagnosis ranged from the neonatal period to 21 years, with a median age of approximately 9 years (Q1-Q3: 2.0-11.5 years). Only one proband was older than 18 years of age at the time of molecular diagnosis (P15). The majority of the confirmed cases (23, 92%) had the 'typical'

~600 kilobase deletion, while the distal ~220 kb BP2–BP3 deletion was detected only in P6 and her mother. P2 could not be evaluated comprehensively for many clinical features due to early-onset aspiration and subsequent severe neurological sequelae, while P7 passed away on the second postnatal day, limiting the availability of detailed phenotypic data. Autism spectrum disorder (ASD) and/or attention deficit hyperactivity disorder (ADHD) was diagnosed or strongly suspected in nearly half of the cohort (13, 52%).

Neurodevelopmental and cognitive findings

Developmental delay, mainly speech and learning problems, was the dominant feature among patients (18, 72%), with expressive language more severely affected than receptive abilities. Intellectual disability (ID) and/or learning difficulties were documented in 17 patients (68%). Most patients had mild or mild-moderate intellectual disability. Neuromotor delay and hypotonia were frequent, in terms of neuromotor development, 10 (40%) of the patients showed varying degrees of delay and, only five (20%) also had hypotonia in early infancy. Brain magnetic resonance imaging (MRI) abnormalities were observed in several individuals, including hypoplasia of the corpus callosum, idiopathic intracranial hypertension, and nonspecific gliotic changes. MRI was available for 14 cases (56%) and only five of these (35.7%) had brain abnormalities. Macrocephaly was identified in five cases (20%), three of whom (12%) overlapped with the group with brain anomalies were detected on MRI.

Epilepsy and seizure disorders

Epilepsy or recurrent seizures occurred in 13/25 patients (52%). EEG findings demonstrated generalized epileptic activity in several cases, while others showed focal discharges. Two patients had febrile seizures, and one presented with absence seizures.

Psychiatric and behavioural features

Five patients (20%) in the cohort had a diagnosis of autism spectrum disorder and eight (32%) of them had attention deficit and/or hyperactivity without symptoms or a diagnosis of autism. Ten (40%) of the patients had a history of psychiatric problems such as repetitive stereotypies, aggressive behaviour, obsessive–compulsive disorder, and tics. Psychiatric manifestations frequently co-occurred with ID and/or language impairment.

Growth and metabolic features

Overweight or obesity was observed in 10/25 patients (40%). Four (16%) of the cases had hyperphagia without obesity. Hepatic steatosis, insulin resistance, endocrine problems and abnormalities of lipid metabolism were additional metabolic findings. Conversely, a subset of patients presented with underweight or normal growth trajectories. Two of the cases had short stature.

Dysmorphic and skeletal features

Varying degrees of dysmorphic features were reported in 11 (44%) patients, albeit without a consistent pattern. Common findings included synophrys, wide or downslanting palpebral fissures, deep philtrum, and a thin upper lip. Aside from dysmorphic findings skeletal manifestations included pes equinovarus in 5 (20%) patients and scoliosis in one patient.

Other systemic findings

Ophthalmologic problems, including strabismus, optic disc changes, and papilledema were documented in several patients. Only three (12%) patients had hearing loss and cardiac examinations were normal in all patients in whom they were available. Constipation was recurrent in four (16%) cases across the cohort. Less frequent findings included hepatosplenomegaly, primary amenorrhea,

and cleft palate. Ten (40%) of the probands had a history of prenatal abnormal findings or problems at birth such as polyhydramnios, prenatal macrocephaly, hyperechogenic bowel, preeclampsia, fetal distress, preterm labour, abnormal presentation, meconium aspiration.

Inheritance patterns

Parental testing revealed seven (28%) familial cases, of which five were maternally inherited and two were paternally inherited. Most of the carrier parents were either mildly affected or asymptomatic. Interestingly, some carrier parents displayed mild features (such as obesity, constipation, or subtle cognitive / behavioural issues), underscoring variable expressivity. In 14 cases (56%) parental microarray studies were not available; among the remaining cases, four (36%) were found to be *de novo* inheritances. Detailed characteristics of the cohort are presented in Table I, Table II, and Supplementary Table S1.

Additional genetic testing was performed in some cases mainly due to unexpected clinical features or initial clinical suspicion, including karyotyping, MLPA, exome sequencing, and targeted gene panels. In a few patients, variants of uncertain significance (VUS) or unrelated findings were detected (e.g., 4p15.32 duplication in P2). P16 had molecularly proven dual genetic diagnoses with heterozygous likely pathogenic *MC4R* variant (NM_005912: c.496G>A p.(Val166Ile)) in addition to the 16p11.2 deletion (Table I).

Discussion

This cohort of 25 individuals with 16p11.2 deletions highlights the remarkable clinical heterogeneity and multisystem involvement associated with this recurrent CNV. Consistent with existing literature, neurodevelopmental delays—particularly speech delay—emerged as hallmark features, present in the majority of cases. The prominence of expressive language deficits, often more severe than receptive language difficulties, aligns with previously published cohorts that emphasize language impairment as a key diagnostic clue. In our genetic diagnostic centre, the chromosomal microarray cohort comprises approximately 4,500 samples, and the 16p11.2 deletion was identified as the most prevalent deletion.

The recurrent 16p11.2 microdeletion encompasses approximately 29 genes, several of which have been implicated in neurodevelopment, energy homeostasis, and synaptic function, thereby contributing to the variable clinical spectrum observed in affected individuals. Among these, *KCTD13* has been highlighted as a key dosage-sensitive gene influencing brain volume (micro/macrocephaly) and neurodevelopmental outcomes, especially within the autism spectrum, with both animal and human studies demonstrating its role in neurocognitive phenotypes.[6] *MAPK3*, a critical component of the MAPK/ERK signalling pathway, is involved in neuronal differentiation, synaptic plasticity, and learning processes, and its haploinsufficiency has been associated with intellectual disability and behavioural abnormalities.[7] *KIF22* expression is confined to proliferating cells and peaks during mitosis, whereas *ALDOA* is ubiquitously expressed across cell types with stable expression throughout the cell cycle, collectively supporting the hypothesis that disrupted cortical neurogenesis may contribute to ASD in individuals with 16p11.2 CNVs.[8] Additionally, *DOC2A* and *TAOK2* are involved in synaptic vesicle trafficking and neuronal migration, respectively, and are considered contributors to the autism spectrum disorder and behavioural phenotypes observed in this deletion.[9,10] Metabolic and obesity-related features frequently reported in 16p11.2 deletion carriers may be partially explained by genes such as *SH2B1*, located in BP2-3 region, which plays a role in leptin and insulin signalling pathways and has been linked to abnormal weight gain and the regulation of energy balance.[11] While several studies have suggested that obesity is independent of the neuropsychiatric phenotypes frequently observed among CNV

Table I. Demographic and additional genetic information of patients.

Patient ID	Age	Sex	Age at diagnosis	Inheritance	Additional genetic test	Consanguinity	Additional Genetic Findings and Pathogenicity
P1	8	M	6	DNM	Karyotype N *FMR1* Repeat N Angelman-Prader Willi MLPA N	-	-
P2	2	F	8 mo	NA	Karyotype N WES N Mitochondrial DNA N	-	arr[GRCh37] 4p15.32p15.31 (16824676_17818885)x3 VUS
P3	12	M	10	Paternal	Karyotype N	-	-
P3 father	47	M	47	NA	Karyotype N	-	-
P4	11	M	10	Parental Karyotypes N Microarray NA	Karyotype N *FMR1* Repeat N	-	arr[GRCh37] 9p23p21.3 (11374988_23957619)x3 VUS
P5	2.5	M	1y	Maternal	Karyotype N CES N	-	-
P5 mother	27	F	25.5	NA	-	-	-
P6	2	F	2y	Maternal	Karyotype N	-	-
P6 mother	30	F	30	NA	Karyotype N	-	-
P7*	2 days	F	Post mortem	Maternal	Karyotype N	-	-
P7 mother	31	F	29	NA	Karyotype N	+	-
P8	17	F	17	NA	Karyotype/*SHOX* MLPA N	-	-
P9	3	F	9 mo	DNM	-	-	-
P10	3	M	1	DNM	Karyotype N	-	-
P11	9	M	8	Maternal	Karyotype N	-	-
P11 mother	41	F	41	NA	Karyotype N	+	-
P12	19 mo	M	11 mo	DNM	Karyotype N DiGeorge syndrome FISH N CES N	-	-

Age and age at diagnosis are expressed as years, unless indicated otherwise.
*Patient deceased on the second day of life.
CES: Clinical Exome Sequencing, DNM: de novo variation, F: Female, M: Male, MLPA: Multiplex Ligation-dependent Probe Amplification, MO: months old, N: Normal, NA: Not available, VUS: Variant of unknown significance, WES: Whole Exome Sequencing.

Table I. Continued.

Patient ID	Age	Sex	Age at diagnosis	Inheritance	Additional genetic test	Consanguinity	Additional Genetic Findings and Pathogenicity
P13	5	M	4	Maternal	Angelman-Prader Willi MLPA N Karyotype N	-	-
P13 mother	45	F	45	NA	Karyotype N	+	-
P14	15	M	14	NA	Karyotype N *FMR1* Repeat N	-	-
P15	21	F	20	NA	Karyotype N *GNAS* Sequencing N	-	-
P16	9	M	9	NA	Karyotype N	-	*MC4R* likely pathogenic variation (exome sequencing)
P17	4	M	3	Paternal	Karyotype N *FMR1* Repeat N	-	-
P17 father	32	M	32	NA	Karyotype N	-	-
P18	6	F	6	NA	CES N	-	-

Age and age at diagnosis are expressed as years, unless indicated otherwise.
*Patient deceased on the second day of life.
CES: Clinical Exome Sequencing, DNM: de novo variation, F: Female, M: Male, MLPA: Multiplex Ligation-dependent Probe Amplification, MO: months old, N: Normal, NA: Not available, VUS: Variant of unknown significance, WES: Whole Exome Sequencing.

Table II. Overview of clinical features of cases with typical 16p11.2 BP4-BP5 deletion and distal 16p11.2 BP2-BP3 deletion in our cohort

Clinical category	Finding	Frequency (n=25)	Percentage (%)
Neurodevelopmental & cognitive	Developmental delay (mainly speech)	18/25	72%
	Intellectual disability / learning difficulties	17/25	68%
	Neuromotor delay	10/25	40%
	Hypotonia	5/25	20%
Neurological	Epilepsy / recurrent seizures	13/25	52%
	Abnormal brain MRI findings (evaluated in n=14)	5/14	35.7%
	Macrocephaly	5/25	20%
Psychiatric & behavioural	ADHD	13/25	52%
	ADHD with ASD	5/25	20%
	Behavioural problems (Stereotypy, aggression, obsessive compulsive disorder, tics)	10/25	40%
Metabolic	Overweight or obesity (>2SD)	10/25	40%
	Hyperphagia	12/25	48%
	Hepatic steatosis	4/25	16%
	Insulin resistance / abnormal glucose metabolism	3/25	12%
	Abnormal lipid profile	2/25	8%
Dysmorphic & skeletal	Dysmorphic facial features	11/25	44%
	Pes equinovarus	5/25	20%
	Cleft palate	2/25	8%
	Short stature	2/25	8%
	Pectus anomalies	2/25	8%
	Syndactyly - polydactyly	2/25	8%
	Pes valgus	1/25	4%
	Scoliosis	1/25	4%
Other findings	Frequent infection	5/25	20%
	Ophthalmologic (Papilledema, abnormal optic disc)	3/25	12%
	Strabismus	2/25	8%
	Constipation	4/25	16%
	Hearing loss	3/25	12%
	Refraction problems (myopia astigmatism)	2/25	8%
	Micropenis - buried penis	3/25	12%
	Hypospadias	1/25	4%
Prenatal & perinatal	Abnormal prenatal history / birth findings	10/25	40%

ADHD: Attention Deficit/Hyperactivity Disorder, ASD: Autism Spectrum Disorder, MRI: Magnetic Resonance Imaging, SD: Standard Deviation.

carriers, and no single gene or gene set within the BP4–BP5 region has been definitively linked to obesity, recent reports nevertheless hint at a potential interplay between metabolic and neurological phenotypes.[12,13] The combined haploinsufficiency of these genes likely underlies the marked phenotypic variability and incomplete penetrance observed among

carriers, including those with inherited deletions, as demonstrated in our cohort.

The most common symptoms in the cohort were cognitive impairments (17, 68%), speech delay observed in 18 cases (72%), seizure disorders (13, 52%) and obesity (10, 40%) (Table II). Neurodevelopmental impairments are observed in the vast majority of individuals with 16p11.2 deletions and often serve as the primary reason for initiating genetic evaluation. Most patients had either mild-to-moderate intellectual disability or significant learning difficulties. Epilepsy and abnormal EEG findings were present in more than half of the cohort. Seizure types varied, and although some were transient or febrile, others showed more complex patterns, emphasizing the need for routine neurological screening and longitudinal follow-up.

In line with the "mirror phenotype" hypothesis, macrocephaly and obesity were seen in many deletion carriers, whereas duplications, which were not analysed in the current study, are more often associated with microcephaly and low BMI.[14] Almost half of the cohort was overweight or had obesity highlighting the metabolic risk associated with this deletion. Deletions in this region have been proposed in some publications as the second most common genetic cause of obesity after point mutations in the *MC4R* and previous studies have concluded that individuals carrying this deletion face a markedly elevated risk—estimated at 43 times higher—of developing morbid obesity, reflecting its high penetrance.[15,16]

Behavioural and psychiatric comorbidities were noted in half of the cohort. Isolated ADHD was only noted in eight (32%) cases while another five (20%) of the cases had a history of both ASD and ADHD. Heterozygous deletions in this region represent one of the most frequently identified genetic risk factors for autism spectrum disorder, occurring in approximately 0.5% of large ASD cohorts.[17] Other psychiatric symptoms such as aggression, stereotypy, and obsessive-compulsive behaviour were also observed. These findings underscore the importance of comprehensive psychiatric evaluation and early intervention in children with 16p11.2 deletions. Neuropsychiatric atypia together with pervasive language disorders in these individuals may result in an underestimation of intelligence potential, although severe intellectual disability is reported to be rare. There is no single candidate gene for the neurodevelopmental features of proximal 16p11.2 deletions; rather, studies implicate complex, potentially synergistic interactions between several encompassed genes with some evidence for sex-specific neuroanatomical characteristics.[18] The 16p11.2 deletion has thus far been reported from Türkiye in a limited number of studies, derived primarily from autism-related or autism-diagnosed cohorts.[19,20] In this context, our study uniquely encompasses both a broader patient population and a more comprehensive analysis of genotype-driven phenotype correlations focused specifically on 16p11.2 deletions.

In addition to the typical ~600 kb BP4–BP5 deletions, our cohort included two individuals (P6 and her mother) with a smaller, approximately 220–269 kb deletion spanning the distal 16p11.2 BP2–BP3 region. These distal deletions are less frequently reported in the literature and are thought to have lower penetrance for neurodevelopmental disorders compared with the typical proximal deletions.[21] However, our findings suggest that clinical involvement may still be significant. P6 presented with severe expressive and receptive language delay, global neuromotor delay with lack of ambulation by age 2, and moderate intellectual disability. Behavioural signs such as stereotypic movements were also observed. Interestingly, her mother, who carried the same CNV, was mostly asymptomatic aside from a high BMI (31.3) and hepatic steatosis. This familial observation further supports the notion of variable expressivity and incomplete penetrance associated with BP2–BP3 deletions. The stark phenotypic difference between the child and her carrier mother underscores the

need for careful clinical evaluation and long-term follow-up even in cases in which parental carriers appear unaffected.

Dysmorphic features and congenital anomalies, while not universal, supported clinical suspicion in many patients. These findings further emphasize that the clinical diagnosis of 16p11.2 deletion cannot rely solely on syndromic appearance. Skeletal abnormalities, endocrine findings, or ophthalmologic involvement necessitate multidisciplinary care. Interestingly, nearly half of the patients had a history of abnormalities during the prenatal period or problems at birth. This may also be important for precision medicine since probands with a 16p11.2 deletion may require closer follow up during the pregnancy and birth.

One of the important associations regarding the 16p11.2 deletion is the potentially increased risk of neuroblastoma observed in affected individuals. Although studies have shown that the risk of detecting the 16p11.2 deletion is significantly higher in children with neuroblastoma compared with control groups without the disease, the fact that this lethal cancer type is observed in only a very small proportion of individuals with the 16p11.2 deletion suggests that the deletion alone is not sufficient for oncogenesis.[22] Moreover, increased neuroblastoma risk has also been reported in association with other copy number variations beyond the 16p11.2 region.[23-25] In our cohort, none of the molecularly confirmed individuals had been diagnosed with neuroblastoma by the time of this study.

A particularly important observation was the presence of inherited deletions in several families, where carriers were either asymptomatic or mildly affected. This reinforces the concepts of variable expressivity and reduced penetrance, which are critical for genetic counseling. In some cases, family history revealed neuropsychiatric conditions or growth abnormalities in relatives without genetic confirmation, which may suggest underdiagnosis in adult carriers (Supplementary Table S1). In the cohort, parental origin could be determined in seven cases. While no clear parental sex bias has been consistently reported in the literature, the maternal predominance in our sample may warrant further investigation in larger cohorts. In reported cases of 16p11.2 deletions, a *de novo* mechanism of occurrence is frequently observed. While the exact rates vary across different cohorts, in our cohort the *de novo* occurrence rate was found to be 36% (4/11 cases with available parental analysis). It should be noted, however, that a considerable proportion of families did not undergo segregation analysis.

With the increasing accessibility of genetic testing, multilocus genomic variants, including dual diagnosis, double diagnosis, and concurrent genetic disorders) have become more readily encountered and are now familiar topics for professionals in the field of genetics. The literature already includes various publications offering different perspectives, furthermore, we previously conducted a comprehensive study on this subject.[26-28] Notably, even within this specific and technically limited cohort, a dual-diagnosis case was identified: an individual carrying both a 16p11.2 deletion and a heterozygous likely pathogenic *MC4R* variant (P16). We acknowledge that this finding may act as a phenotypic modifier, given that 16p11.2 deletions themselves represent one of the most penetrant genetic risks for obesity, the coexistence of these two genetic factors was interpreted as potentially additive rather than confounding. In such patients, clinical management and the concept of precision medicine gain even greater importance.

The main limitation of this study is that segregation analyses could not be performed for a substantial proportion of probands' families. Consequently, it was not possible to provide an accurate estimate of the number of *de novo* versus familial cases in the cohort. In addition, for two patients, one who died in the early postnatal period (P7) and another who was affected by perinatal complications (P2), reliable correlations between phenotypic features and the deletion could not be

established. Additionally, in some individuals, such as P2 and P15, the clinical presentation was more complex than typically observed in classic 16p11.2 deletion syndrome. Although further genetic investigations were conducted, no additional molecular findings were identified that could fully explain the expanded phenotype. However, due to the absence of more advanced genomic techniques such as whole genome sequencing or optical genome mapping in these cases, we refrained from attributing these atypical clinical features to the 16p11.2 deletion alone.

In summary, our cohort of 25 Turkish patients with 16p11.2 deletions highlights the characteristic yet heterogeneous nature of this CNV, with developmental and psychiatric features as the most consistent findings, alongside a higher epilepsy burden, and frequent obesity with systemic comorbidities. Comparisons with larger cohorts emphasize both shared patterns and population-specific variability. These observations underscore the importance of early recognition, multidisciplinary follow-up, and careful family-based counselling, particularly given the variable expressivity observed in carrier parents.

Supplementary materials

Supplementary materials for this article are available online at https://doi.org/10.24953/turkjpediatr.2026.7003

Ethical approval

The study was approved by Ethics Committee of Ankara Etlik City Hospital (date: 16.07.2025, number: AEŞH-BADEK1-2025-280).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: AK; data collection: AK, AB, ET, FDB, AKK, MAK, EA, DM, AE, AO, İE; analysis and interpretation of results: AK, AB, ET, FDB, AKK, MAK, EA, DM, AE, AO, İE; draft manuscript preparation: AK. 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

Compensatory kidney enlargement and blood pressure patterns in children with a solitary functioning kidney

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ABSTRACT

Background. Children with a solitary functioning kidney (SFK) are at risk for hypertension and kidney injury despite compensatory renal growth. However, the relationship between compensatory enlargement and blood pressure abnormalities remains controversial. This study is an exploratory observational study aimed at assessing ambulatory blood pressure monitoring (ABPM) parameters in children with an SFK and to evaluate the relationship between compensatory kidney enlargement and blood pressure indices.

Methods. Thirty-three children aged 6–18 years with an SFK (22 renal agenesis, 11 atrophic kidneys) were evaluated. Compensatory enlargement was defined as kidney length >97.5th percentile for height. All participants underwent anthropometric assessment, serum creatinine measurement, estimated glomerular filtration rate (GFR) calculation, and 24-hour ABPM. ABPM values were expressed as standard deviation scores (SDS) adjusted for age and sex.

Results. Compensatory enlargement was present in 17 (51.5%) patients. Those with compensatory enlargement showed significantly higher 24-hour systolic BP SDS (0.64±1.07 vs. –0.22±1.03, p=0.024), nighttime systolic BP SDS (1.36±1.04 vs. 0.38±0.93, p=0.008), nighttime diastolic BP SDS (1.42±1.17 vs. 0.48±0.70, p=0.009), and nighttime MAP SDS (1.43±0.99 vs. 0.48±0.84, p=0.006). Kidney length SDS correlated positively with 24-h systolic BP SDS (r=0.44, p=0.01) and nighttime MAP SDS (r=0.45, p=0.009). Logistic regression analysis revealed that compensatory enlargement independently predicted elevated blood pressure (OR 10.06, 95% CI 1.03–97.77, p=0.047) after adjustment for age, height SDS, and weight SDS.

Conclusions. Compensatory hypertrophy in SFK may not be entirely benign and could reflect an adaptive process associated with altered blood pressure regulation. Higher nocturnal blood pressure in patients with compensatory enlargement may suggest subclinical hemodynamic stress. These findings suggest that children with compensatory kidney enlargement may exhibit subtle alterations in ambulatory blood pressure patterns, warranting further investigation in larger longitudinal studies.

Key words: ambulatory blood pressure measurement, compensatory hypertrophy, hypertension, kidney length, renal adaptation, solitary functioning kidney.

Solitary functioning kidney (SFK) refers to an anatomical or functional absence of one kidney. A rough estimation of SFK has been reported as one in every 1400 births.[1,2] SFK can result from a variety of congenital and acquired conditions, ranging from renal agenesis, cystic dysplasia and multicystic dysplastic kidney (MCDK) to post-nephrectomy states due to congenital

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kidney and urinary tract abnormalities (CAKUT) or tumors or atrophic kidneys due to renal scarring.

Despite the prevailing belief that having only one SFK was no worse than having two kidneys, mounting evidence now indicates that patients with an SFK may experience less favorable long term clinical outcomes than previously assumed and living with an SFK may expose these people to certain risks such as hypertension and kidney injury.[3-9] Elevated blood pressure is an important risk factor in terms of preservation of kidney functions even in people with two kidneys. The prevalance of masked and ambulatory hypertension in SFK has been reported as approximately 15% and 27%, respectively in different studies.[10] The assessment of blood pressure in children is commonly based on casual blood pressure measurement, whereas in recent years ambulatory blood pressure monitoring (ABPM) has been widely used in the assessment of high blood pressure in children. Although there are opinions against the routine use of ABPM in patients with SFK[10], there has been an increasing number of reports encouraging the use of ABPM in the blood pressure monitoring of patients with SFK and these studies commonly indicate that blood pressure abnormalities may actually be more frequent than previously thought in patients with SFK.[3-5,8,9,11] Limited data exists on the correlation between blood pressure and kidney size in SFK.[5,12]

The relationship between compensatory renal enlargement and hypertension remains unclear. While some studies suggest an inverse association between compensatory enlargement and hypertension, others report no significant relationship.[3,11] In contrast, some authors have proposed that greater enlargement of the remaining kidney may be associated with higher blood pressure.[5] The debate in the literatüre regarding the relationship between compensatory enlargement in SFK and blood pressure abnormality prompted us to design the current study.

In this study, we aimed to evaluate ambulatory blood pressure (ABP) profiles in children with an SFK and to investigate the relationship between compensatory kidney enlargement and ABP indices.

Material and Methods

The study was conducted on children admitted to the pediatric nephrology clinic at a tertiary medical centre between January 2018 and January 2021, all were diagnosed with an SFK. All procedures contributing to this work complied with the ethical standards of the relevant national guidelines on human medical regulations and the Helsinki Declaration of 1975, as revised in 2008 and ethical approval was obtained from the hospital's local ethics committee. Patients with an SFK between 6-18 years of age, who had not receieved antihypertensive treatment before were included as the study group. A total of 51 pediatric patients with an SFK were initially enrolled in the study. Patients who exhibited renal scarring, cysts, kidney masses or additional CAKUT in SFK were excluded. According to the study protocol, 18 patients were excluded due to conditions that could compromise the assessment: 4 with MCDK/ cystic dyslasia without involution, 5 with a history of nephrectomy (4 nehprectomy due to CAKUT, 1 nehprectomy due to Wilms tumor), 1 lacking 24-hour ABPM data, 1 with incomplete ultrasonographic measurements, 1 with a horseshoe kidney, 2 with cortical hypofunction, 3 with renal scarring, and 1 with marked increased parenchymal echogenicity. Consequently, 33 patients were included in the final analysis (Fig. 1). The SFK cases included 22 patients with congenital renal agenesis/aplasia and 11 small atrophic/ hypofunctioning kidney with tracer uptake below 5 % on dimercapto succinic acid (DMSA)/ mercapto acetyl triglycine (MAG3).

In this study, the diagnosis of SFK was confirmed using renal ultrasonography and Tc-99m DMSA or Tc-99m MAG3 scintagraphy.

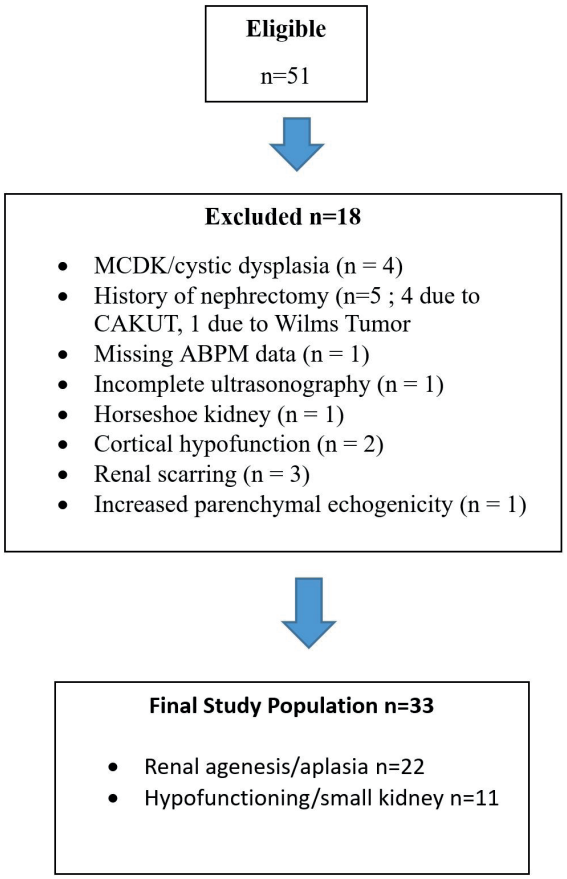

Fig. 1. Flow diagram of study design.

MCDK: multicystic dysplastic kidney, CAKUT: congenital kidney and urinary tract abnormalities, ABPM: ambulatory blood pressure monitor.

SFK was characterized by the absence of functional kidney tissue on ultrasound and/or on DMSA/MAG3 scintigraphy (kidney with tracer uptake below 5 % on DMSA/MAG3).[8] Weight (kg), height (cm), and body mass index (BMI) (kg/m^2) values, along with their corresponding standard deviation scores (SDS), were collected and analyzed based on predefined norms for Turkish children.[13] Serum creatinine levels were assessed and the bedside Schwartz glomerular filtration rate (GFR) equation was employed to estimate the glomerular filtration rate (eGFR).[14,15] The office blood pressure measurements were conducted by a pediatric nephrologist using auscultation. Prior to measurement, the patients were given a 30-minute rest. The readings were taken at least three times on the non-dominant arm, using an appropriately sized cuff.[16] For ABPM, an oscillometric device (Suntech, Morrisville, USA) was used.[17] The monitoring frequency during the day was every 20 minutes, and during the night, it was every 30 minutes. To differentiate between awake and sleep periods, the patients' self-reported sleep-wake times were recorded in a diary. Nocturnal dipping was defined as a 10% decline in mean systolic and diastolic ABP levels from day to night.[18] Blood pressure load was calculated as the percentage of valid measurements above the 95th percentile of blood pressure for age, gender, and height.[19] Blood pressure (BP) load parameters were analyzed as exploratory indicators of BP burden rather than as diagnostic criteria, in accordance with recent American Heart Association (AHA) recommendations. To assess BP values accurately, SD (standard deviation) scores (95th percentile correspondes to 1.645 SD) of mean systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial blood pressure (MAP) were calculated based on normative data presented by Wühl et al. with the "Child Metrics" computer program to standardize measurements according to age and gender (https://www.ceddcozum.com).[19] Blood pressure was then categorized using the scheme suggested by Flynn et al.[20]

Ultrasonography

Ultrasonography was performed using a LOGIQ P9 (GE Healthcare) machine equipped with a multi-frequency 4–6 MHz probe by an experienced pediatric radiologist who was blinded to the ABPM results. Kidney measurements were obtained with the children in the supine position. Kidney length (maximum bipolar length) was measured in the coronal plane. In pediatric populations, kidney size correlates more closely with height than chronological age; therefore, kidney length SDS were calculated based on height-adjusted normative data, rather than age-based references. This approach accounts for individual variations in somatic growth and avoids misclassification in children with

growth retardation or accelerated growth so compensatory enlargement of the SFK in our study was defined as a kidney length greater than the 97.5th percentile or a corresponding SDS score ≥ 1.96, based on normative data presented by Obrycki et al.[21,22]

Standardization of measurements according to patient height was performed using the calculator available at https://www.kidneylength.com.[21,22]

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 25.0 (IBM Corp., Armonk, NY, USA). The normal distribution of the variables was evaluated using histograms and probability graphs and with Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive analysis was performed using frequency tables for categorical variables, while means and standard deviations were used to describe normally distributed variables. Medians and quartiles (Q1–Q3) were used to describe variables with non-normal distribution. Results were evaluated with a confidence interval of 95%, and $p<0.05$ was considered statistically significant. Student's t test and Mann-Whitney U test was used to compare the means and medians of continuous variables. Spearman's Correlation Analysis was used to determine the relationship between SDS scores of ABPM parameters and kidney length SDS. The relationship between normal and elevated blood pressure with age, weight, height and presence of compensatory enlargement of SFK evaluated by univariate and multiple binary logistic regression analysis.

Results

The study included a total of 33 patients, 22 (66.7%) of whom were diagnosed with renal agenesis and 11 (33.3 %) with a small hypofunctioning kidney. Compensatory enlargement was present in 17 (51.5%) patients, whereas 16 (48.5%) patients did not demonstrate compensatory enlargement. There were no significant differences in age or anthropometric measurements and corresponding SDSs between patients with compensatory enlargement and those without. The median GFR values were similar in both groups. A significant association was observed between sex and compensatory kidney enlargement based on height-adjusted SDS values. Among female patients, 84.6% demonstrated compensatory enlargement, whereas only 30.0% of male patients showed this finding. The difference between sexes was statistically significant ($\chi^2 = 9.41$, df = 1, $p = 0.002$; Fisher's exact test $p = 0.004$) (Table I). Among the study population, hypertension was more prevalent in patients with compensatory kidney enlargement compared to those without (47.1% vs. 12.5%). However, this difference did not reach statistical significance (Fisher's exact test, two-sided $p = 0.054$).

Based on the results of ABPM, the group with compensatory enlargement had significantly higher 24-h systolic BP SDS (0.64±1.07 vs.-0.22±1.03 p=0.024), night systolic BP SDS (1.36±1.04 vs. 0.38±0.93 p= 0.008), night diastolic BP SDS (1.42±1.17 vs. 0.48±0.70 p= 0.009), night MAP SDS (1.43±0.99 vs. 0.48±0.84 p = 0.006) compared to the group without compensatory enlargement, respectively (Table II).

Patients with compensatory kidney enlargement exhibited significantly higher nighttime BP loads compared to those without compensatory enlargement. Median nighttime systolic BP load was 31% (12–70) versus 9% (0–29.5) ($p = 0.012$), and median nighttime diastolic BP load was 35% (12.5–53.5) versus 14% (6.25–25), respectively ($p = 0.019$) (Table II).

Although the proportion of nondippers was higher among patients with compensatory hypertrophy compared with those without (82.4% vs 68.8%), the difference did not reach statistical significance (p=0.36) (Table II). However, mean systolic and diastolic dipping percentages were significantly higher in patients without compensatory hypertrophy ($p = 0.034$ and $p = 0.011$, respectively).

Table I. Demographic features of the patients.

		Patients without compensatory enlargement (n=16)	Patients with compensatory enlargement (n=17)	p
Sex, n (%)	Female	2 (15.4)	11(84.6)	0.002
	Male	14 (70)	6 (30)	
SFK etiology, n (%)	Renal agenesis	9 (27.3)	13 (39.4)	0.218
	Small non-functioning kidney	7 (21.2)	4 (12.1)	
Age (years)		12.16±3.19	11.89±2.86	0.800
Weight (kg)		40.81±12.05	40.73±14.93	0.986
Weight SDS		-0.75±1.16	-0.36±0.97	0.302
Height (cm)		149.71±16.01	143.55±16.44	0.287
Height SDS		-0.46±0.86	-0.70±0.98	0.463
BMI (kg/m^2)		17.84±2.82	19.01±2.97	0.253
BMI SDS		-0.68±1.18	-0.02±0.90	0.081
Creatinine (mg/dl)		0.55 [0.49–0.75]	0.51 [0.44–0.60]	0.110
eGFR (mL/min/1.73m^2)		142.53 [120.04–155.03]	154.60[134.20–186.24]	0.136

SFK: Solitary functioning kidney SD: standard deviation score BMI: body mass index eGFR: estimated glomeruler filtration rate

Values are presented as mean ± SD or median (Q1–Q3). Mann–Whitney U test was used for non-normally distributed variables.

Spearman's correlation analysis demonstrated a significant positive association between SFK length SDS and several ABP parameters. Kidney length SDS showed a moderate positive correlation with 24-hour mean systolic BP SDS (r = 0.44, p = 0.010), nighttime mean systolic BP SDS (r = 0.45, p = 0.009), nighttime mean diastolic BP SDS (r = 0.47, p = 0.006), 24-hour mean arterial pressure SDS (r = 0.41, p = 0.017), and nighttime mean MAP SDS (r = 0.45, p = 0.009). A low positive correlation was observed with daytime mean systolic BP SDS (r = 0.38, p = 0.031) (Table III).

When subgroup analyses were performed, distinct patterns emerged between patients with and without compensatory kidney enlargement. In the agenesis subgroup, patients with compensatory enlargement showed significantly higher office systolic BP SDS values compared with those without enlargement (p = 0.001; large effect size, Cohen's d = 1.65). In contrast, no other ABP indices differed significantly in this subgroup (Table IV).

In the small atrophic kidney subgroup, patients with compensatory enlargement demonstrated markedly higher nocturnal BP indices, including night systolic BP SDS (p = 0.006), night diastolic BP SDS (p = 0.002), and night MAP SDS (p = 0.002), with large effect sizes (Cohen's d ≈ 2). These findings indicate that patients with compensatory kidney enlargement tended to have significantly higher nocturnal BP indices compared with those without enlargement (Table IV). In univariate analysis, compensatory kidney enlargement was associated with an increased likelihood of hypertension, with an odds ratio (OR) of 6.22 (95% confidence interval [CI] 1.06–36.21, p = 0.042). When adjusted for age, height SDS, and weight SDS in multivariate logistic regression, compensatory enlargement remained significantly associated with elevated BP (OR 10.06, 95% CI 1.03–97.77, p = 0.047). Age demonstrated a trend toward association with hypertension in both univariate and multivariate analyses (p = 0.067 and p = 0.059, respectively), whereas height SDS and weight SDS were not significant predictors (Table V).

Table II. Comparision of ABPM profiles according to existence of compensatory enlargement in SFK.

BP parameters		SFK without compensatory enlargement (n= 16)	SFK with compensatory enlargement (n=17)	p
Office BP	Office systolic BP SD score	-0.55±0.79	0.09±0.45	0.007
	Office diastolic BP SD score	0.27±0.50	0.52±0.42	0.136
24-h ABPM values	24-h systolic BP SDS	-0.22±1.03	0.64±1.07	0.024
	24-h diastolic BP SDS	-0.53±0.92	-0.06±1.07	0.191
	24-h MAP SDS	-0.29±0.83	0.39±1.08	0.050
	Day systolic BP SDS	-0.46±0.98	0.16±1.05	0.086
	Day diastolic BP SDS	-0.86±0.72	-0.82±1.03	0.886
	Day MAP SDS	-0.57±0.78	-0.27±1.02	0.353
	Night systolic BP SDS	0.38±0.93	1.36±1.04	0.008
	Night diastolic BP SDS	0.48±0.70	1.42±1.17	0.009
	Night MAP SDS	0.48±0.84	1.43±0.99	0.006
BP load and dipping*	24-h systolic BP load (%)	6.5[0–20)]	20[5.5–28.5]	0.068
	24-h diastolic BP load (%)	11.5[3.75–16]	12[8–17]	0.657
	Day systolic BP load (%)	3[0–18.5]	10[2–19.5]	0.326
	Day diastolic BP load (%)	4[0–12.75]	4[0–8.5]	0.657
	Night systolic BP load (%)	9[0–29.5]	31[12–70]	0.012
	Night diastolic BP load (%)	14[6.25–25]	35[12.5–53.5]	0.019
	Systolic BP dipping	8.84±4.74	4.76±5.71	0.034
	Diastolic BP dipping	11.52±5.22	4.28±9.36	0.011
BP dipping#	Dipper, n (%)	5 (31.2%)	3 (17.6%)	0.438
	Non-dipper, n (%)	11 (68.8%)	14 (82.4%)	
BP profile**	Normal, n (%)	14 (42.4)	9 (27.3)	0.057
	HT, n (%)	2 (6.1)	8 (24.2)	

ABPM: ambulatory blood pressure monitör, SFK: solitary functioning kidney MAP: mean arterial pressure BP: blood pressure SD: standard deviation SDS: standard deviation scores *Mann-Whitney U Test ** Pearson Chi –square #Fisher's Exact Test (2-tailed)
Values are presented as mean ± SD or median (Q1–Q3) according to data distribution.

Table III. Correlation analysis of SFK kidney length SDS and mean ambulatory BP SDS.

	Kidney length SDS, (n=33)	
	Spearman's rho	p
24H-mean SBP SDS	0.440	0.010
24H-mean DBP SDS	0.282	0.112
Day mean SBP SDS	0.377	0.031
Day mean DBP SDS	0.160	0.373
Night mean SBP SDS	0.447	0.009
Night mean DBP SDS	0.472	0.006
24h-mean MAP SDS	0.411	0.017
Day mean MAP SDS	0.292	0.099
Night mean MAP SDS	0.446	0.009

SFK: solitary functioning kidney, SBP: systolic blood pressure DBP: diastolic blood pressure, MAP: mean arterial blood pressure, SDS: standard deviation scores

Table IV. Comparison of ambulatory blood pressure SDS values between patients with and without compensatory renal enlargement in agenesis and small kidney subgroups, and corresponding effect sizes.

Subgroup	Parameter	Compensatory enlargement		Cohen's *d*	Hedges' *g*	*p*-value
Agenesis, (n=22)		Absent, (n=9)	Present, (n=13)			
	Office SBP SDS	-0.55±0.37	0.09±0.32	1.65	1.58	0.001
	Office DBP SDS	0.18±0.39	0.56±0.45			0.055
	24-h systolic BP SDS	0.001±1.16	0.48±1.04			0.319
	24-h diastolic BP SDS	-0.53±1.01	-0.22±1.09			0.508
	24-h MAP SDS	-0.26±0.90	0.22±1.06			0.278
	Day systolic BP SDS	-0.25±1.13	-0.004±0.97			0.590
	Day diastolic BP SDS	-0.89±0.80	-0.98±1.03			0.829
	Day MAP SDS	-0.55±0.91	-0.44±0.98			0.786
	Night systolic BP SDS	0.61±1.00	1.23±1.13			0.203
	Night diastolic BP SDS	0.64±0.74	1.28±1.30			0.201
	Night MAP SDS	0.70±0.91	1.27±1.05			0.206
Small atrophic kidney, (n=11)		Absent, (n=7)	Present, (n=4)			
	Office SBP SDS	-0.54±1.17	0.10±0.83			0.360
	Office DBP SDS	0.38±0.63	0.38±0.36			0.998
	24-h systolic BP SDS	-0.51±0.82	1.17±1.13	1.64	1.55	0.018
	24-h diastolic BP SDS	-0.54±0.88	0.44±0.97			0.124
	24-h MAP SDS	-0.37±0.79	0.94±1.11			0.051
	Day systolicBP SDS	-0.2±0.74	0.73±1.25			0.098
	Day diastolic BP SDS	-0.82±0.66	-0.28±0.95			0.294
	Day MAP SDS	-0.59±0.63	0.27±1.06			0.120
	Night systolic BP SDS	0.09±0.80	1.78±0.64	2.24	2.10	0.006
	Night diastolic BP SDS	0.26±0.64	1.88±0.43	2.19	2.05	0.002
	Night MAP SDS	0.19±0.70	1.94±0.58	2.13	1.99	0.002

Effect sizes (Cohen's d, Hedges' g) were calculated only for parameters showing statistically significant group differences
SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial blood pressure, SDS: standard deviation scores.
Values are presented as mean ± SD or median

Table V. Logistic regression analysis of confounding factors related with elevated blood pressure.

Variable	Blood pressure			Univariate associations			Multivariate associations		
	Normal BP (n=23)	Hypertension (n=10)	p	OR	CI	p	OR	CI	p
Age	11.40±2.84	13.46±2.93	0.067	1.28	0.97-1.68	0.075	1.42	0.98-2.05	0.059
Height SDS	-0.61±0.91	-0.52±1.00	0.816	1.10	0.48-2.52	0.809	1.18	0.25-5.53	0.826
Weight SDS	-0.60±1.18	-0.42±0.77	0.664	1.17	0.57-2.40	0.653	1.07	0.25-4.48	0.919
Compensatory (+)	9 (27.3%)	8 (24.2%)	0.057	6.22	1.06-36.21	0.042	10.06	1.03-97.77	0.047
enlargement* (-)	14 (42.4%)	2 (6.1%)							

OR: odss ratio CI: confidence interval SDS: standard deviation scores * Fisher's exact test
Values are presented as mean ± SD or median (Q1–Q3) according to data distribution.

Discussion

In this observational exploratory study, we evaluated ABPM profiles in children with an SFK and investigated the relationship between compensatory kidney enlargement and BP indices. A significant association between sex and compensatory kidney enlargement was observed in our cohort, with a higher proportion of females exhibiting compensatory enlargement. However, given the relatively small sample size, this finding should be interpreted with caution, as limited statistical power may influence the robustness and generalizability of the association.

In our study, 24-h systolic BP SDS, night systolic BP SDS, night MAP SDS as well as night systolic BP load and night diastolic BP load were observed to be higher in the group exhibiting compensatory growth compared to the group without a compensatory response. Subgroup analyses revealed that the pattern of BP elevation varied by the etiology of SFK. In the agenesis group, only office systolic BP SDS differed significantly according to compensatory enlargement, whereas in patients with a small atrophic kidney, the association extended to 24-hour and nocturnal ABP parameters, with large effect sizes. Subgroup analyses suggested that nocturnal BP indices tended to be higher among patients with small atrophic kidneys; however, given the limited sample size, these observations should be interpreted cautiously. In our study, a comparison of hypertension prevalence between patients with and without compensatory kidney enlargement showed a higher proportion of hypertensive cases in the compensatory enlargement group (47.1%) compared to the non-enlargement group (12.5%) but it did not reach statistical significance. These findings suggest a trend toward increased hypertension in patients with compensatory kidney enlargement; however, the small sample size warrants cautious interpretation. Although no statistically significant difference in hypertension prevalence was ultimately detected between the groups, this may reflect both the limited sample size and the diagnostic criteria used to define hypertension. In earlier studies, patients were more frequently classified as having masked or ambulatory hypertension because diagnostic definitions incorporated BP load as part of the criteria. In contrast, recent AHA guidelines no longer include BP load in the definition of ambulatory hypertension[20], which may have contributed to the lower observed prevalence in the present cohort.

Previously Dursun et al. reported an increased risk of elevated BP in children with SFK without compensatory hypertrophy based on the observation of inverse correlation between kidney size SDS and 24-h MAP SDS, 24-h systolic and diastolic BP load SDS.[3] However Seeman et al. could not find any significant correlation between kidney length/volume and daytime or night-time SBP/DBP in their cohort, which included MCDKs.[11] Mei-Zahav et al. reported that enlargement of the remaining kidney could potentially indicate an elevation in BP and serve as a prognostic indicator.[5] Our findings, in accordance with those of Mei-Zahav et al.[5] led us to think that the term "compensatory hypertrophy" does not necessarily indicate that everything is functioning perfectly in the remaining kidney. While compensatory hypertrophy may be a morphological sign that the kidney is adapting to the functional nephron loss, it may not be without consequences. Many studies in the literature hypothesize that the lack of compensatory hypertrophy in SFK may be a sign of a worse prognosis in terms of preserving kidney function and the evolution of hypertension. However, it is crucial to emphasize that each person's kidney reserve capacity and kidney characteristics are not the same. This implies that the capacity of the remaining kidney to increase single nephron GFR varies between individuals. Additionally, even among individuals born with two kidneys, there is a wide variation in nephron numbers, ranging from 500,000 to as high as 1,200,000 for each kidney. This inherent variation in nephron numbers may further contribute to the differing abilities of SFK to maintain normal kidney function and blood pressure regulation.

In essence, individuals with SFK who have a higher number of nephrons in the upper range of normal and those with a lower number of nephrons in the lower range may exhibit different responses in terms of developing high BP and preserving kidney function.

In patients with an SFK, not only the presence of compensatory enlargement but also its timing should be considered. In solitary kidneys that appear in the antenatal period before 36 weeks of gestation, when nephrogenesis is completed, compensation occurs to a certain extent by nephron hyperplasia and hypertrophy in the solitary kidney, whereas in solitary kidneys that appear after the completion of nephrogenesis, compensatory growth occurs mainly by hypertrophic response.[23] The presence of compensatory enlargement occurring in early childhood and even in the antenatal period before termination of nephrogenesis due to nephron hyperplasia may offer an advantage for the preservation of long-term kidney function and the attainment of normotension in certain patients with a single kidney. In our study, while no significant differences in ABP indices were observed in the renal agenesis group, the significant elevations in nocturnal BP parameters among patients with atrophic kidneys appear to support this association. However, the limited sample size necessitates cautious interpretation of these findings and represents the main limitation affecting the generalizability of the results. Studies in animal models have shown that extremely high functional kidney mass reductions (70%) in rats resulted in increased glomerular and systemic hypertension.[24] The decreased surface area for filtration and limited excretion of sodium lead to extracellular volume expansion, resulting in increased cardiac output and total peripheral vascular resistance, ultimately leading to systemic hypertension. This process creates a cycle of hypertension and sclerosis, further diminishing the kidney reserve for adaptation to the decreased functional nephrons. In our study, it was observed that mean ABP were higher in patients with SFK with compensatory growth compared to the group without compensatory response and there was a positive correlation between kidney size and mainly nocturnal mean ABP indices. Logistic regression analysis suggested a potential association between compensatory enlargement and elevated BP. In multivariable models adjusted for age, height SDS, and weight SDS, compensatory enlargement appeared to be associated with elevated BP (OR 10.06, 95% CI 1.03–97.77; Table V), whereas anthropometric parameters were not significant predictors. Given the small sample size and wide confidence interval, this result should be interpreted with caution and regarded as exploratory rather than confirmatory.

Our study has several limitations. It was a single-center, cross-sectional study with a relatively small sample size, which may limit the generalizability and statistical power of the findings. Wide confidence intervals in regression analyses reflect instability of the estimates, likely due to the limited number of hypertensive cases. Therefore, these findings should be interpreted with caution. Additionally, the imbalance in sex distribution between groups may have acted as a potential confounder, as sex-related differences in kidney anthropometry and blood pressure regulation are recognized in pediatric populations.

Conclusion

To conclude, our findings suggest that compensatory hypertrophy in children with an SFK may not uniformly represent a benign adaptive response. Although kidney enlargement is generally interpreted as an indicator of adequate compensatory capacity, it may also coincide with subtle alterations in BP regulation. The observation of higher nocturnal BP indices supports the possibility that structural compensation could be accompanied by mild hemodynamic stress rather than purely reflecting healthy adaptation.

These observations should be interpreted cautiously, given the relatively small sample

size and cross-sectional nature of our study. Nevertheless, they emphasize the need for careful, long-term clinical monitoring in children with SFK, as the presence of compensatory enlargement alone may not reliably indicate preserved kidney health. Future multicenter longitudinal studies with larger cohorts are warranted to better elucidate the temporal relationship between the degree and timing of compensatory kidney growth and blood pressure regulation, and to clarify the long-term implications of compensatory enlargement for kidney outcomes.

Ethical approval

The study was approved by Van Research and Education Hospital Ethics Committee (date: 21.01.2021, number: 2021/02).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: AYK, DB; data collection: AYK; analysis and interpretation of results: AYK, DB; draft manuscript preparation: AYK, DB. 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

Clinical features associated with *Pseudomonas aeruginosa* colonization in children under 2 years of age: a retrospective study of Cystic Fibrosis Registry

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ABSTRACT

Background. Respiratory colonization with *Pseudomonas aeruginosa* is associated with increased morbidity and mortality in cystic fibrosis (CF) patients. This study aims to assess the clinical characteristics and associated factors of CF infants under two years of age with *P. aeruginosa* colonization in Türkiye.

Method. Of the 1637 patients registered in the Cystic Fibrosis Registry of Türkiye in 2019, 284 patients under two years of age were included in this retrospective cross-sectional study. Patients were classified into two groups: those with *P. aeruginosa* colonization (Group 1) and those without (Group 2). Cystic fibrosis transmembrane conductance regulator (*CFTR*) gene functions were categorized according to *CFTR* mutation functional class.

Results. Twenty-three patients (8.1%) were categorized as Group 1 and 262 participants (91.9%) were classified as Group 2. Infants with *P. aeruginosa* colonization (Group 1) were more likely to have minimal CFTR function compared with those without colonization (87% vs. 39.8%, $p = 0.017$). In addition, both *Staphylococcus aureus* colonization (47.8% vs. 7.3%, $p < 0.001$) and methicillin-resistant *S. aureus* positivity (17.4% vs. 6.1%, $p = 0.042$) were observed more commonly in Group 1. There were no statistical differences between the groups in terms of age at diagnosis, gender, mean z-scores of weight and height, newborn screening test positivity, sweat chloride test results, and pancreatic insufficiency ($p > 0.05$). Univariate logistic regression analysis did not identify significant associated factors for *P. aeruginosa* colonization.

Conclusions. Our findings suggest that minimal CFTR function and *S. aureus* colonization are associated with *P. aeruginosa* colonization in CF patients under two years of age. Further studies are needed to investigate associated factors for early *P. aeruginosa* colonization, eradication treatment effectiveness, and longitudinal outcomes of in CF patients under two years of age.

Key words: Cystic fibrosis, *Pseudomonas aeruginosa*, colonization, children, registry.

Cystic fibrosis (CF) is the most common inherited disease in Caucasian populations caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, which encodes the ion channel-associated CFTR protein.[1] CFTR dysfunction leads to the colonization of an opportunistic Gram-negative pathogen, *Pseudomonas aeruginosa*.[2] Chronic infection with *P. aeruginosa* is one of the leading causes of morbidity and mortality in CF patients by contributing to progressive decline in pulmonary function.[2] With new modulator therapies, advances in supportive care, and enhanced treatment of respiratory infections and other complications, the predicted life expectancy of CF patients has increased to almost 50 years.[3] Therefore, recognition and effective treatment of initial *P. aeruginosa* colonization is essential in maintaining lung health and long-life expectancy in children with CF.[4]

Longitudinal studies in children with CF assessed with bronchoscopy and oropharyngeal cultures have demonstrated a high prevalence of *P. aeruginosa* in the first 2 years of life.[5-8] Moreover, although chronic *P. aeruginosa* colonization is not commonly expected during the first years of life, very early acquisition in infancy represents a critical and vulnerable period, as initial airway colonization during this stage may have a disproportionate impact on subsequent disease severity and long-term outcomes, including mortality in young children with CF.[7,9,10] However, the specific risk factors and clinical implications of *P. aeruginosa* colonization in infants remain inadequately understood, particularly in populations with genetic and environmental diversity. The fact that the prevalence of *P. aeruginosa* is not decreasing in our country, unlike in the United Kingdom, the United States, and European countries, makes the investigation of infant CF patients with *P. aeruginosa* colonization more important.[11-14]

Based on our hypothesis that very early *P. aeruginosa* colonization during the first years of life represents a distinct and sensitive clinical entity, we specifically focused on infants under 2

years of age. In this retrospective cross-sectional study, we aimed to assess the clinical features of CF patients with *P. aeruginosa* colonization under 2 years of age, in order to evaluate the associated factors for *P. aeruginosa* colonization.

Methods

Study design

We conducted a retrospective cross-sectional study on children with CF aged under 2 years of age who had available data on *P. aeruginosa* colonization status in the Cystic Fibrosis Registry of Türkiye (CFRT) for 2019. Patients aged <2 years were divided into two groups: those with *P. aeruginosa* colonization (Group 1) and those without *P. aeruginosa* colonisation (Group 2). All analyses were compared with these two groups.

Data input to the registry was approved by the local ethics committee, and all patients and/or their parents signed written consent for the data entry. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Hacettepe University Ethics Board, date: 12 April 2007, reference number: HEK 07/16-21 and date: 5 June 2018, reference number: GO 18/473-31) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Diagnosis of P. aeruginosa colonization in cystic fibrosis

Cystic fibrosis diagnosis was established according to the European Cystic Fibrosis Society (ECFS) guideline.[15] Chronic *P. aeruginosa* colonization was defined according to "modified Leeds criteria" as applied in the ECFSPR guideline: > 50% of the samples (sputum/other) collected over a 12-month period should be positive; at least 4 samples collected.[15,16] Samples were obtained at each outpatient clinic visit or during hospital stays using cough swabs or oropharyngeal swabs, as the study population was unable to expectorate sputum, as reported in the literature.[7,17] Infants are recommended to attend an outpatient clinic visits within the first 3 months of life after the diagnosis, then every 3-6 months until 2 years of age.[18]

Data variables

Age at the study period, age at diagnosis, gender, weight, height, z-scores of weight and height, history of meconium ileus, newborn screening test results, sweat chloride test results, medications, and results of *CFTR* genotype analysis were noted. As recommended by the CDC, Z-scores of weight and height measurements were assessed by using the World Health Organization growth charts for children < 24 months of age.[19,20] CF patients with classic symptoms and signs of exocrine pancreatic insufficiency who also have fecal elastase values <200 μg/g are said to have pancreatic insufficiency.[15]

CFTR functions were categorized according to CFTR mutation functional class: minimal function (presence of only class I, II, or III mutations) and residual function (at least one class IV or V mutation).[21-23] Minimal function mutations are severe and commonly associated with advanced lung disease and pancreatic insufficiency, whereas residual function mutations are milder and linked to less severe clinical phenotypes.

The presence of microorganisms in respiratory cultures recorded during the 2019 registry year, such as *Staphylococcus aureus,* methicillin-resistant *S. aureus* (MRSA), and *Haemophilus influenzae, Stenotrophomonas maltophilia,* and *Achromobacter* species were noted. The colonization status of *P. aeruginosa, S. aureus,* and the *Burkholderia cepacia* complex were recorded. The data regarding associated complications, including pseudo-Bartter syndrome (PBS), CF-related liver disease, gastroesophageal reflux, sinusitis, pneumothorax, and hemoptysis, were also documented.

Statistical analysis

Statistical Package for the Social Sciences (SPSS for Windows Version 20) was used for statistical analyses. In the descriptive statistics section, categorical variables are presented with numbers, percentages, and continuous variables with mean ± standard deviation or median and interquartile range (IQR, Q1-Q3). The distribution of normality in groups was evaluated by Kolmogorov-Smirnov and Shapiro-Wilk tests. A comparison of the median values of two independent groups was measured by the Mann-Whitney U test. The percentage distribution of categorical data between groups was measured using the $\chi 2$ test. Values of $p < 0.05$ were considered statistically significant. Because of the limited number of outcome events, logistic regression analyses were restricted to univariate models.

Results

A total of 1637 patients were registered in the Cystic Fibrosis Registry of Türkiye in 2019. Among these, 284 (17.3%) patients under 2 years of age were included in this retrospective cross-sectional study.

In the study population (n = 284), 23 participants (8.1%) were assigned to group 1, while 262 participants (91.9%) were assigned to group 2. The eligibility assessment of patients included in the study is shown in Fig. 1.

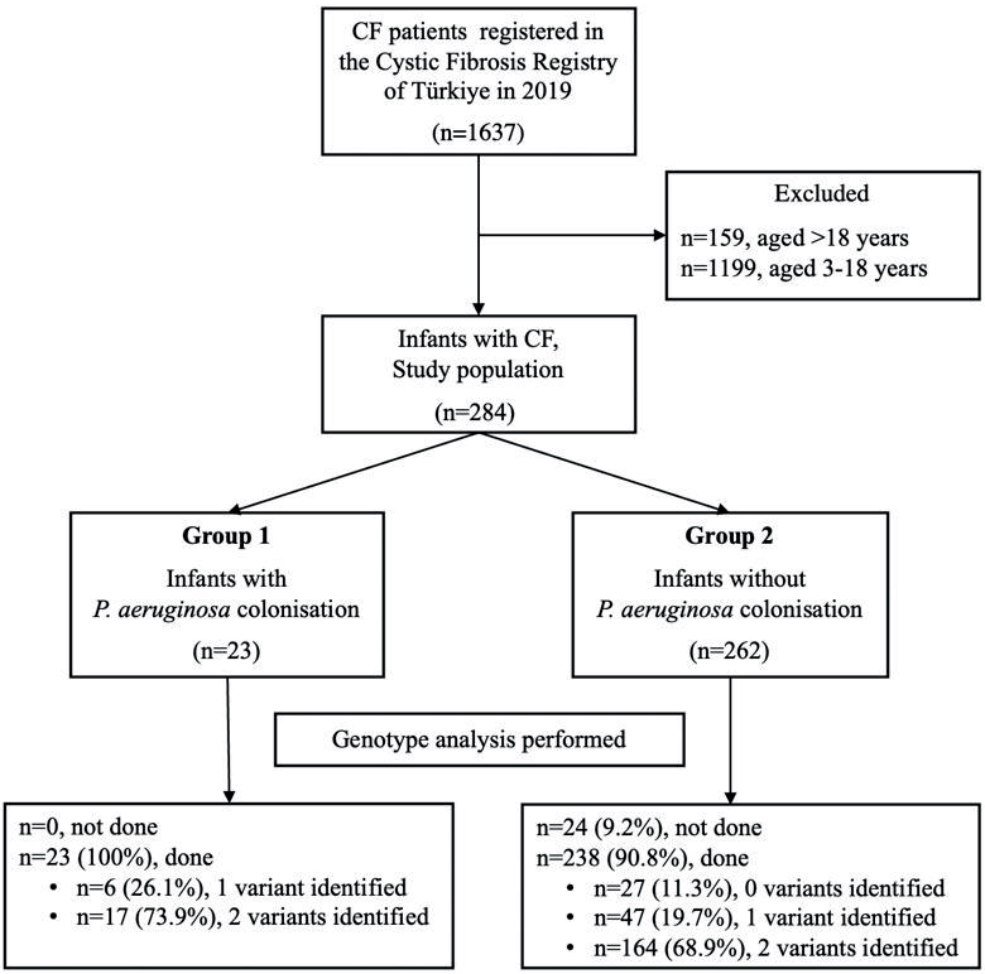

Fig. 1. Flow chart of study population.
CF: cystic fibrosis.

Demographic and clinical characteristics

Demographic and clinical characteristics of the study population according to *P. aeruginosa* colonization status are shown in Table I. Since newborn screening for CF was introduced in Türkiye on January 1st, 2015, all patients had undergone newborn screening. Among those screened, 17 patients (73.9%) in Group 1 and 201 patients (77.0%) in Group 2 had a positive newborn screening result. There were no statistical differences between the groups in terms of age, age at diagnosis, gender, mean z-scores of weight and height, newborn screening test positivity, sweat chloride test results, and pancreatic insufficiency ($p > 0.05$).

CFTR genotype analysis

Genotype analysis was performed on all patients in Group 1 (Fig. 1). F508del homozygous and heterozygous mutations were present in one patient each. According to the CFTR functional classification, 20 (87%) patients had minimal CFTR function, and 1 (4.8%) had residual CFTR function.

In Group 2, at least one variant was detected in 201 of the 238 patients who were genotyped (Fig. 1). Nineteen patients (7.3%) were homozygous for the F508del mutation, and 38 (14.5%) were heterozygous for F508del. According to the CFTR functional classification, 84 patients (39.8%) had minimal CFTR function,

Table I. Comparison of demographic and clinical features of patients with cystic fibrosis under 2 years of age according to *P. aeruginosa* colonization

Variables	Group 1 Patients with early *P. aeruginosa* colonization (n = 23)	Group 2 Patients without early *P. aeruginosa* colonization (n = 262)	p-value
Age at diagnosis, months, median (IQR)	2 (1-4)	2 (1-4)	0.659[a]
Age*, months, median (IQR)	21 (11-24)	15 (9-24)	0.468[a]
Gender, male, n (%)	12 (52.2)	132 (50.4)	0.869
Weight, kg, mean ± SD	10.1 ± 3.1	9.9 ± 3.0	0.743[b]
Height, cm, mean ± SD	81.3 ± 10.0	78.3 ± 10.5	0.178[b]
z-score for weight for age, mean ± SD	-1.43 ± 2.2	- 1.2 ± 1.5	0.352[b]
z-score for height, mean ± SD	-0.7 ± 1.4	-1.2 ± 1.6	0.860[b]
Diagnosis by newborn screening, n (%)	17 (73.9)	201 (77)	0.144
History of meconium ileus, n (%)	0 (0.0)	15 (5.7)	0.238
Sweat chloride test, mmol/L, mean ± SD	71.5 ± 35.5	69.7 ± 22.9	0.717[b]
Pancreatic insufficiency, n (%)	4 (17.3)	24 (9.1)	0.528
CFTR genotype analysis, done, n (%)	23 (100)	238 (90.8)	0.122
Homozygous F508del genotype, n (%)	1 (4.3)	18 (6.9)	0.641
Heterozygous F508del genotype, n (%)	1 (4.3)	38 (14.5)	0.178
CFTR classification, n (%)	n = 23	n = 211	
Minimal function	20 (87)	84 (39.8)	**0.017**
Residual function	1 (4.3)	35 (16.6)	
Unclassified	2 (8.7)	92 (43.6)	

*Age at the time of data entry for the 2019 registry year.
[a]Group comparisons were done using Mann-Whitney U test.
[b]Group comparisons were done using Student's t test
CFTR: cystic fibrosis transmembrane conductance regulator, IQR: interquartile range, SD: standard deviation.

and 35 (16.6%) had residual CFTR function. There was no statistical difference between the two groups regarding F508del homozygous and heterozygous mutations (p > 0.05). Patients in group 1 had a higher prevalence of minimal CFTR function than those in group 2 (p = 0.017).

Microbiological features

The prevalence of *S. aureus* (58.3% vs. 23.9%, p = 0.007) and MRSA (17.4% vs. 6.1%, p = 0.042) on recent respiratory culture and *S. aureus* colonization (47.8% vs 7.3%, p < 0.001) were significantly higher in Group 1, compared with Group 2 (Table II).

Both *P. aeruginosa* and *S. aureus* colonization were present in five patients. In three cases, *S. aureus* colonization preceded *P. aeruginosa* colonization.

Table II. Treatments, microbiological results, and accompanying complications of the study cohort of cystic fibrosis patients under 2 years of age

	Group 1 Patients with early *P. aeruginosa* colonization (n = 23), n (%)*	Group 2 Patients without early *P. aeruginosa* colonization (n = 262), n (%)*	p-value
Treatment			
DNase	23 (100)	217 (82.8)	**0.030**
Vitamin	21 (91.3)	196 (74.8)	0.073
Pancreatic enzymes	18 (78.3)	210 (80.2)	0.782
Inhaled hypertonic saline	3 (13)	10 (3.8)	**0.042**
Inhaled antibiotics	6 (26.1)	5 (1.9)	**< 0.001**
Oxygen therapy	2 (8.7)	2 (0.8)	**0.034**
Annual IV antibiotics days due to PEx, median (IQR)*	15.1 (0-59)	4.5 (0-70)	**< 0.001**[a]
Microbiological findings**			
Haemophilus influenzae	1 (4.3)	26 (9.9)	0.708
Staphylococcus aureus	7 (58.3)	58 (23.9)	**0.007**
MRSA	4 (17.4)	16 (6.1)	**0.042**
Stenotrophomonas maltophilia	1 (4.3)	5 (1.9)	0.399
Achromobacter	0	2 (0.7)	0.674
Chronic colonization			
Staphylococcus aureus	11 (47.8)	19 (7.3)	**< 0.001**
Burkholderia cepacia	1 (4.3)	0	0.081
Complications			
Pseudo-Bartter syndrome	5 (21.7)	35 (13.4)	0.267
CF-related liver disease	2 (0.7)	21 (7.4)	0.442
Gastroesophageal reflux	1 (4.3)	16 (6.1)	0.901
Sinusitis	1 (4.3)	4 (1.5)	0.589

*Data given as number (percentage), except for annual IV antibiotic days due to PEx, presented as median (interquartile range).
**Presence of microorganisms in respiratory cultures during the 2019 registry year
[a]Group comparisons were done using Mann-Whitney U test.
CF: cystic fibrosis, IV: intravenous, MRSA: methicillin-resistant *Staphylococcus aureus*, PEx: pulmonary exacerbations

CF-related medical treatments and CF-related complications

Patients in Group 1 had statistically longer duration of antibiotic therapy for pulmonary exacerbations (15.1 vs. 4.5, $p < 0.001$), more oxygen therapy support (8.7% vs. 0.8%, $p = 0.034$), higher prevalence of DNase (100% vs. 82.7%, $p = 0.003$), inhaled hypertonic saline (13% vs. 3.8%, $p = 0.042$), and inhaled antibiotic treatments (26.1% vs. 1.9%, $p < 0.001$) than patients in Group 2. A comparison of the treatments, microbiological results, and accompanying complications of the groups is given in Table II.

There were no significant differences between the groups in terms of accompanying complications, including PBS, CF-related liver disease (elevated transaminases without cirrhosis), gastroesophageal reflux, and sinusitis ($p > 0.05$). No other complications were recorded in any patients (Table II). None of the patients in the study cohort were receiving CFTR modulator therapy during the study period.

In the univariate logistic regression analyses, no relationship was found between gender, age at diagnosis, newborn screening test positivity, sweat chloride test results, and pancreatic insufficiency on the probability of *P. aeruginosa* colonization.

Discussion

We described the characteristics of infants under 2 years of age with *P. aeruginosa* colonization in our country. The prevalence of *P. aeruginosa* colonization was found to be 8.1% under 2 years of age. *S. aureus* infection and colonization were significantly higher in patients with *P. aeruginosa* colonization. We demonstrated *P. aeruginosa* colonization was more frequent in infants with minimal CFTR function compared to those with residual CFTR function.

Age-specific data on *P. aeruginosa* colonization in early childhood are limited and inconsistently reported in annual registry summaries.[13,15,24-27] For example, the prevalence of *P. aeruginosa* colonization has been reported as 2.1% in children under 3 years of age in the United Kingdom CF Registry and 6% in children under 4 years of age in the French CF Registry.[13,27] In contrast, the overall prevalence of *P. aeruginosa* colonization across all pediatric age groups has been reported as approximately 3.3% in the UK and 20% in France. In this context, our study provides age-specific data for infants under 2 years of age and demonstrates a prevalence of chronic *P. aeruginosa* colonization of 8.1% in this early and vulnerable period, compared with an overall colonization rate of 20% reported in the national registry.[24]

The age at initial *P. aeruginosa* acquisition is likely influenced by a complex interaction of bacterial, host-related (especially genetics), and environmental factors.[4,28-30] Pulmonary microbial diversity—defined as the richness and relative abundance of different microorganisms within the airway—is highest in early childhood and has been shown to influence disease progression and susceptibility to early *P. aeruginosa* colonization in patients with CF.[28,31] Moreover, studies have shown that increased airway inflammation, even in the absence of overt infection, may lead to early tissue damage and create a permissive environment for subsequent *P. aeruginosa* acquisition even in early infancy.[4,32] These mechanisms may partly explain why early-life colonization occurs in a particularly vulnerable period of lung development.

In infants who do not expectorate sputum, respiratory surveillance commonly relies on oropharyngeal or cough swabs to identify *P. aeruginosa*.[15,33] Although concerns remain about their diagnostic accuracy, a randomized controlled study demonstrated comparable clinical outcomes between bronchoalveolar lavage–guided and oropharyngeal culture–guided treatment strategies in young

children with CF.[34] Manos et al. showed that persistent *P. aeruginosa* strains in infants varied independently from isolation sites, such as upper or lower airways, and prior exposure of the airway to *P. aeruginosa*.[35] Taken together, these findings suggest that although the specific methods used for respiratory sample collection were not available in our study, the interpretation of our results remains reliable and consistent with existing evidence.

Patient characteristics such as lower socio-economic status, female gender, *CFTR* genotype, and microbial diversity in the lungs have been associated or identified as risk factors for the initial acquisition of *P. aeruginosa.*[4,10,17,30,36,37] Rosenfeld et al. evaluated risk factors for initial *P. aeruginosa* acquisition in order to inform prevention strategies and identify high-risk populations.[30] They concluded that none of the modifiable risk factors evaluated, including cigarette smoke, hot tub use, breastfeeding, and newborn screening positivity, was associated with age at *P. aeruginosa* acquisition. Rosenfeld and other studies have demonstrated that minimal CFTR function is associated with earlier *P. aeruginosa* acquisition compared to those with residual CFTR function.[23,30] Most of these studies have been conducted in the US, where the frequency of the F508del mutation is over 80%. However, due to the mutation diversity in our country, the frequency of the F508del mutation, the most common variant, is only 25%.[24] In the only study conducted in our country on CFTR function classification, no association was found between minimal and residual CFTR function classification and FEV1 decline.[38] However, we found the frequency of *P. aeruginosa* colonization was higher in those with minimal CFTR function compared to those with residual CFTR function under the age of 2 years. This causality analysis is beyond the scope of our study; however, the potential correlation between CFTR function classification in CF patients and disease severity at follow-up, including the risk of *P. aeruginosa* colonization, represents a significant research question for future investigations in our country.

The prevalence of *S. aureus* and MRSA isolation on recent respiratory culture positivity and *S. aureus* colonization were significantly higher in patients with *P. aeruginosa* colonization under 2 years of age. The relationship between *P. aeruginosa* and *S. aureus* in patients with CF is controversial in the literature. While Maselli et al. showed that *S. aureus* is a risk factor for initial *P. aeruginosa* acquisition, another study demonstrated *S. aureus* infection is significantly lower in the chronic *P. aeruginosa* group.[16,17] In our study, although higher rates of *S. aureus* and MRSA were observed in infants with *P. aeruginosa* colonization, the limited sample size precluded robust statistical inference regarding the nature of this association. Therefore, larger studies are required to better clarify the relationship between *S. aureus* and early *P. aeruginosa* colonization.

CF registries are a valuable resource for research because they provide access to large populations; however, they also have inherent limitations due to the restricted scope of available data. By focusing on a single time point, we were unable to evaluate the long-term progression of *P. aeruginosa* colonization and its impact on pulmonary function over time. An important limitation of the present study is the lack of detailed data on eradication therapies and treatment outcomes, which precluded evaluation of the effectiveness of different therapeutic approaches in preventing chronic *P. aeruginosa* colonization. Similarly, environmental factors such as air quality and climate were not assessed, which may play a role in colonization variability across regions and centers. Future studies incorporating genetic analysis, environmental factors, and documenting treatment regimens could yield more comprehensive risk assessments. Another limitation is that our study preceded the widespread availability of CFTR modulators in Türkiye. The absence of patients receiving these therapies in our cohort may limit the generalizability of our findings to current cystic fibrosis management, as these treatments may potentially alter airway microbiology.

The relatively small number of infants with *P. aeruginosa* colonization reduced statistical power and limited the ability to perform reliable multivariable analyses, increasing the risk of type II error. Therefore, logistic regression was restricted to a small number of clinically relevant, non-treatment variables, and the absence of significant independent predictors should be interpreted with caution. Although the use of standardized Leeds criteria for colonization diagnosis enhances the study's reliability, longitudinal follow-up studies are essential to evaluate the persistence of colonization, the effectiveness of interventions, and to clarify causal relationships and risk factors.

In conclusion, this study highlights the clinical characteristics and associated factors associated with *P. aeruginosa* colonization in infants with CF in Türkiye. The higher prevalence of colonization compared to other countries underscores the need for targeted preventive strategies. Our findings suggest that minimal CFTR function may contribute to an increased risk of colonization, and the association with *S. aureus* colonization further emphasizes the complexity of early respiratory infections in CF patients. However, the lack of data on eradication therapies and treatment outcomes limits our ability to assess intervention effectiveness. Future longitudinal studies incorporating genetic, environmental, and microbiome analyses are essential to better understand the dynamics of *P. aeruginosa* acquisition and to improve early intervention strategies in CF infants.

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Hacettepe University Ethics Board, date: 12 April 2007, reference number: HEK 07/16-21 and date: 5 June 2018, reference number: GO 18/473-31) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: EO, GC; Data collection: EY, NK, VŞ, HSŞ, DUA, HÇ, HY, ED, EDe, AB, YC, ATA, KH, MK, AÖ, NÇ, ZGGA, ÖK, HYü, ŞÖ, ET, GÇ, DC, PK, MKı; analysis and interpretation of results: GDT, SEP, DAT, BÖ, AAK, HY, GÜ, AİY, İI, GKÖ, EB, NS, PA, MH, GÖ; draft manuscript preparation: TŞE, SP, EÇ, NE, UÖ, DD. 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

Ocular manifestations in newly diagnosed acute leukemia: diagnostic performance of age, hemoglobin and platelets for retinal haemorrhages

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ABSTRACT

Background. Ocular involvement in the diagnosis of leukemia is clinically important but has been reported variably. Our aim was to define its prevalence and spectrum and to identify hematologic predictors, specifically age, hemoglobin level (Hb), platelet count (PLT), mean platelet volume (MPV), and platelet mass index (PMI).

Methods. This retrospective, single-center study evaluated all newly diagnosed leukemia patients between January 2023 and March 2025. All patients were examined by an ophthalmologist at the time of diagnosis and, if present, ocular involvement was identified.

Results. Among 78 pediatric patients, ocular involvement was present in 17 of 78 patients (21.8%). The most common ocular manifestation was retinal hemorrhage (16.7%). Ocular involvement was more frequent in acute myeloid leukemia (AML) than in acute lymphoblastic leukemia (ALL) (46.7% vs. 15.9%, p= 0.016). Older age (for ocular involvement: median 13 years [6–15] vs. 5 years [3–11], p = 0.006; for retinal hemorrhage: median 14 years [10–15] vs. 5 years [3–11], p = 0.001) and lower hemoglobin (for ocular involvement: 6.68 ± 2.31 g/dL vs. 8.46 ± 2.47 g/dL, p = 0.01; for retinal hemorrhage: 6.33 ± 2.26 g/dL vs. 8.43 ± 2.46 g/dL, p= 0.006) were associated with a higher risk. In multivariate models, age and Hb were independent predictors of hemorrhage (age: odds ratio [OR] 1.29, 95% confidence interval [CI] 1.10–1.52 per year; Hb: OR 0.60, 95% CI 0.38–0.95 per g/dL). ROC analyses showed that age provided the best discrimination (area under the curve [AUC] 0.796; 95% CI 0.651–0.940; cut-off ≥10 years: 73% sensitivity, 70% specificity), followed by Hb (AUC 0.756; 95% CI 0.604–0.908; cut-off 6.95 g/dL: sensitivity 76%, specificity 76%), whereas PLT showed weaker discrimination (AUC 0.682; 95% CI 0.553–0.812; cut-off 48,000/mm³: sensitivity 62%, specificity 65%).

Conclusion. Approximately one in five children had ocular involvement at diagnosis, most commonly retinal hemorrhage. Age and hemoglobin independently predicted retinal hemorrhage and provided useful discrimination. These data support a "hemoglobin-first" triage that prioritizes initial and follow-up ocular fundus testing in older children and those with an Hb ≲7 g/dL, with external validation of the proposed thresholds warranted.

Key words: childhood, acute leukemia, ocular involvement, retinal hemorrhage.

Leukemia is the most common malignancy in childhood and accounts for approximately one third of pediatric cancers worldwide.[1,2] In recent decades, survival rates have improved significantly due to advances in risk stratification and therapy. Nevertheless,

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the challenge of extramedullary involvement, particularly ocular manifestations, remains a critical clinical problem.[3,4]

Ocular involvement in pediatric leukemias has a complex spectrum and can occur at diagnosis, during therapy, or at relapse. These manifestations can be seen either directly (primary) or secondarily. Primary involvement involves direct infiltration of leukemic cells into ocular tissues, leading to findings such as proptosis, leukemic retinopathy, and optic neuropathy. Secondary effects occur due to hematologic abnormalities such as anemia and thrombocytopenia, resulting in retinal hemorrhages and papilledema.[5,6] Although direct leukemic infiltration of ocular structures is relatively rare, it has a significant impact on visual function and may even be the first sign of leukemia. Conversely, secondary ocular complications such as retinal hemorrhages and papilledema are among the most frequently reported findings. These are often the result of profound cytopenias or hyperviscosity, particularly in acute myeloid leukemia (AML) and advanced disease.[4] A significant proportion of ocular manifestations are asymptomatic and can only be identified by systematic ophthalmologic examination. This emphasizes the importance of routine ophthalmologic examinations in all newly diagnosed patients.

The prevalence of ocular involvement at diagnosis of pediatric leukemia, as reported in the literature, varies widely, ranging from 10% to 35%.[4,7-9] These findings are more common in older children, in patients with AML, and in patients with severe anemia or marked thrombocytopenia. Most studies do not show a direct impact of ocular involvement at diagnosis on overall survival.[10,11] However, the presence of such findings may indicate a more advanced stage of disease and therefore warrants careful clinical monitoring.[7] With these considerations in mind, regular ophthalmologic examination at the time of diagnosis is increasingly recommended to detect and monitor ocular complications early, particularly in high-risk subgroups. Early detection and intervention are crucial for preventing irreversible visual impairment and enhancing the quality of life for pediatric leukemia survivors.

In this retrospective, single-center study, we aimed to evaluate the prevalence and spectrum of ocular involvement at the time of diagnosis in children with acute leukemia and to analyze its association with clinical and hematological parameters.

Materials and Methods

Study design and patient population

This retrospective, single-center study was conducted at Ankara Etlik City Hospital in Ankara, Türkiye. The medical records of children diagnosed with leukemia were reviewed between January 2023 and March 2025. A total of 78 patients aged 0–18 years were included in the analysis.

Inclusion and exclusion criteria

We included pediatric patients aged 0–18 years diagnosed with acute lymphoblastic leukemia (ALL) and AML at our center between 2023 and 2025. Eligible patients underwent a complete ophthalmologic examination at the time of diagnosis. The diagnosis of leukemia relied on hematologic, morphologic, and immunophenotypic criteria. Only patients with complete medical and laboratory records were included.

Patients were excluded if the diagnosis was made outside our center without an ophthalmologic examination being performed at the time of diagnosis, if they had concomitant ocular or systemic diseases that could influence the ophthalmologic findings (e.g. congenital ocular anomalies, diabetes mellitus, hypertension, sickle cell anemia, or coagulopathies), if they had suffered ocular trauma or intraocular surgery in the past, or if they had infectious diseases known to cause ocular involvement (e.g. toxoplasmosis, cytomegalovirus retinitis). In addition, patients diagnosed with mixed

phenotype acute leukemia, chronic myeloid leukemia, or relapse cases were not included in the study.

Data collection

Demographic variables (age at diagnosis and sex), leukemia subtype, and the risk group defined in the protocol were recorded. Baseline complete blood counts including hemoglobin (Hb), platelet count (PLT), white blood cell (WBC) count, and mean platelet volume (MPV) were obtained at diagnosis prior to any transfusion and therapy.

Platelet Mass Index (PMI): As a bleeding-related composite parameter, platelet mass index was calculated as PMI = (MPV × PLT) / 1000, where MPV is reported in femtoliters (fL) and PLT in $\times 10^9$/L. The PMI was calculated using the same baseline complete blood count obtained at diagnosis and analyzed in the regression models as a continuous candidate predictor of bleeding.

Ophthalmological examination

At the time of leukemia diagnosis, all patients underwent a comprehensive ophthalmological evaluation performed by an experienced ophthalmologist. The assessment included best-corrected visual acuity measurement (performed with age-appropriate methods when feasible), ocular motility testing, anterior segment examination using slit-lamp biomicroscopy, and dilated fundus examination via indirect ophthalmoscopy after pharmacological mydriasis.

Ocular involvement was documented systematically for each eye and classified as follows:

- Retinal hemorrhage: intraretinal, preretinal, or subhyaloid hemorrhages observed in the posterior segment
- Retinal leukemic infiltration: yellow-white, ill-defined retinal lesions suggestive of leukemic cell accumulation
- Swollen optic disc: optic disc elevation consistent with papilledema or optic disc edema
- Retinal detachment: separation of the neurosensory retina from the underlying retinal pigment epithelium
- Cotton wool spots: localized retinal nerve fiber layer infarcts appearing as fluffy white patches
- Optic disc pallor: pale appearance of the optic nerve head, indicative of optic atrophy or ischemia
- Macular pallor: diminished coloration of the macula, potentially reflecting ischemia or degeneration
- Subconjunctival hemorrhage: well-demarcated hemorrhage beneath the conjunctiva, visible on anterior segment examination

All findings were recorded during the initial ophthalmic assessment. Patients without any ocular involvement were also documented accordingly. Fundus photography or optical coherence tomography (OCT) was performed when clinically indicated to support the diagnostic evaluation.

Definition of Ocular Involvement: Ocular involvement was defined as the presence of any abnormal ophthalmologic finding identified during a comprehensive eye examination at the time of leukemia diagnosis and considered attributable to leukemia or leukemia-related hematologic abnormalities. This definition encompassed both primary ocular involvement, reflecting direct leukemic infiltration of ocular tissues (e.g., retinal leukemic infiltration and optic disc infiltration), and secondary ocular involvement, resulting from systemic hematologic disturbances such as anemia, thrombocytopenia, or hyperviscosity (e.g., retinal hemorrhage, papilledema, and cotton wool spots). Patients without any of these findings were classified as having no ocular involvement.

Statistical analysis

Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY). Patients were grouped into subgroups according to the presence of ocular involvement and hemorrhage. Continuous variables were tested for normality and presented as mean ± standard deviation when normally distributed, and as median (Q1–Q3) when non-normally distributed. Comparisons between groups were performed using the t-test for independent samples or the Mann-Whitney U-test for continuous variables and the chi-square test or Fisher's exact test for categorical variables.

Univariate and multivariate logistic regression analyses were performed to identify independent predictors of ocular involvement and hemorrhage. Odds ratios (OR) with 95% confidence intervals (CI) were reported. Model calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test, model discrimination was evaluated based on the percentage of correctly classified cases from the classification table, and model explanatory performance was quantified using Nagelkerke R^2. Variables with $p < 0.20$ in the univariate analysis were considered candidate variables and were included in the multivariate logistic regression model. Multicollinearity among candidate variables was assessed using the variance inflation factor (VIF) derived from collinearity diagnostics in a linear regression model including all candidate predictors. Variables showing substantial multicollinearity were identified and evaluated before inclusion in the multivariate logistic regression model. Because PMI is derived from platelet count and mean platelet volume, it showed severe multicollinearity and was therefore excluded from the final multivariate model. The discriminatory ability of hemoglobin, platelet count, and age for predicting hemorrhage was evaluated using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC), sensitivity, specificity, and optimal cut-off values were calculated, and optimal cut-off points were determined using the Youden index.

Ethical approval

This study was approved by the local institutional ethics committee (AEŞH-BADEK1-2025-535) and conducted in accordance with the principles of the Declaration of Helsinki.

Results

At the time of diagnosis, a total of 78 pediatric patients (45 boys and 33 girls; median age 6 years [3-13]) with acute leukemia were evaluated. Of these patients, 63 (80.8%) were diagnosed with ALL and 15 (19.2%) with AML. The baseline demographic and laboratory data of the study population are summarized in Table I.

Table I. Demographic and clinical characteristics of the study population

Variable	Value (n = 78)
Age (years), median (Q1-Q3)	6.0 (3.0 - 13.0)
Sex, n (%)	
Male	45 (57.7%)
Female	33 (42.3%)
Leukemia subtype, n (%)	
Acute lymphoblastic leukemia	63 (80.8%)
B-cell ALL	53 (84.1%)
Standard risk	0
Medium risk	36 (67.9%)
High risk	17 (32.1%)
T-cell ALL	10 (15.9%)
Medium risk	1 (10.0%)
High risk	9 (90.0%)
Acute myeloid leukemia	15 (19.2%)
Standard risk	1 (6.7%)
Medium risk	7 (46.7%)
High risk	7 (46.7%)

Percentages for ALL and AML cases are calculated out of the total study population. Percentages for B-cell ALL and T-cell ALL are calculated within the ALL group. Percentages for risk groups are calculated within their respective leukemia subtypes (B-cell ALL, T-cell ALL, or AML).
ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia.

Table II. Baseline hematologic parameters at diagnosis by leukemia subtype (ALL vs. AML)

	ALL (n=63)	AML (n=15)	All study group (n=78)	p
WBC (/mm³) (median, Q1-Q3)	13,150 (3,905–46,805)	40,580 (2,525–98,495)	13,375 (3,500–51,310)	0.766
Hb (g/dL) (mean, SD)	8.16 ± 2.59	7.71 ± 2.34	8.07 ± 2.53	0.535
PLT (/mm³) (median, Q1-Q3)	65,000 (24,000–131,500)	51,000 (38,500–127,000)	58,500 (25,000–136,000)	0.990
MPV (fL) (median, Q1-Q3)	10.00 (9.25 – 10.75)	10.30 (9.90-10.9)	10.10 (9.30-10.80)	0.211
PMI index (median, Q1-Q3)	713.80 (241–1,202)	577.50 (409.70–1,119)	604.10 (243.60–1,210)	0.944

ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; Hb: hemoglobin; MPV: mean platelet volume; PLT: platelet; PMI: platelet mass index; WBC: white blood cells.

In the 78 patients who participated in the study, the median WBC count was 13,375/mm³ (3,500–51,310), the mean Hb level was 8.07 g/dL (standard deviation: 2.53), the median PLT count was 58,500/mm³ (25,000–136,000), the median MPV level was 10.1 fL (9.3–10.8) and the median PMI value was 604 (243–1,210). The comparative results for the ALL and AML subgroups are shown in Table II.

Seventeen of the 78 patients (21.8%) with leukemia presented with ocular involvement. Of these findings, 70.5% were secondary manifestations and 29.5% represented primary leukemic infiltration. The most common ocular manifestation was retinal hemorrhage, which was observed in 13 patients (16.7%), followed by retinal infiltration in 4 patients (5.1%). Less common findings were cotton wool spots, papilledema, nasal blurring of the optic disc margin, and mild macular pallor, each observed in a single patient (1.3%) (Table III). Ocular involvement was observed in 10 of 63 patients with ALL (15.9%) and in 7 of 15 patients with AML (46.7%) (p=0.016). Retinal hemorrhages were observed in 6 patients with ALL (9.5%) and in 7 patients with AML (46.7%), with a significantly higher incidence in the AML group (p= 0.002). When analyzed by leukemia subtype, retinal hemorrhages were observed in 5 of 53 patients with B-cell ALL (9.4%) and in 1 of 10 patients with T-cell ALL (10%), with no statistically significant difference between the groups. Furthermore, no significant difference in ocular involvement was found when comparing the risk groups for ALL and AML. On the other hand, the time from symptom onset to hospitalization did not differ between patients with and without ocular involvement (median 13 days [3–60] vs. median 15 days [3–90], respectively; p = 0.300).

Table III. Distribution of ocular involvement detected at the time of leukemia diagnosis (N=78)

Findings	n (%)
Retinal hemorrhage	13 (16.7)
Retinal leukemic infiltration	4 (5.1)
Nasal blurring of the optic disc	1 (1.3)
Retinal detachment	1 (1.3)
Cotton wool spot	1 (1.3)
Optic disc pallor	1 (1.3)
Macular pallor	1 (1.3)
Subconjunctival hemorrhage	1 (1.3)

Percentages are calculated based on the total number of patients (n=78). Since many patients had no ocular involvement, the sum of the percentages is less than 100%.

Patients with any ocular involvement were significantly older than those without ocular involvement (median age 13 years [6–15] vs. 5 years [3–11.5], p=0.006). Similarly, when retinal hemorrhage was evaluated as a specific ocular manifestation, patients with hemorrhage had a higher median age compared with those without hemorrhage (median age 14 years [10–15] vs. 5 years [3–11], p = 0.001).

In the comparison between patients with and without retinal hemorrhage, the Hb level (6.33 ± 2.26 g/dL vs. 8.43 ± 2.46 g/dL, p = 0.006) and platelet counts (median 42,000/mm³ [22,000–55,000] vs. 68,000/mm³ [26,000–157,000], p = 0.039) were significantly lower in the hemorrhage group. In contrast, MPV values were higher in patients with hemorrhage (median 11.0 fL [10.3–11.2] vs. 10.0 fL [9.2–10.5], p = 0.008) (Table IV). In multivariate logistic regression analysis including age, hemoglobin, platelet count and MPV; only older age and lower Hb levels remained independently associated with retinal hemorrhage (age: OR 1.29, 95% CI 1.10–1.52, p=0.002; Hb: OR 0.60, 95% CI 0.38–0.95, p=0.030). The logistic regression model was statistically significant (χ^2 = 25.840, p < 0.001), showed acceptable calibration according to the Hosmer–Lemeshow goodness-of-fit test (p = 0.387), and correctly classified 93.6% of the cases (Nagelkerke R^2 = 0.475) (Table V). Similarly, in patients with ocular involvement,

Table IV. Baseline hematologic parameters at diagnosis by retinal hemorrhage status and ocular involvement

	Retinal hemorrhage absent (n=65)	Retinal hemorrhage present (n=13)	p	Ocular involvement absent (n=61)	Ocular involvement present (n=17)	p
WBC (/mm³) (median, Q1–Q3)	13,150 (3,860–46,750)	28,900 (2,790–130,000)	0.634	13,600 (3,950–46,750)	10,000 (2,790–130,000)	0.770
Hb (g/dL) (mean, SD)	8.43 ± 2.46	6.33 ± 2.26	0.006	8.46 ± 2.47	6.68 ± 2.31	0.010
PLT (/mm³) (median, Q1–Q3)	68,000 (26,000–157,000)	42,000 (22,000–55,000)	0.039	68,000 (28,000–157,000)	42,000 (22,000–75,000)	0.050
MPV (fL) (median, Q1–Q3)	10.00 (9.20-10.50)	11.00 (10.30-11.20)	0.008	10.00 (9.20-10.50)	10.40 (10.00-11.20)	0.028
PMI (median, Q1–Q3)	717.60 (249.60–1,460)	390.60 (240.00–603.00)	0.084	717.60 (252.50–1,460)	390.60 (240.00–765.00)	0.080

Hb: hemoglobin; MPV: mean platelet volume; PLT: platelet; PMI: platelet mass index; WBC: white blood cells.

Table V. Logistic regression analysis of parameters associated with retinal hemorrhage and ocular involvement

Variable	Retinal hemorrhage Univariate OR (95% CI), *p*	Retinal hemorrhage Multivariate OR (95% CI), *p*	Ocular involvement Univariate OR (95% CI), *p*	Ocular involvement Multivariate OR (95% CI), *p*
Age (years)	1.26 (1.08-1.46), p=0.002	1.29 (1.10-1.52), p=0.002	1.16 (1.04-1.30), p=0.008	1.19 (1.05-1.36), p=0.007
Hb (g/dL)	0.65 (0.48-0.90), p=0.010	0.60 (0.38–0.95), p=0.030	0.71 (0.55–0.93), p=0.014	0.69 (0.49–0.98), p=0.037
PLT (x10³/μL)	0.98 (0.96–0.99), p=0.055	0.99 (0.97–1.01), p=0.459	0.99 (0.97–1.00), p=0.056	0.99 (0.98–1.00), p=0.507
MPV (fL)	1.96 (1.14-3.36), p=0.015	1.16 (0.61–2.19), p=0.642	1.64 (1.01–2.67), p=0.042	1.07 (0.62–1.87), p=0.786
WBC (x10³/μL)	1.01 (0.99–1.02), p=0.874		1.00 (0.99–1.00), p=0.339	
PMI	0.99 (0.99–1.01), p=0.070		0.99 (0.99–1.00), p=0.070	

Variables not significant in univariate analysis (WBC and MPV×PLT) were not included in the multivariate model.
CI: confidence interval; Hb: hemoglobin; MPV: mean platelet volume; OR: odds ratio; PLT: platelet; PMI: platelet mass index; WBC: white blood cells.

Hb levels (6.68 ± 2.31 g/dL vs. 8.46 ± 2.47 g/dL, p = 0.01) and platelet counts (median 42,000/mm³ [22,000–75,000] vs. 68,000/mm³ [28,000–157,000], p = 0.050) were significantly lower compared to those without ocular involvement, whereas MPV values (median 10.4 fL [10.0–11.2] vs. 10.0 fL [9.2–10.5], p = 0.028) were higher (Table IV). In multivariate logistic regression analysis including age, hemoglobin, platelet count and MPV, older age and lower Hb levels were independently associated with ocular involvement (age: OR 1.19; 95% CI, 1.05–1.36; p=0.007; Hb: OR 0.69; 95% CI, 0.49–0.98; p=0.037). The logistic regression model was statistically significant (χ^2 = 18.797, p = 0.001), showed acceptable calibration according to the Hosmer–Lemeshow goodness-of-fit test (p = 0.488), and correctly classified 85.9% of cases (Nagelkerke R^2 = 0.330) (Table V).

ROC curve analysis revealed that age was a significant predictor of retinal hemorrhage (AUC=0.796; 95% CI, 0.651–0.940; p=0.001), with a cut-off point of 10 years resulting in a sensitivity of 73% and a specificity of 70%. Hemoglobin also showed good discrimination (AUC=0.756, 95% CI: 0.604–0.908, p=0.004), with a cut-off value of 6.95 g/dL yielding a sensitivity of 76% and a specificity of 76%. The platelet count showed a moderate discriminative performance (AUC=0.682, 95% CI: 0.553–0.812, p=0.039), and a cut-off of 48,000/mm³ provided a sensitivity of 62% and a specificity of 65%. The ROC analysis showed that age was the strongest discriminator of retinal hemorrhage (AUC=0.796; 95% CI, 0.651–0.940; p=0.001), compared with Hb (AUC=0.756; 95% CI, 0.604–0.908; p=0.004) and platelet count (AUC=0.682; 95% CI, 0.553–0.812; p=0.039) (Fig. 1). These results support the conclusion that age and Hb values together represent an independent risk factor for the prediction of retinal hemorrhage, while PLT may serve as a complementary parameter with potential clinical utility.

Discussion

The prevalence of ocular manifestations in pediatric patients diagnosed with acute leukemia is of great concern, as several studies emphasize the need for a thorough ophthalmologic examination at diagnosis. In this study, 78 pediatric acute leukemia patients

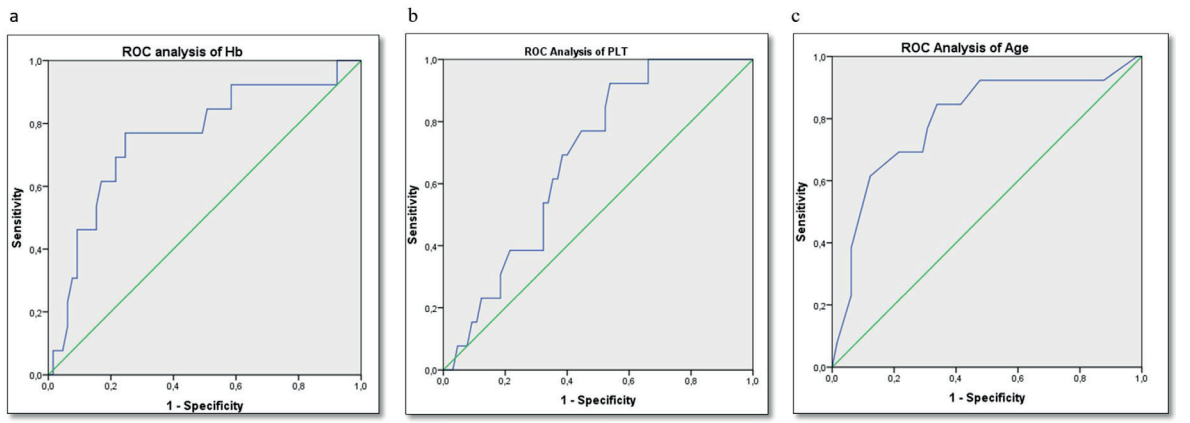

Fig. 1. a. Receiver-operating characteristic (ROC) curve for hemoglobin (Hb) at diagnosis to discriminate the presence of hemorrhage. AUC = 0.756 (95% CI, 0.604–0.908; p = 0.004). The optimal cut-off of 6.95 g/dL provided 76% sensitivity and 76% specificity. The diagonal line denotes chance performance. **b.** ROC curve for platelet count (PLT) at diagnosis to discriminate the presence of hemorrhage. AUC = 0.682 (95% CI, 0.553–0.812; p = 0.039). The cut-off of 48,000/mm³ provided 62% sensitivity and 65% specificity. The diagonal line denotes chance performance. **c.** ROC curve for age at diagnosis to discriminate the presence of hemorrhage. AUC = 0.796 (95% CI, 0.651–0.940; p = 0.001). The prespecified cut-off of ≥10 years yielded 73% sensitivity and 70% specificity. The diagonal line denotes chance performance.

AUC: area under the curve; CI: confidence interval.

were evaluated, 21.8% of whom had abnormal ocular involvement at diagnosis. These findings are consistent with the existing literature, which reports a prevalence of ocular involvement ranging from 10 to 35% in acute leukemia cases.[4,5,7,9] Furthermore, a recent meta-analysis including 2,989 patients from 14 studies, found a prevalence of 20.32% for ocular involvement in newly diagnosed leukemia, underscoring the importance of ocular examinations in this patient group.[4]

The most frequently observed ocular manifestation in this cohort was retinal hemorrhage, which was noted in 13 patients (16.7%). This is consistent with the findings of Bitirgen et al. who described retinal hemorrhages as round or flame-shaped lesions that may show the accumulation of leukemic cells or platelet-fibrin aggregates.[9] They pointed out that such hemorrhagic events usually resolve with remission, emphasizing the dynamic relationship between underlying disease status and ocular health. Understanding these presenting ocular signs is critical as they may provide important prognostic insights into the behavior of the hemorrhagic disease and potential clinical outcomes.[8,12]

Age showed the best discrimination for hemorrhage (AUC = 0.796; 95% CI, 0.651–0.940) and remained independently associated after adjustment, with a prespecified threshold of ≥10 years yielding a sensitivity of 73% and specificity of 70%. This is consistent with pediatric reports showing that ocular involvement increases with age at diagnosis- particularly in AML- even when hematologic indices are comparable.[10] As age cut-offs in pediatrics are not standardized, our threshold of ≥10 years should be considered provisional and subject to external validation.[7]

Hemoglobin demonstrated moderate discrimination (AUC = 0.756; 95% CI, 0.604–0.908) with an optimal cut-off value of 6.95 g/dL (76% sensitivity/specificity), which closely follows current restrictive transfusion guidelines for stable hospitalized patients.[13] Pediatric acute leukemia series also demonstrates an association between lower Hb levels and retinal hemorrhages. For example, Benvenuto et al. reported mean Hb level of 7.4 g/dL in children with retinal hemorrhages at diagnosis, confirming the validity of our cut-off value.[7] Given the heterogeneity of the cohorts (e.g. suggestions of ≤9.9 g/dL with weaker AUC), external validation of the 7 g/dL threshold is warranted.[14] In practice, children with an Hb level <7 g/dL - especially those who are older or symptomatic - should be prioritized for initial and follow-up ocular fundus examinations, while transfusion decisions remain individualized and guideline-driven.[13]

Several studies have identified hematologic laboratory parameters as key correlates of retinal hemorrhages, with anemia and, to a lesser extent, thrombocytopenia as notable examples.[15-17] Of these factors, Hb level remains the most reliable independent risk factor. This study confirms that lower hemoglobin levels are independently associated with the presence of retinal hemorrhage at the time of leukemia diagnosis. Similar associations between severe anemia and hemorrhagic retinal manifestations have been consistently reported in pediatric acute leukemia cohorts.[7,11] Furthermore, comparisons between pediatric and mixed-age cohorts indicate an age-related gradient in ocular manifestations, which supports the plausibility of age-dependent susceptibility. Nevertheless, pediatric-specific age thresholds are not standardized. Hence, our threshold of 10 years or older should be considered hypothesis-generating and requires external validation. Finally, platelet indices showed weak and non-independent performance in our models. This reflects studies in which platelets provide limited discrimination once hemoglobin, age, or disease subtype are taken into account.[7]

Severe anemia reduces retinal oxygenation, promoting hypoxia-induced capillary fragility and disruption of the inner blood-retinal barrier; this biologically explains the stronger association between low Hb and hemorrhage. The rheology of leukemic blood (e.g. leukostasis / viscosity) may further impair microvascular

flow, while platelet-fibrin microthrombi (Roth spots) mark endothelial damage. In AML, choroidal/leukemic infiltration may also impair choriocapillaris flow, triggering retinal pigment epithelial pump failure and hemorrhagic/exudative phenotypes.[11] Taken together, these mechanisms support a "hemoglobin-first" triage for ophthalmologic monitoring and explain why platelet indices offer little additional discriminatory power once Hb (and age) are taken into account.

In our cohort, MPV differed between groups in univariate analysis but was not independent after adjustment. In contrast, age and hemoglobin remained independent predictors, while platelet count, like MPV, was not an independent risk factor. Furthermore, neither the platelet mass index nor the WBC count showed any association with hemorrhage. This observed pattern is consistent with findings in pediatric leukemia suggesting that anemia is the most important hematologic determinant of ocular/retinal hemorrhage, while platelet-based metrics (PLT, MPV, and thus PMI) provide limited additional value when Hb and age are taken into account.[7,10,14,18] Taken together, these results support a "hemoglobin-first" triage approach for ocular involvement in pediatric acute leukemia. On the other hand PLT/MPV parameters serve as complementary indicators. Nevertheless, given biological plausibility and potential timing/assay variability, MPV and PMI should be reassessed in adequately powered, prospective, leukemia-specific cohorts with standardized CBC timing and ophthalmic endpoints.

At presentation, abnormal ocular involvement was more frequent and/or pronounced in AML than in ALL. No significant differences were observed between the various immunophenotypic subtypes of ALL (B-ALL vs. T-ALL). Clinically, this pattern supports prioritizing baseline and repeated fundoscopic examinations during diagnosis and induction in AML, particularly in older or markedly anemic patients. Prompt supportive care—correcting anemia and managing coagulopathy—should also be provided to reduce ocular complications. In acute leukemia, a universal screening approach remains appropriate regardless of immunophenotype. Ophthalmic surveillance should mainly be stratified by hematologic burden (especially hemoglobin level) and age, rather than by B-ALL or T-ALL classification.

Our study has several limitations; including its retrospective nature and the retrospective collection of data. Additionally, it is a single-center study with a relatively small patient cohort. Although patients underwent ophthalmologic examinations within 24-48 hours of diagnosis, these examinations were performed by different ophthalmologists. Additionally, we were unable to perform a survival analysis comparing patients with and without ocular involvement.

Conclusion

Abnormal ocular manifestations occur in about a quarter of children with newly diagnosed acute leukemia, with retinal hemorrhages and leukemic infiltrations being the most common findings. Ocular involvement is particularly increased in AML, in older children, and in children with lower hemoglobin levels. We recommend routine ophthalmologic examinations at the diagnosis of acute leukemia, even if the patient is asymptomatic. A multidisciplinary management approach, incorporating both pediatric hematology and ophthalmology, is crucial for timely intervention and to optimize patient outcomes in this vulnerable population. This study may guide the re-evalution of transfusion policies in acute leukemia with ocular involvement, particularly in retinal hemorrhage, in the future.

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No additional individuals or institutions contributed beyond standard clinical duties.

Ethical approval

The study was approved by Ankara Etlik City Hospital Ethics Committee (date: 03.09.2025, number: AEŞH-BADEK1-2025-535).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: AF, VK; data collection: VK, OMÇ, FTY; analysis and interpretation of results: AF, VK, AYS, CK; draft manuscript preparation: AF, VK. 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

Procalcitonin and proadrenomedullin in pediatric acute leukemia: biomarkers for infection and beyond

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ABSTRACT

Background. The clinical utility of procalcitonin (PCT) and proadrenomedullin (ProADM) in children with malignancies remains inadequately characterized. This study was designed to assess baseline PCT and ProADM levels at the time of leukemia diagnosis and to compare their profiles during subsequent episodes of febrile neutropenia (FN).

Methods. Children aged 18 years or younger with newly diagnosed acute leukemia, including acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), were prospectively recruited for this study. Serum levels of PCT and ProADM were measured at baseline, prior to the initiation of chemotherapy at the time of diagnosis, and were reassessed during subsequent episodes of FN.

Results. A total of 80 children with acute leukemia were prospectively enrolled, with a median age of 5 years (interquartile range [IQR]: 3-7 years). The study population comprised of ALL in 67.5% of cases and AML in 32.5%. At the time of diagnosis, prior to chemotherapy initiation (n=80), the median serum PCT level was 0.19 ng/mL (IQR: 0.07–0.54), while the median ProADM level was 0.04 nmol/L (IQR: 0.01–0.07). Among the 80 patients, 32 children subsequently developed FN and had paired serum samples available for comparative analysis. During FN episodes, both biomarkers showed a significant increase relative to baseline values. Median PCT increased from 0.16 ng/mL (0.08–0.52) at diagnosis to 0.32 ng/mL (0.08–0.50) during FN ($P = 0.03$), while median ProADM increased from 0.03 nmol/L (0.006–0.05) to 0.41 nmol/L (0.20–0.81) ($P < 0.001$). At the time of leukemia diagnosis, splenomegaly was the only clinical factor significantly associated with elevated baseline PCT levels ($P = 0.010$). Subgroup analysis revealed distinct biomarker patterns: in children with ALL, PCT levels remained largely unchanged between diagnosis and FN, possibly reflecting an underlying baseline inflammatory state, whereas ProADM showed a significant rise during FN, suggesting greater specificity for infectious events. In contrast, in AML, both PCT and ProADM increased significantly during FN, indicating their potential utility as infection-related biomarkers in this subgroup.

Conclusion. Both PCT and ProADM were significantly elevated in FN when patients with acute leukemia were analyzed as a whole. However, subgroup analysis revealed differing patterns: in ALL, only ProADM remained significantly associated with FN, whereas PCT showed no significant association. In contrast, in AML, both biomarkers were significantly elevated. These findings suggest that ProADM may have greater clinical utility in guiding the management of febrile episodes, particularly in ALL.

Key words: leukemia, procalcitonin, proadrenomedullin, febrile neutropenia, children.

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Infectious complications remain a leading cause of morbidity and mortality in children with acute leukemia. Current management strategies primarily rely on empirical antimicrobial therapy, often resulting in overuse and associated adverse consequences. Procalcitonin (PCT) and proadrenomedullin (ProADM) are infection-related biomarkers that have been extensively studied in the general population; however, their utility in immunocompromised cohorts, such as pediatric patients with acute leukemia, remains underexplored. Given their potential to differentiate between infectious and non-infectious inflammatory states, these biomarkers may serve as valuable adjuncts in the management of febrile episodes in this vulnerable population.[1,2]

Elevated PCT levels serve as a valuable biomarker for assessing the risk of bacterial infections, thereby aiding in the judicious use of antibiotics. This targeted approach to antimicrobial stewardship is crucial for minimizing unnecessary antibiotic exposure, which in turn helps mitigate the emergence of antibiotic resistance.[3] Secmeer et al. demonstrated that serial PCT measurements provide superior diagnostic value compared with C-reactive protein (CRP) in pediatric patients with neutropenic fever, particularly for assessing infection severity, fever duration, and potential etiology.[4] The diagnostic and prognostic significance of PCT has been explored in various malignancies.[5-9] Patients with solid tumors and metastatic disease, even in the absence of clinical or microbiological evidence of infection, exhibited significantly elevated PCT levels. This increase was especially pronounced in individuals with widespread metastatic involvement.[10] Additionally, elevated PCT levels have demonstrated potential utility in the diagnosis and monitoring of various non-infectious conditions, such as hypercalcemia, autoimmune, and immunological disorders.[11] Adrenomedullin (ADM) is a rapidly degraded peptide, and its biologically inactive fragment ProADM is generated as a more stable surrogate marker.[12]

These two biomarkers, PCT and ProADM, are not neutrophil-specific and are primarily derived from thyroidal C cells and the adrenal medulla, respectively. Consequently, their measurement remains valid and reliable even in the context of profound neutropenia.[13] No study has specifically evaluated the role of PCT and ProADM at the time of diagnosis in pediatric acute leukemia. This study aimed to assess their baseline levels before chemotherapy initiation and to compare them with levels measured during subsequent episodes of febrile neutropenia (FN).

Materials and Methods

Study population

A prospective observational study was conducted from June 2020 to March 2023 at the Department of Pediatrics of a tertiary care referral institute. Ethical clearance for this study was obtained from the Institute Ethics Committee (IEC-459/01.09.2017, RP-09/2017, OP-13/06.12.2019, RP-43/2019). Children aged ≤18 years with newly diagnosed acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) were eligible for enrollment, provided that informed consent was obtained from a parent or legally authorized representative (LAR), along with assent from children aged over 7 years. Patients who had received antibiotic therapy within the 14 days preceding their acute leukemia diagnosis were excluded from the study.

Data collection

At the time of leukemia diagnosis, data collection included demographic and clinical parameters, the underlying malignancy subtype, complete blood counts, and, following the initiation of chemotherapy, detailed information related to episodes of febrile neutropenia (FN).

Outcome assessment

The primary objective of the study was to evaluate PCT and ProADM levels at the time

of leukemia diagnosis and to compare them with those measured during episodes of febrile neutropenia. The secondary objective was to identify clinical and laboratory determinants associated with elevated levels at the time of acute leukemia diagnosis.

Sample collection and processing

Baseline investigations, including complete blood counts (CBC), serum electrolytes, renal function tests (RFTs), and liver function tests (LFTs), were obtained at the time of acute leukemia diagnosis. During episodes of FN, the routine diagnostic work-up included CBC, serum electrolytes, RFTs, LFTs, chest radiography (CXR), blood cultures, and sensitivity testing, along with other microbiological investigations as indicated. In addition, 2 mL of serum samples were collected for biomarker estimation of PCT and ProADM at the time of leukemia diagnosis, and subsequently during FN presentation. All patients presenting with FN were monitored for overall clinical outcomes.

Serum PCT levels were measured using the ARCHITECT BRAHMS PCT assay, a chemiluminescent microparticle immunoassay (CMIA) with a quantification range of 0.02 to 100 ng/mL. ProADM levels were estimated using the Human Proadrenomedullin ELISA Kit (MBS3803630; MyBioSource, USA) in the Department of Reproductive Biology.[2] Threshold values of PCT ≥ 0.21 ng/mL and ProADM ≥ 0.18 nmol/L were considered clinically significant in this analysis, as these cutoffs have been previously associated with systemic infections and adverse clinical outcomes in pediatric populations with cancers.[2] Serum samples were also collected from age- and sex-matched healthy children to serve as controls.

Definitions

- Febrile neutropenia (FN)[14]: This was defined as either a single axillary temperature ≥38.5 °C, or ≥38.0 °C on two occasions at least 1 hour apart, in the presence of an absolute neutrophil count (ANC) <500/mm^3.
- Classification of FN: Febrile neutropenia episodes were categorized into three groups based on clinical and microbiological findings:
  - Microbiologically documented infection (MDI): Isolation of a pathogenic microorganism from blood or another normally sterile site.
  - Clinically documented infection (CDI): Presence of a clinically identifiable focus of infection on physical examination, without microbiological confirmation.
  - Unexplained fever (NF): Fever without an identifiable clinical focus or microbiological documentation.
- In cases where both clinical evidence and microbiological confirmation were present, the episode was classified as MDI.

Statistical methods

Dichotomous variables were presented as proportions (%), while continuous variables were expressed as mean ± standard deviation (SD) for normally distributed data and as median with interquartile range (IQR) for non-normally distributed data. The Wilcoxon signed-rank test was employed to compare biomarker levels (PCT and ProADM) between the time of acute leukemia diagnosis and during febrile neutropenia episodes. Associations between categorical variables were assessed using the chi-square or Fisher s exact test. A p-value of < 0.05 was considered statistically significant. All statistical analyses were performed using Stata version 14 (StataCorp, College Station, TX, USA).

Results

At the time of acute leukemia diagnosis, a total of 80 patients were enrolled in the study after excluding 13 patients due to the following reasons: lack of informed consent (n = 2), recent antibiotic use within the preceding 14 days (n =6), and sampling errors (n = 5).

Baseline demographic and clinical characteristics of all included patients at the time of acute leukemia diagnosis (n=80) are summarized in Table I. The median age of the study cohort (n=80) was 5 years (IQR: 3-7 years), with a male predominance. The majority of patients (67.5%) were diagnosed with ALL. The most common presenting symptoms included fever in 70 patients (87.5%), anorexia in 45 (56.3%), bleeding in 22 (27.5%), lethargy in 20 (25%), abdominal pain in 21 (26.3%), and cough in 9 (11.3%).

In our cohort of 80 patients, at the time of acute leukemia diagnosis, the median PCT was 0.19 ng/ml (IQR: 0.07-0.54), and the median ProADM was 0.04 nmol/L (IQR: 0.01-0.07). Serum levels of PCT and ProADM in age- and gender-matched healthy controls (n = 40) were below the targeted cutoff values. Table I summarizes the baseline demographic and clinical characteristics of patients with acute leukemia who developed febrile neutropenia (n = 32). Among the 32 patients who developed FN, the most common presenting symptoms were fever (28; 87.5%), anorexia (14; 43.8%), lethargy (10; 31.3%), and abdominal pain (7; 21.9%). Of these patients, 80% had an identifiable focus of infection, with respiratory involvement being the most common (45%), followed by gastrointestinal (30%) and other sites (25%). Overall, 77% were classified as clinically documented infection (CDI), 3% as microbiologically documented infection (MDI), and 20% as fever of unknown origin (NF). Two patients succumbed to sepsis, and blood culture in one of them yielded Haemophilus influenzae.

Primary outcomes

At the time of leukemia diagnosis (n=32), the median serum PCT level was 0.16 ng/

Table I. Baseline demographics and laboratory characteristics of children with acute leukemia at diagnosis (N=80) and those who subsequently developed febrile neutropenia (N=32).

	All patient with acute leukemia (N=80)	Acute leukemia patients who developed febrile neutropenia (N=32)
Demographics		
Median age (years)	5 (3-7)	4.8 (2-8)
Male : Female ratio	7:1	2.2:1
Median weight (Kg)	15 (12-20)	14 (11-19.8)
Mean height (cm)	108.6 (23)	107.3 (23.3)
BMI (kg/m^2)	14.4 ± 4	13.9 ± 4
Primary diagnosis		
ALL	54 (67.5%)	20 (62.5%)
AML	26 (32.5%)	12 (37.5%)
Baseline laboratory parameters		
Hemoglobin (g/dL)	7.7 ± 2	8 ± 2
TLC (/mm^3)	9,600 (3400-27,300)	8,885 (2180-20,320)
ANC (/mm^3)	750 (283-2,000)	760 (321-1,524)
Platelets (/mm^3)	33,000 (16,000-56,500)	26,000 (15,850-50,000)
Biomarkers at leukemia diagnosis		
Median PCT (ng/ml)	0.19 (0.07-0.54)	0.16 (0.08-0.52)
Median ProADM (nmol/L)	0.04 (0.01-0.07)	0.03 (0.006-0.05)

Continuous variables are presented as mean ± SD or median (Q1-Q3) according to their distribution characteristics and categorical variables are presented as number (percentage).
ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; ANC: Absolute neutrophil count; BMI: Body mass index; IQR: Interquartile range; PCT: Procalcitonin, ProADM: Proadrenomedullin; TLC: Total leukocyte count.

mL (IQR: 0.08 0.52), and the median ProADM level was 0.03 nmol/L (IQR: 0.006 0.05). At the presentation of febrile neutropenia (Day 1) (n=32), the median PCT increased to 0.32 ng/mL (IQR: 0.08 0.50; p=0.03), while the median ProADM rose substantially to 0.41 nmol/L (IQR: 0.20 0.81; p=<0.001) (Table II).

In the subgroup analysis, among patients with ALL, the median PCT level at diagnosis was 0.25 ng/mL (IQR: 0.12 0.65) and remained comparable during the FN episode (Day 1), with a median of 0.26 ng/mL (IQR: 0.07 0.50; p = 0.50). However, the median ProADM level increased significantly from 0.03 nmol/L (IQR: 0 0.05) at diagnosis to 0.42 nmol/L (IQR: 0.24 0.80) during FN presentation (p = 0.001) (Table II).

In patients with AML, the median PCT level increased significantly from 0.07 ng/mL (IQR: 0.09 0.30) at diagnosis to 0.33 ng/mL (IQR: 0.19 2.70) during FN (p < 0.001). Similarly, the median ProADM level rose from 0.02 nmol/L (IQR: 0 0.05) at diagnosis to 0.40 nmol/L (IQR: 0.16 0.83) during FN (p = 0.002) (Table II).

Secondary outcomes

Positive procalcitonin at the time of leukemia diagnosis was significantly associated only with splenomegaly (p=0.010). Age, sex, type of malignancy, hepatomegaly, and ANC were not significantly associated with PCT positivity. Notably, all patients had undetectable ProADM levels at diagnosis; therefore, an analysis of determinants associated with elevated ProADM was not performed. Table III presents the clinical and laboratory factors associated with elevated PCT levels at the time of leukemia diagnosis.

Discussion

This study assessed the utility of two biomarkers PCT and ProADM at the time of acute leukemia diagnosis and compared their levels during episodes of febrile neutropenia in pediatric patients. A statistically significant increase in both PCT and ProADM levels was observed during FN episodes compared with baseline levels at leukemia diagnosis, prior to the initiation of chemotherapy. These findings underscore the potential of PCT and ProADM as biomarkers for infection-related conditions, capable of distinguishing infectious episodes from baseline inflammatory states associated with malignancy. PCT, in particular, has been extensively studied as a marker of systemic bacterial infections and sepsis, with growing evidence supporting its role in antibiotic stewardship by guiding the initiation and discontinuation of antimicrobial therapy.[15,16] Similarly, ProADM has shown promise as a prognostic indicator in infectious

Table II. Comparison of biomarkers at acute leukemia diagnosis and during febrile neutropenia, and subgroup analysis of comparison of biomarkers (n=32).

Laboratory parameters	Biomarkers at diagnosis	Biomarkers at Day 1 of FN presentation	P-value
PCT (ng/mL)	0.16 (0.08-0.52)	0.32 (0.08-0.50)	0.03
ProADM (nmol/L)	0.03 (0.006-0.05)	0.41 (0.2-0.81)	<0.001
Subgroup analysis			
Acute lymphoblastic leukemia (n=20)			
PCT (ng/mL)	0.25 (0.12-0.65)	0.26 (0.07-0.50)	0.5
ProADM (nmol/L)	0.03 (0-0.05)	0.42 (0.24-0.80)	<0.001
Acute myeloid leukemia (n=12)			
PCT (ng/mL)	0.07 (0.09-0.30)	0.33 (0.19-2.7)	0.001
ProADM (nmol/L)	0.02 (0-0.05)	0.40 (0.16-0.83)	0.002

Variables are presented as median (Q1-Q3).
ALL: Acute lymphoblastic leukemia, AML: Acute myeloid leukemia, FN: Febrile neutropenia, IQR: Interquartile range, PCT: Procalcitonin, ProADM: Proadrenomedullin.

Table III. Summarizing the determinants of positive procalcitonin (PCT) at leukemia diagnosis (cutoff ≥ 0.21 ng/mL) (n=32).

Parameters	PCT positive, n (%)	PCT negative, n (%)	P-value
Age			0.16
≤ 5 years	3 (15)	3 (15)	
> 5 years	0	0	
Sex			0.96
Male	9 (41)	9 (41)	
Female	4 (40)	4 (40)	
Type of malignancy			0.16
ALL	10 (50)	10 (50)	
AML	3 (25)	3 (25)	
Presence of fever			0.07
Present	13 (46.4)	13 (46.4)	
Absent	0	0	
Hepatomegaly			0.68
Present	5 (45.6)	5 (45.6)	
Absent	8 (38)	8 (38)	
Splenomegaly			0.010
Present	4 (100)	4 (100)	
Absent	9 (32.1)	9 (32.1)	
ANC			0.19
< 500/mm^3	5 (50)	5 (50)	
≥ 500/mm^3	10 (46)	10 (46)	

ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; ANC: Absolute neutrophil count.

and inflammatory conditions, including sepsis and pneumonia, due to its vasodilatory and immunomodulatory properties.[17,18] Recently, Meena et al.[2] evaluated the diagnostic and prognostic performance of PCT and ProADM in febrile neutropenic children with both hematological malignancies and solid tumors (n=345). Although PCT demonstrated effectiveness in distinguishing MDI, CDI, and NF, and additionally predicted 30-day mortality, highlighting its potential utility in guiding risk stratification and management of FN in the pediatric oncology setting, this study did not provide subgroup-specific biomarker analysis, in contrast to the index study, which reports biomarker findings separately for ALL and AML. Additionally, Meena et al.[2] measured biomarkers at presentation and on days 3 and 7 of FN, whereas the current study assessed biomarkers at baseline (at the time of leukemia diagnosis) and compared them with values obtained during FN episodes (Day 1).

In the subgroup analysis, patients with ALL showed no significant change in serum PCT levels from baseline (at diagnosis) to during FN episodes. This suggests that PCT may reflect underlying inflammation or para-inflammatory processes associated with the leukemic process itself. Previous studies have reported elevated baseline PCT levels in certain malignancies, including hematological cancers, likely due to cytokine-mediated stimulation independent of infection.[10,19] In contrast, ProADM levels in ALL patients increased significantly during FN episodes compared with baseline, reinforcing its role as a more infection-specific biomarker in this subgroup. ProADM is known to be upregulated in response to microbial toxins and

inflammatory stimuli, with well-documented prognostic value in infections and sepsis.[17,18]

Interestingly, in patients with AML, both PCT and ProADM levels rose significantly during FN episodes compared with levels at diagnosis. This suggests that, unlike in ALL, the baseline inflammatory milieu in AML may not elevate PCT to the same extent, making subsequent increases more reflective of infectious processes. These findings may reflect disease-specific differences in immune and cytokine activation patterns between ALL and AML, with implications for interpreting biomarker kinetics during infectious episodes.

At the time of acute leukemia diagnosis, splenomegaly was the only clinical variable significantly associated with elevated serum PCT levels. This association may reflect subclinical inflammation related to leukemic infiltration and immune activation. However, splenomegaly may also represent a confounding factor, as it can result either from infectious processes or direct disease involvement. Additionally, tissue remodelling or necrosis in the spleen may release damage-associated molecular patterns (DAMPs), stimulating cytokine-mediated PCT production even in the absence of overt infection.[20]

PCT and ProADM have been extensively studied as diagnostic biomarkers for infectious diseases. PCT has consistently demonstrated high sensitivity and specificity for identifying bacterial infections, making it a valuable tool in differentiating bacterial from viral etiologies.[21-23] Similarly, ProADM levels have been shown to be significantly higher in patients with localized bacterial infections and bloodstream infections compared with healthy individuals.[24] Its role in reflecting endothelial dysfunction and systemic inflammatory burden enhances its potential as a marker for infection severity and prognosis.

Both PCT and ProADM have been extensively studied as biomarkers for prognosticating sepsis, either individually or in combination, alongside established disease severity scoring systems. PCT reflects systemic bacterial infection and is produced in response to proinflammatory cytokines, particularly interleukin-6 and tumor necrosis factor-alpha. In contrast, ProADM has been linked to endothelial dysfunction and vasodilation, both hallmarks of severe sepsis and septic shock.[17,20]

Patients with cancer, including those with neutropenia, often have elevated baseline inflammatory markers due to malignancy or treatment-related complications. Severely immunocompromised individuals may also exhibit a diminished inflammatory response. These factors can limit the reliability of standard inflammatory biomarkers in this population. Most studies on PCT-guided antibiotic therapy have excluded immunocompromised patients due to safety concerns. Hence, the applicability of PCT and ProADM in cancer patients remains uncertain and requires further evaluation.

Several studies have demonstrated that baseline PCT levels are higher in cancer patients than in healthy individuals.[10,25,26] Among afebrile cancer patients, those with stage IV disease tend to have significantly elevated PCT levels relative to those with early-stage cancer.[10,25] Additionally, in the absence of fever, PCT levels are generally higher in patients with hematologic malignancies than in those with solid tumors.[25] PCT concentrations are elevated in medullary thyroid carcinoma, probably due to ectopic production and release by tumor cells into the bloodstream.[27] Baseline PCT elevations have also been reported in individuals with hepatocellular carcinoma[28], ovarian cancers[29], gastrointestinal neuroendocrine tumors[5,30] and lung cancer.[7,31-33]

Existing studies involving immunocompromised cancer patients are limited and highly heterogeneous in cancer type, comorbidities, and immunosuppression levels. Further research in well-defined, homogeneous populations is needed for clearer insights. PCT and ProADM may serve as valuable, complementary biomarkers for diagnosing sepsis and bacterial infections in

oncology settings. However, it is important to recognize that malignancy itself can contribute to elevated baseline levels of these biomarkers, particularly PCT. In the present study, however, no significant baseline elevation of PCT or ProADM was observed at the time of acute leukemia diagnosis, suggesting minimal non-infectious upregulation in this cohort.

Strengths and limitations

A key strength of this study is its prospective design. It is the first to evaluate and compare biomarker levels (PCT and ProADM) both at the time of acute leukemia diagnosis and during febrile neutropenia episodes. Another notable strength is the recruitment of a homogenous patient cohort, limited to children with acute leukemia, thereby reducing clinical variability and enhancing the internal validity of the findings. However, the study has certain limitations. A major limitation is the absence of biomarker measurements during leukemia remission, which could have provided additional insights by enabling comparisons across disease states diagnosis, remission, and infection. Additionally, the relatively small sample size may limit both the statistical power and the generalizability of the findings, particularly for subgroup analyses. Future studies with larger cohorts and the inclusion of remission-phase sampling are needed to validate and expand upon these findings.

In conclusion, this study underscores the potential of PCT and ProADM as biomarkers to distinguish infectious episodes from baseline inflammatory states in children with acute leukemia. Compared with levels at diagnosis, ProADM was significantly elevated during febrile neutropenia in both ALL and AML. In contrast, PCT showed a significant rise only in the AML subgroup, with no significant elevation observed in ALL. These findings suggest that ProADM may serve as a more consistent and reliable biomarker across leukemia subtypes. Taken together, these results support the integration of biomarker assessment into standard FN evaluation protocols in pediatric oncology. Future studies should aim to validate these findings in larger, multicenter cohorts and assess the clinical utility of these biomarkers in real-time therapeutic algorithms. Research should also focus on dynamic trends of these markers over the course of infection, stratified by leukemia subtype and treatment phase, to refine their diagnostic and prognostic accuracy.

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Ethical approval

The study was approved by the Institute Ethics Committee, All India Institute of Medical Sciences, New Delhi, India (date: 17.12.2019, number: IEC-459/01.09.2017, RP-09/2017, OP-13/06.12.2019, RP-43/2019).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: JPM; data collection: HM, SB, RSPR; analysis and interpretation of results: JPM, HM; draft manuscript preparation: JPM, HM, SB, RSPR, AKG, AH, RS. 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

Bullying victimization in pediatric patients with celiac disease

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ABSTRACT

Background. In this study, we aimed to investigate peer bullying and its psychosocial consequences in children with celiac disease. We examined the relationship between adherence to diet and anxiety and depressive symptoms.

Methods. The sample in this cross-sectional study consisted of 124 pediatric celiac patients on a gluten-free diet for one year or more. One hundred thirty-nine healthy children comparable in age and sex were enrolled as the control group. The Revised Olweus Bully Victim Questionnaire (OBVQ) was used to evaluate the peer victimization. The Revised Child Anxiety and Depression Scale and Strengths and Difficulties Questionnaire were used to assess children's anxiety and depressive symptoms, and emotional and behavioral symptoms, respectively. Hierarchical logistic regression analysis was performed to identify independent predictors of dietary non-adherence.

Results. The proportion of children classified as bullying victims based on the OBVQ was significantly higher in the celiac disease group than in the healthy controls. Children who did not comply with diet therapy experienced significantly higher rates of peer bullying than those who adhered to the diet (p=0.004). However, multivariate analysis indicated that depressive symptoms appeared to account for this relationship - while bullying initially predicted dietary non-adherence (odds ratio [OR]: 3.274, p=0.004), this effect became non-significant when depression was controlled (OR: 2.177, p=0.098), whereas depression remained a significant independent predictor (OR: 1.093, p=0.044). Significant positive correlations were observed between peer bullying and anxiety and depression symptom scores. Peer bullying also exhibited positive correlations with emotional and behavioral symptoms.

Conclusions. The study findings show that children with celiac disease experience higher rates of peer bullying than their healthy peers. More importantly, our results suggest that the association between bullying and dietary adherence may be largely explained by co-occurring depressive symptoms. We therefore recommend that depressive symptom screening and treatment should be integrated into the management of celiac disease in children, particularly for those experiencing peer victimization.

Key words: victim, psychiatric disorders, depressive symptoms, anxiety symptoms, gluten-free diet.

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Celiac disease (CD) is a chronic, gluten induced enteropathy that occurs in genetically susceptible individuals.[1] The prevalence of CD is influenced by genetic and environmental factors, with an estimated occurrence of 0.5-2% in the general population, averaging approximately 1%.[2,3] A gluten-free diet (GFD) is so far the only known treatment.[4] However, children and adolescents may have problems adhering strictly to this. Children with CD are also at a higher risk of psychological problems, including anxiety and depression.[5] These psychological issues can also adversely impact adherence to the GFD.[6]

Bully victimization refers to intentional, repeated aggressive behaviors directed by more powerful peers against individuals with lower social power.[7] Bullying victimization can cause physical and psychological problems in children and can also lead them to engage in more risky behaviors.[8,9] Children with chronic illnesses are more vulnerable to bullying victimization, and the victimization they experience during their school years can have lifelong adverse consequences.[10,11] Critically, for youth with chronic conditions, peer victimization has been associated with worse disease management and reduced adherence to essential treatment regimens.[12] Exposure to bullying victimization among children with CD may impair their adherence to a GFD.

The primary objective of this study was to determine the prevalence of bullying behaviors in children with CD compared with healthy controls. The secondary objectives were i: to investigate whether exposure to peer bullying affects dietary adherence in children with CD, and ii: to explore the psychosocial consequences of being bullied, including emotional and behavioral problems, and anxiety and depressive symptoms.

Materials and Methods

Study design

This study was performed as a cross-sectional analytical investigation with a control group. Children with CD aged 12-18 years participated in the study. Healthy children of similar age and sex distribution comprised the control group. The study protocol was approved by the Antalya Training and Research Hospital Scientific Research Ethics Committee, (Approval Date 09/01/2025, Approval Number 2025-08) prior to commencement. Written and verbal informed consent was obtained from both the participating children and their parents prior to enrollment. The study was conducted in accordance with the Declaration of Helsinki regarding human and animal rights and with local laws and regulations.

Sample size

G Power software version 3.1.9.7 was applied with an alpha of 0.05 (two-sided) and 95% power. The sample size was calculated based on the mean difference between two independent groups (CD and healthy). Means and standard deviation depression values were taken from a previous similar study (CD case 13.9 ± 6.2, healthy control 9.3 ± 4.0).[13] Since we used the Strengths and Difficulties Questionnaire (SDQ)[14], the expected difference between the two groups was 2, and the minimum required sample size was 100 participants in both groups.

Participants

All patients with a confirmed diagnosis of CD based on the guidelines approved by the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)[15], and on a GFD for at least one year and who consented to take part were included in the study. Children were excluded if they had an acute illness at the time of recruitment and in the presence of a developmental disability.

Control Group Selection: Children who were comparable in age and sex, and who were examined at the same hospital's pediatric outpatient clinics due to mild physical symptoms (e.g., common cold and rhinitis) and who had no chronic medical or psychiatric conditions, composed the control group.

Data collection

Sociodemographic data form

This form was designed to collect sociodemographic information about the children and their parents. It included details such as the participants' age and gender, parental education levels, marital status and ages of the parents', and the family's monthly income level. " family's monthly income level was categorized as 'good,' 'average,' or 'poor' based on multiples of the national gross minimum wage (MW): 'poor' (income < 1 MW), 'average' (1–3 MW), and 'good' (> 3 MW).

Anthropometric measurements

Measurements of body weight and height were taken when the children were wearing light clothing and were barefoot. Body mass index (BMI) was calculated using the following formula: weight (kg)/ height^2 (m^2). BMI z-score was calculated according to the standards defined by the World Health Organization.[16]

The Strengths and Difficulties Questionnaire (SDQ)

The SDQ is a behavioral screening questionnaire developed by Goodman et al. in 1997 to assess parents' perceptions of both positive (prosocial) and challenging behaviors in children.[14] It consists of 25 items grouped into five subscales: (i) conduct problems, (ii) hyperactivity/ inattention, (iii) emotional symptoms, (iv) peer relationship problems, and (v) prosocial behavior. Higher scores on the first four subscales indicate behavioral difficulties. The sum of these four subscales yields the "total difficulties score". The prosocial behavior score reflects positive social behaviors and is interpreted separately as a strength, rather than as a problem area. In addition to the subscale scores, we calculated two composite scores as recommended in the SDQ literature: the internalizing problems score (sum of the emotional problems and peer relationship problems subscales) and the externalizing problems score (sum of the conduct problems and hyperactivity-inattention subscales). The Turkish adaptation by Güvenir et al. demonstrated good reliability, with a Cronbach alpha of 0.73.[17]

The Revised Child Anxiety and Depression Scale (RCADS)

Developed in 2010 as a screening tool for anxiety disorders and depression in children and adolescents[18], the RCADS exists in both child and parent report versions. The present study employed the child self-report form. The scale uses a four-point Likert-type scoring system (0=Never, 1=Sometimes, 2=Often, 3=Always) and consists of 47 items. RCADS consists of six subscales: social phobia, panic disorder, major depressive disorder, separation anxiety, generalized anxiety, and obsessive-compulsive disorder. Eight scores can be calculated upon completion of the scale. There are six individual subscale scores, a total anxiety score (sum of five anxiety subscales), and a total internalizing score (combined anxiety and depression). The validity and reliability study for the Turkish version was conducted by Görmez et al., and confirmatory factor analysis confirmed the original six-factor structure. The internal consistency of the Turkish version of the scale is strong/excellent, with a Cronbach alpha score of 0.95. Cronbach alpha values for the subscales range from 0.75 to 0.86.[19] In this study, we employed raw RCADS scores rather than age- and gender-adjusted T-scores to enable straightforward comparisons of mean values between the study groups.

Revised Olweus Bully Victim Questionnaire (OBVQ)

Originally developed by Dan Olweus in 1996[20], the OBVQ is a 39-item instrument that includes a detailed definition of peer bullying. The questionnaire assesses retrospective recall, with items phrased "In the past few months..." to capture recent experiences. The answers to the questions are defined in detail (e.g., "This hasn't happened to me/I haven't bullied others in the past months," "Only once or twice," "2 or 3 times a month," "About once a week," or

"Several times a week"). In order to classify an individual as a bully or victim, these behaviors are expected to occur "2 or 3 times a month or more." Marking any answer above the cut-off point in questions 4-13 of the questionnaire indicates victim status, while meeting the same condition in questions 24-33 indicates bullying. Adolescents who meet the assessment criteria in both the bully and victim sections of the questionnaire are classified as bully/victim. For the primary analyses in this study, OBVQ responses were used to create a dichotomous variable indicating peer victimization status (victim present vs. absent). The original questionnaire was adapted into Turkish by Sipahi et al., with a Cronbach alpha value of 0.81.[21]

Celiac serology

Serum anti-tissue transglutaminase IgA (tTG IgA) levels were measured using standardized ELISA kits (Inova Inc., San Diego, CA, USA) according to the manufacturer's instructions. Briefly, microplates were pre-coated with human tissue transglutaminase antigen. Donor plasma samples were incubated in antigen-coated plates. Unbound antibodies were removed through standardized washing procedures. Next, an enzyme-linked anti-human IgA conjugate was added, chromogenic substrate was added for enzymatic color development, and optical density was measured using an integrated plate reader. tTG IgA levels >20 U/L were considered indicative of non-adherence to GFD in the CD patients and of potential ongoing gluten exposure. For comparative purposes, continuous tTG IgA values are also reported.

Statistical analysis

Statistical evaluations were performed using Statistical Package for the Social Sciences (SPSS) software for Windows version 26.0 (IBM Corp., Armonk, NY, USA). Normality of distribution was evaluated using the Kolmogorov-Smirnov test. In comparisons between the CD and control groups, the independent sample t test was applied for normally distributed data and the Mann-Whitney U test for non-normally distributed data. Categorical data were compared using the chi-square test. Descriptive statistical values including mean and standard deviation were presented for continuous data, and median and interquartile range (IQR) for non-parametric data. In evaluating relationships between the sociodemographic data and scale scores of the celiac and control groups, Pearson's correlation analysis was used for parametric data, and Spearman's correlation analysis for non-parametric data. For correlations involving the dichotomous peer victimization variable, point-biserial correlation coefficients are reported. Logistic regression analysis was conducted to evaluate the factors affecting peer bullying.

In addition, we conducted multivariate logistic regression to identify independent predictors of dietary non-adherence. The analysis followed a hierarchical approach with three sequential models: Model 1 examined the crude effect of peer victimization (present/absent) on dietary adherence; Model 2 adjusted for psychological covariates including depression scores (from RCADS) and emotional problems (from SDQ); Model 3 further controlled for demographic variables (age and gender). This model building strategy allowed us to examine whether the effect of bullying on dietary adherence was attenuated by psychological factors. Model fit for each step of the hierarchical logistic regression was assessed using the -2 log likelihood statistic, model chi-square (χ^2) with degrees of freedom (df) and p-value, Nagelkerke's R^2, and the change in R^2 (ΔR^2) between successive models. The goodness-of-fit for the final model was evaluated using the Hosmer-Lemeshow test, and its overall classification accuracy was reported. The hierarchical (blockwise) entry of variables was based on a conceptual framework regarding their temporal and theoretical relationships. In the first model (Model 1), only peer victimization was entered to examine its unadjusted (crude) association with dietary adherence. In the second model (Model 2), psychological variables (depressive symptoms

and emotional problems) were added. This step tested whether the initial association between bullying and adherence could be explained by these potential psychological consequences of victimization. In the final model (Model 3), demographic variables (age and sex) were included to control for potential confounding and to examine whether the observed relationships were independent of these basic characteristics. Sociodemographic characteristics (age, sex, parental education and income) were also compared between diet-adherent and non-adherent celiac patients using independent samples t-test, Mann-Whitney U test, or chi-square test, as appropriate. A p value of < 0.05 was considered statistically significant.

Results

A total of 290 individuals were assessed for eligibility. Of these, 8 were excluded due to acute disease, 4 had incomplete clinical data, and 15 declined to participate. The remaining 263 children were included in the final analysis, comprising 124 patients with celiac disease and 139 healthy controls. All participants were recruited from the Antalya Education and Research Hospital Pediatric Gastroenterology Department between 01 January and 30 June, 2025.

Sociodemographic characteristics

The participants' baseline characteristics are shown in Table I. The median age of the 263 children in the study was 13.5 years (IQR: 8-17), and 68.4% were girls. There was no significant difference between the two groups in terms of age, gender, education level, maternal age, paternal age, maternal and paternal education levels, or family income status ($p>0.05$).

A comparison of scales between the CD and control groups

Assessment of peer victimization using the OBVQ (Table II), revealed that 25.8% of children with CD met the criteria for victim status, while 1.6% engaged in bullying behavior. In the control group, these rates were 7.9% and 2.9%, respectively. Children with CD experienced bullying significantly more frequently than the healthy controls ($p=0.013$, odds ratio [OR]: 6.78). Table III compares the SDQ and RCADS scores between the CD and control groups. There was no difference between the groups in terms of anxiety and depressive symptom scores. The total difficulties scores in the SDQ were also similar between the groups. However, among the SDQ subscales, emotional problems were significantly higher in the CD patients (3.76±2.74 vs. 3.09±2.71, $p=0.047$).

A comparison of scales according to dietary adherence

When the CD patients were divided into two subgroups based on GFD adherence, non-adherent children experienced significantly higher rates of peer bullying than those who adhered to the diet (41.9% vs 17.3%, respectively; Table II). SDQ subscale analysis revealed that non-adherent children exhibited more severe emotional problems, conduct issues, hyperactivity-inattention difficulties, and peer relationship problems than their diet- adherence counterparts. Notably, children with poor dietary adherence exhibited significantly elevated anxiety and depressive symptom scores on the RCADS compared to the control group. The most pronounced difference emerged in major depressive disorder scores (non-adherent group 10.95±6.53 vs 6.59±5.16, $p<0.001$), highlighting the substantial psychological burden associated with GFD non-adherence (Table IV). In addition, sociodemographic characteristics of diet-adherent and non-adherent patients are presented in Supplementary Table S1. The groups did not differ significantly in terms of patient age, sex, or parental age (all $p>0.05$). However, non-adherent patients had significantly lower levels of maternal and paternal education, lower household income, and were more likely to have parents who were divorced (all $p <0.05$). As expected, non-adherent patients had significantly higher mean

Table I. The participants' sociodemographic characteristics.

	Control group (n=139)	Celiac patients (n=124)	p
Age (yr), mean ± SD	13.38±2.63	12.91±2.63	0.157[a]
Sex, n (%)			0.972[c]
Male	44 (31.7%)	39 (31.5%)	
Female	95 (68.3%)	85 (68.5%)	
BMI z-score, mean ± SD	0.10±0.65	-0.08±0.88	0.053[a]
Maternal age, median (IQR)	41.0 (37.0-45.0)	41.0 (36.25-46.0)	0.529[b]
Paternal age, mean ± SD	46.04±6.04	44.85±6.89	0.148[a]
Maternal education, n (%)			0.220[c]
Illiterate	8 (5.8%)	7 (5.6%)	
Elementary education	55 (39.6%)	51 (41.1%)	
High school	50 (36.0%)	32 (25.8%)	
Higher or beyond	26 (18.6%)	34 (27.4%)	
Paternal education, n (%)			
Illiterate	4 (2.9%)	3 (2.4%)	0.303[c]
Elementary education	53 (38.1%)	45 (36.3%)	
High school	53 (38.1%)	38 (30.6%)	
Higher or beyond	29 (20.9%)	38 (30.6%)	
Marital status, n (%)			
Married	129 (92.8%)	116 (93.5%)	0.812[c]
Divorced	10 (7.2%)	8 (6.5%)	
Household income, n (%)			
Good	32 (23.0%)	30 (24.2%)	0.682[c]
Average	94 (67.6%)	86 (69.4%)	
Poor	13 (9.4%)	8 (6.5%)	
Residential area, n (%)			
Rural	9 (6.5%)	7 (5.6%)	0.803[c]
Urban	130 (93.5%)	117 (94.4%)	

Data are presented as mean ± standard deviation, median (interquartile range), or number (percentage). Superscript letters indicate the statistical test used to obtain the p-value: [a] independent samples t-test; [b] Mann-Whitney U test; [c] chi-square test. All p-values are two-sided.
BMI: body mass index, IQR: interquartile range, SD: standard deviation.

tTG IgA levels compared to adherent patients (100.25 ± 68.10 U/L vs. 8.88 ± 5.90 U/L, p<0.001).

Correlations between scale scores for the CD and control groups

The relationships between peer victimization status (a dichotomous variable: present/absent) and the scale scores were analyzed using point-biserial correlation, with results detailed in Table V. In both groups, significant positive correlations were observed between victimization status and the total RCADS score and its subscales, as well as with all SDQ subscales except prosocial behavior, indicating that bullying exposure was consistently associated with greater emotional and behavioral difficulties.

Multivariate logistic regression analysis for dietary non-adherence

The hierarchical logistic regression analysis revealed significant findings regarding

Table II. Comparison of peer victimization status based on the Revised Olweus Bully Victim Questionnaire between celiac patients and healthy controls, and according to dietary adherence within the celiac group.

OBVQ Status	Control (n=139)	Celiac (n=124)	OR (95% CI)	p
Victim only	11 (7.9%)	32 (25.8%)	6.78 (1.49–30.92)	0.013
Bully only	4 (2.9%)	2 (1.6%)	0.56 (0.13–2.32)	0.889
Bully + Victim	7 (5.0%)	3 (2.4%)	0.51 (0.22–2.20)	0.220
OBVQ Status	Non-adherent (n=43)	Adherent (n=81)	OR (95% CI)	p
Victim only	18 (41.9%)	14 (17.3%)	3.45 (1.49–7.95)	0.004
Bully only	2 (4.7%)	0 (0%)	–	–
Bully + Victim	2 (4.7%)	1 (1.2%)	3.86 (0.34–43.8)	0.253

Note: Data are presented as number (percentage). OR, odds ratio; CI, confidence interval. p-values were calculated using the chi-square test. The reference category for the upper panel is the absence of celiac disease; for the lower panel, it is dietary adherence.
CI: Confidence Interval; OBVQ: Revised Olweus Bully Victim Questionnaire; OR: Odds ratio.

Table III. A comparison of Strengths and Difficulties Questionnaire, and Revised Child Anxiety and Depression Scale between the celiac disease patients and control group.

	Control group (n=139)	Celiac patients (n=124)	Effect Size (d)	p
SDQ				
Emotional problems	3.09±2.71, 2.55 (0.76-5.15)	3.76±2.74, 3.34 (1.52-5.79)	0.24	0.047*
Conduct problems	1.81±1.53, 1.58 (0.65-2.66)	1.76±1.78, 1.38 (0.36-2.81)	0.03	0.801
Hyperactivity-inattention	3.76±2.13, 3.51 (2.05-5.39)	3.77±2.43, 3.62 (2.11-5.28)	0.01	0.969
Peer relationship problems	2.68±1.52, 2.60 (1.47-3.82)	2.69±1.50, 2.66 (1.53-3.75)	0.01	0.937
Pro-social behavior	7.94±1.96, 8.31 (6.64-9.54)	8.10±1.81, 8.43 (7.03-9.54)	0.08	0.481
SDQ Internalizing score	5.77±3.53, 5.00 (3.00-9.00)	6.46±3.63, 6.00 (4.00-9.00)	0.19	0.119
SDQ Externalizing score	5.58±3.25, 5.00 (3.00-8.00)	5.53±3.59, 5.00 (3.00-8.00)	0.01	0.923
Total difficulties score	11.34±5.39, 10.69 (6.65-15.35)	12.01±6.33, 11.61 (7.65-15.62)	0.11	0.382
RCADS				
Separation anxiety disorder	4.58±3.86, 3.58 (1.56-6.32)	4.46±3.90, 3.50 (1.65-6.55)	0.03	0.814
Generalized anxiety disorder	6.50±3.87, 5.96 (3.48-9.31)	6.87±3.80, 6.38 (4.46-9.06)	0.03	0.428
Panic disorder	6.39±5.99, 5.06 (1.48-9.27)	7.29±6.50, 5.62 (1.86-10.75)	0.14	0.289
Social phobia	8.92±6.26, 7.50 (4.11-12.22)	9.55±6.11, 8.66 (5.14-13.13)	0.10	0.414
Obsessive–compulsive disorder	5.44±3.92, 4.65 (2.51-8.20)	5.66±4.04, 5.07 (2.48-7.94)	0.05	0.657
Major depressive disorder	8.10±6.02, 6.88 (3.14-11.87)	8.92±7.29, 7.35 (3.11-13.45)	0.12	0.322
Total anxiety score	34.01±10.13, 31.08 (26.19-39.52)	31.78±10.15, 30.12 (23.76-38.91)	0.22	0.374
Total score	43.01±16.01, 40.89 (34.15-48.47)	39.88±14.90, 37.99 (32.87-45.60)	0.20	0.326

Data are presented as mean ± SD and median (IQR). All comparisons between the celiac disease patients and the control group were performed using the Mann-Whitney U test.
*Statistically significant
IQR: interquartile range; RCADS: Revised Child Anxiety and Depression Scale; SD: standard deviation; SDQ: Strengths and Difficulties Questionnaire.

predictors of dietary non-adherence (Table VI). In the unadjusted Model 1, peer bullying showed a strong and significant association with dietary non-adherence (OR: 3.274, 95% confidence interval [CI]: 1.466–7.309, p=0.004), indicating that bullied children had approximately 3.3 times higher odds of being non-adherent to the GFD compared to non-bullied children. When

Table IV. A comparison of Strengths and Difficulties Questionnaire, and Revised Child Anxiety and Depression Scale, according to dietary adherence in the celiac disease patients.

	Dietary adherence (-), (n=43)	Dietary adherence (+), (n=81)	Effect Size (d)	p
SDQ				
Emotional problems	4.37±1.78, 4.00 (2.18-6.75)	2.41±1.43, 1.69 (0.43-4.22)	1.21	<0.001*[b]
Conduct problems	2.58±1.86, 2.21 (1.19-3.54)	1.40±1.14, 1.30 (0.45-2.21)	0.76	<0.001*[b]
Hyperactivity-inattention	4.90±2.01, 4.86 (3.38-6.41)	3.16±1.95, 2.93 (1.66-4.54)	0.87	<0.001*[b]
Peer relationship problems	3.11±1.31, 3.12 (2.23-3.97)	2.45±1.58, 2.25 (1.20-3.68)	0.45	0.024*[b]
Pro-social behavior	7.95±2.01, 8.28 (6.66-9.55)	7.93±1.94, 8.31 (6.60-9.53)	0.01	0.967[b]
SDQ internalizing score	7.50±3.39, 7.00 (5.00-11.00)	4.87±3.28, 4.00 (2.00-7.00)	0.78	<0.001*[b]
SDQ externalizing score	7.78±3.39, 7.00 (4.00-10.00)	4.56±2.70, 4.00 (2.00-6.00)	1.05	<0.001*[b]
Total difficulties score	15.02±5.72, 15.33 (10.62-19.18)	9.44±4.85, 8.81 (5.15-13.25)	1.05	<0.001*[a]
RCADS				
Separation anxiety disorder	5.37±4.42, 3.77 (2.00-6.80)	4.16±3.49, 3.38 (1.43-6.12)	0.30	0.124[b]
Generalized anxiety disorder	7.58±3.81, 7.33 (4.62-9.81)	5.92±3.81, 5.35 (2.96-8.35)	0.43	0.024*[b]
Panic disorder	8.81±4.61, 7.16 (3.80-12.80)	5.11±3.23, 3.62 (0.94-8.05)	0.92	0.002*[b]
Social phobia	10.79±6.95, 9.00 (5.42-13.83)	7.92±5.65, 6.46 (3.55-11.41)	0.45	0.018*[b]
Obsessive−compulsive disorder	6.65±3.98, 6.30 (3.50-8.90)	4.80±3.75, 3.82 (2.16-7.05)	0.47	0.014*[b]
Major depressive disorder	10.95±6.53, 10.66 (6.20-14.80)	6.59±5.16, 5.56 (2.50-9.70)	0.74	<0.001*[b]
Total anxiety score	39.20±11.52, 38.15 (32.29-45.26)	27.78±10.29, 27.06 (20.10-33.25)	1.04	0.004*[b]
Total score	50.16±16.27, 49.72 (40.32-60.58)	34.36±12.41, 32.47 (25.66-50.59)	1.09	0.001*[b]
tTG IgA level (U/L)	100.25±68.10, 90.00 (47.00-130.00)	8.88±5.90, 8.00 (2.00-12.00)	1.89	<0.001*[b]
BMI z-score	-0.19±0.98, -0.02 [(-0.91)-0.68]	-0.00±0.80, 0.14 [(-0.84)-0.55]	0.21	0.308[a]

Notes: Data are presented as mean ± SD and median (IQR). Superscript letters indicate the statistical test used to obtain the p-value: [a] independent samples t-test; [b] Mann-Whitney U test.
*Statistically significant
BMI, Body mass index; IQR, interquartile range; RCADS, Revised Child Anxiety and Depression Scale; SD, standard deviation; SDQ, Strengths and Difficulties Questionnaire; tTG IgA: anti-tissue transglutaminase immunoglobulin A.

psychological factors (depressive symptoms and emotional problems) were added in Model 2, the magnitude and significance of the association for peer bullying were substantially attenuated (OR: 2.035, 95% CI: 0.827–5.005, p=0.122), while depressive symptoms emerged as a significant predictor (OR: 1.085, 95% CI: 1.000–1.178, p=0.045). In the adjusted Model 3, which also included demographic variables (age and gender), depressive symptoms remained a significant independent predictor of dietary non-adherence (OR: 1.093, 95% CI: 1.002–1.192, p=0.044). In this final model, peer bullying (OR: 2.177, 95% CI: 0.867–5.467, p=0.098), emotional problems, age, and gender were not significantly associated with dietary adherence.

Potential role of anthropometric measures

To address the potential confounding role of growth parameters, we examined the relationship between BMI z-scores and peer victimization. In the entire sample, children who were victims of bullying had significantly lower BMI z-scores compared to non-victims (victims: -0.34 ± 0.96 vs. non-victims: 0.11 ± 0.69; t=3.534, p<0.001). This was consistent with a significant, weak negative correlation between BMI z-score and victimization status (Spearman's rho =

Table V. Point-biserial correlations between OBVQ victimization status (present/absent) and psychological symptom scores (SDQ, RCADS) and BMI z-score in children with celiac disease and healthy controls.

	Control group		Celiac patients	
	r	p	r	p
SDQ				
Emotional problems	0.216	0.011*	0.380	<0.001*
Conduct problems	0.270	0.001*	0.246	0.006*
Hyperactivity- inattention	0.259	0.002*	0.303	0.001*
Peer relationship problems	0.247	0.003*	0.236	0.009*
Pro-social behavior	-0.127	0.138	-0.079	0.384
Total difficulties score	0.318	<0.001*	0.412	<0.001*
RCADS				
Separation anxiety disorder	0.169	0.047*	0.283	0.001*
Generalized anxiety disorder	0.195	0.022*	0.264	0.003*
Panic disorder	0.244	0.004*	0.310	<0.001*
Social phobia	0.174	0.040*	0.214	0.018*
Obsessive–compulsive disorder	0.179	0.035*	0.253	0.005*
Major depressive disorder	0.213	0.012*	0.262	0.003*
Total anxiety score	0.207	0.015*	0.300	0.001*
Total score	0.205	0.016*	0.324	<0.001*
BMI z-score	-0.120	0.160	-0.194	0.036*

This table presents the primary analysis of associations between peer victimization status (a dichotomous variable) and psychological symptom scores. Correlation coefficients (r) for the relationships between peer victimization (a dichotomous variable: present/absent) and continuous scale scores are point-biserial correlations. All p-values are two-sided.
*Statistically significant
BMI, Body mass index; OBVQ, Revised Olweus Bully Victim Questionnaire; RCADS, Revised Child Anxiety and Depression Scale; SDQ, Strengths and Difficulties Questionnaire.

-0.176, p=0.007). Within the celiac disease group, a similar pattern was observed: victims tended to have lower BMI z-scores than non-victims, although this difference was of borderline statistical significance (victims: -0.46 ± 1.14 vs. non-victims: 0.01 ± 0.79; t=2.129, p=0.036). To assess whether growth parameters confounded the main relationship of interest, we examined the association between peer victimization status and BMI z-score (Table V). Furthermore, we incorporated BMI z-score as an additional covariate in Model 3 of our hierarchical regression analysis (Table VI). BMI z-score was not a significant predictor of dietary non-adherence in the final model (OR=1.304, p=0.449), and its inclusion did not alter the fundamental pattern of results.

Discussion

This study represents the first investigation of peer bullying among children with CD. The findings demonstrate that children with the disease experience significantly higher rates of peer victimization compared to their healthy peers. Furthermore, within the CD group, children with poorer adherence to the GFD were more frequently subjected to bullying and exhibited higher levels of anxiety and depressive symptoms.

However, our hierarchical logistic regression analysis revealed a more nuanced relationship: while peer bullying initially showed a strong association with dietary non-adherence, this association was substantially attenuated and

Table VI. Hierarchical logistic regression analysis of factors associated with dietary non-adherence in children with celiac disease.

Model and Fit Indices	Variable	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Model 1	OBVQ victim status (Present vs. Absent)	3.274 (1.466 – 7.309)*	–	–
-2 Log likelihood=151.548				
Nagelkerke R^2=0.092				
Model 2	OBVQ victim status (Present vs. Absent)	–	2.035 (0.827 – 5.005)	–
-2 Log likelihood=138.671	RCADS, Major depressive disorder	–	1.085 (1.000 – 1.178)**	–
Nagelkerke R^2=0.219	SDQ, Emotional problems	–	1.145 (0.953 – 1.376)	–
Model 3	OBVQ victim status (Present vs. Absent)	–	–	2.177 (0.867 – 5.467)
-2 Log likelihood=137.200	RCADS, Major depressive disorder	–	–	1.093 (1.002 – 1.192)**
Nagelkerke R^2 =0.232	SDQ, Emotional problems	–	–	1.141 (0.949 – 1.370)
	Gender (Female vs. Male)	–	–	0.586 (0.240 – 1.430)
	BMI z-score	–	–	1.304 (0.662 – 2.569)
	Age	–	–	1.028 (0.871 – 1.213)

Reference category for the dependent variable: Dietary compliance.
OR > 1 indicates a higher likelihood of dietary non-adherence for the specified category (e.g., presence of peer victimization) compared to the reference category.
Model 1: Crude effect of peer victimization.
Model 2: Adjusted for psychological factors (depressive symptoms and emotional problems).
Model 3: Fully adjusted model (demographic factors).
Model Fit Indices:
Model 1: $\chi^2(1) = 8.52$, $p = 0.004$; Nagelkerke $R^2 = 0.092$; ΔR^2 (from null) = 0.092.
Model 2: $\chi^2(3) = 21.40$, $p < 0.001$; Nagelkerke $R^2 = 0.219$; ΔR^2 (from Model 1) = 0.127.
Model 3: $\chi^2(5) = 22.87$, $p < 0.001$; Nagelkerke $R^2 = 0.232$; ΔR^2 (from Model 2) = 0.013; Hosmer-Lemeshow $\chi^2(8) = 5.14$, $p = 0.742$; Classification Accuracy = 72.6%.
*p < 0.01, **p < 0.05
BMI, Body mass index; CI, Confidence Interval; OBVQ, Revised Olweus Bully Victim Questionnaire; OR, Odds ratio; RCADS, Revised Child Anxiety and Depression Scale; SDQ, Strengths and Difficulties Questionnaire.

lost statistical significance when depressive symptoms were included in the model. This finding suggests that depressive symptoms are a key factor in understanding the link between bullying and dietary non-adherence in this population. The attenuation of the bullying effect when controlling for depressive symptoms is consistent with the possibility that the link between bullying and non-adherence is strongly influenced by, or occurs alongside, depressive symptoms. These results may indicate that peer bullying substantially exacerbates depressive symptoms and adversely affects emotional-behavioral functioning in this population.

Existing research into children with chronic illnesses has consistently demonstrated increased vulnerability to peer bullying compared to healthy peers.[10,11] CD is a chronic condition requiring strict lifelong adherence to GFD as the only known treatment. This study confirms that children with CD experience significantly higher rates of peer bullying than their healthy peers. This finding is of particular

clinical relevance due to the well-documented challenges of maintaining dietary adherence during childhood.[22,23] The high prevalence of peer victimization in this population may further compromise GFD adherence, creating a detrimental cycle. Indeed, the results of this study specifically showed that patients with poorer dietary adherence experienced significantly greater exposure to peer bullying, though our multivariate analyses indicate that this relationship is closely associated with, and may be influenced by, psychological factors, rather than representing a simple direct link. Furthermore, children who were victims of bullying had significantly lower BMI z-scores. This suggests that growth delay or lower body weight—common features in poorly controlled celiac disease—may contribute to the increased vulnerability to peer victimization, potentially by making children appear more physically distinct or vulnerable. However, when the BMI z-score was included as a covariate in our multivariate model predicting dietary non-adherence, it was not a significant independent predictor. This critical finding indicates that while physical factors like lower BMI may be associated with a higher risk of being bullied, they do not directly explain the link between victimization and poor dietary management.

The literature describes various psychiatric disorders associated with CD. While some adult studies report depression as a common comorbidity in such patients[24], others have observed no difference compared to the general population.[25] Although not as widely studied as in adults, a large cohort study demonstrated a 1.4-fold increased risk of psychiatric disorders in pediatric CD patients versus the general population.[26] Similarly, a study evaluating 73 children (42 with CD) reported that psychiatric difficulties were more common in children with CD. However, Esenyel et al.'s smaller study observed no difference in psychiatric symptoms between CD children and controls.[27] Another small-sample study showed no significant difference in depression scores between CD patients and healthy children, though better dietary adherence was correlated with significantly lower depressive symptom scores.[28] The present study determined no differences in anxiety, depressive symptoms, or psychiatric difficulties between the CD patients and controls overall. However, patients with poor dietary adherence exhibited markedly worse psychiatric outcomes than adherent patients. Notably, depressive symptoms emerged as the most consistent predictor of dietary non-adherence in our multivariate models, remaining significant even after controlling for bullying and other psychological factors. Research has suggested that the effects of inflammation and autoimmunity on the gut-brain axis may contribute to anxiety and other psychiatric disorders. Gluten-derived peptides may affect brain function.[29,30] Furthermore, the gut microbiota is known to influence mood and behavior, and changes in the gut microbiota of patients with CD may lead to psychiatric problems such as anxiety and depressive symptoms.[31]

Furthermore, our supplementary analyses revealed that children with dietary non-adherence came from families with significantly lower socioeconomic status, including lower parental education and income, and were more likely to have parents who were divorced. This finding aligns with broader literature on chronic illness management, where socioeconomic disadvantage is a known barrier to treatment adherence.[12] Lower family resources may limit access to gluten-free alternatives, reduce parental capacity to monitor diet, and increase general household stress, all of which could contribute to both non-adherence and vulnerability to psychosocial difficulties such as depressive symptoms. Importantly, in our hierarchical regression models, the association between peer bullying victimization and dietary non-adherence was attenuated when psychological symptoms were controlled for. This suggests that the link between bullying and non-adherence is not merely a reflection of these underlying socioeconomic disparities, but rather operates through the psychological sequelae of victimization.

Our findings have important clinical implications. The observation that the bullying-adherence association was attenuated by depressive symptoms suggests that interventions targeting depressive symptoms may be particularly effective in improving dietary adherence among bullied children with CD. Routine depressive symptom screening should be considered in the follow-up of pediatric celiac patients, especially those reporting peer victimization. While anti-bullying interventions remain important, our results indicate they should be complemented with psychological support addressing the depressive symptoms that are strongly associated with poor dietary adherence.

Another important finding of this study involves the significant mental health impacts of bullying victimization, with bullied students exhibiting markedly higher levels of anxiety and depressive symptoms, stress, behavioral problems, peer relationship difficulties, and overall psychological distress compared to non-victimized peers. These results corroborate previous extensive research documenting strong associations between bullying victimization and mental health problems including depression, anxiety, and general health impairments.[8,9,32] Exposure to bullying may lead to unmanaged stress that triggers depressive symptoms and anger, while longitudinal studies confirm bullied children's heightened long-term vulnerability to anxiety and depressive disorders.[10,11] The particularly high prevalence of peer bullying among patients with CD underscores the critical need for closer mental health monitoring in this population compared to healthy children, along with prioritized anti-bullying interventions to reduce anxiety and depressive symptoms and mitigate stress responses in these patients.

This study has several notable strengths, including the inclusion of a large pediatric CD population across a broad age range and the use of validated instruments to assess peer bullying, anxiety-depressive symptoms, and emotional-behavioral problems. Additionally, the use of hierarchical logistic regression allowed us to examine the complex relationships between bullying, psychological factors, and dietary adherence. However, the limitations of the study can be listed as follows. First, the cross-sectional design may limit our ability to establish direct causal relationships between variables. Specifically, while our findings suggest depressive symptoms are a key factor in the bullying-diet adherence relationship, longitudinal studies are needed to confirm this temporal sequence. Second, the study was conducted at a tertiary referral center specializing in CD, which may have introduced selection bias. Third, peer bullying, anxiety and depressive symptom scores were based on self-reports, potentially introducing bias due to participants' subjective perceptions. In order to partially address this limitation, we supplemented child-reported data with parent-reported assessments using the SDQ to evaluate family attitudes toward children with CD. Fourth, the assessment of psychiatric symptoms relied solely on rating scales (RCADS, SDQ) without confirmation through structured clinical interviews. Therefore, our findings pertain to the level of symptomatology and not to clinically verified diagnoses of depressive or anxiety disorders. Fifth, the RCADS scores are presented as raw scores rather than age- and gender-adjusted T scores. Although this approach is suitable for the group comparisons central to our analysis, it may limit the direct clinical interpretability of individual scores relative to normative data.

Conclusion

This study demonstrates a significant association between CD and peer bullying in childhood. Patients with poor adherence to GFD were more frequently exposed to bullying than their diet-adherent counterparts. More importantly, our multivariate analyses suggest that the impact of bullying on dietary adherence is closely linked to, and may be substantially influenced by, depressive symptoms rather than directly. Furthermore, exposure to bullying had substantial adverse effects on mental health. As the first research to evaluate the relationship

between bullying victimization and CD, the findings of this study underscore the critical need for psychosocial screening and assessment in this population. The results also highlight the need for greater awareness of how peer bullying may impact GFD adherence in children with CD. Based on our findings, we recommend that depressive symptom screening become a routine component of CD management, particularly for children experiencing peer victimization. Further research is now needed to validate these findings and elucidate the underlying social and psychological mechanisms linking CD and bullying experiences.

Supplementary materials

Supplementary materials for this article are available online at https://doi.org/10.24953/turkjpediatr.2026.7149

Ethical approval

The study was approved by Antalya Training and Research Hospital Scientific Research Ethics Committee (Approval Date 09/01/2025, Approval Number 2025-08). Written informed consent was provided by each participant. All study procedures were performed in accordance with the Declaration of Helsinki.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: UEA, KK, KE; data collection: AA, IAI, NS, MS; analysis and interpretation of results: UEA, KK, AA, IAI, NS, MS, AA, CFO, HAI; draft manuscript preparation: UEA, AA, CFO, KK, HAI, KE. 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 impact of intraoperative peritoneal fluid cultures on empirical antibiotic therapy and postoperative complications in pediatric perforated appendicitis

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ABSTRACT

Background. This study retrospectively evaluates the microbiological profile, antibiotic susceptibility patterns, and the effectiveness of empirically initiated antibiotic therapies in children with perforated appendicitis, based on intraoperative peritoneal fluid culture and antibiogram results.

Methods. A total of 154 pediatric patients (97 boys, 57 girls; mean age 9.15 ± 4.08 years) underwent surgery for perforated appendicitis between 2014 and 2020. Before surgery, patients received one of three empirical antibiotic combinations: (1) Ampicillin/sulbactam, metronidazole, and amikacin; (2) ceftriaxone and metronidazole; (3) cefotaxime and metronidazole. Peritoneal fluid samples collected intraoperatively were cultured, and microbial growth and susceptibility profiles were analyzed.

Results. A total of 167 strains were isolated. The most common microorganisms were *Escherichia coli* (79.0%), *Pseudomonas aeruginosa* (13.8%), *Klebsiella pneumoniae* (2.4%), *Enterobacter cloacae* (1.8%), *Enterococcus raffinosus* (2.4%), and *Staphylococcus hominis* (0.6%). Before surgery, Combination 1 was administered to 97 patients (63.0%), Combination 2 to 38 patients (24.7%), and Combination 3 to 19 patients (12.3%). Antibiotic susceptibility of the isolated microorganisms was as follows. *E. coli*: ampicillin/sulbactam 23%, ceftriaxone 60%, cefotaxime 92%, amikacin 99%. *P. aeruginosa*: ampicillin/sulbactam 8%, ceftriaxone 16%, cefotaxime 0%, amikacin 99%. *K. pneumoniae*: ceftriaxone 75%, cefotaxime 75%, amikacin 100%. *E. raffinosus*: ceftriaxone 33%, cefotaxime 100%, amikacin 100%. Postoperative modification of empirical therapy was required in 102 cases (66.2%)

Conclusions. High resistance rates to commonly used empirical antibiotics were observed among isolated microorganisms, highlighting the need for regular revision of empirical treatment protocols and greater reliance on intraoperative culture results in pediatric perforated appendicitis.

Key words: empirical antibiotic therapy, peritoneal fluid microbiology, antibiotic resistance patterns, postoperative infectious complications, antimicrobial stewardship programs.

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Perforated appendicitis is the most common cause of community-acquired intra-abdominal infections in children.[1,2] The optimal management of perforated appendicitis in children remains controversial.[3] Urgent appendectomy has traditionally been considered the standard approach.[4-6] However, emergency surgery may be technically challenging due to an edematous and fragile appendix and the surrounding intestinal loops and tissues. A second reasonable option is initial nonoperative management with broad-spectrum antibiotics to stabilize the patient and avoid a troublesome operation.[7]

Timely initiation of empirical antibiotic therapy is critical, as delays increase the risk of postoperative complications such as intra-abdominal abscesses. Antibiotic selection varies across institutions and surgeons, requiring a balance between antimicrobial resistance, clinical efficacy, and cost.[5,8-12] Although the spectrum of pathogens in perforated appendicitis has remained relatively consistent, susceptibility patterns differ by region and evolve over time, underscoring the importance of local microbiological surveillance.[1,2,11-15]

In our clinic, empirical antibiotic regimens have long been guided by the recommendations of the Surgical Infection Society and the Infectious Diseases Society of America.[3]These guidelines recommend broad-spectrum coverage targeting aerobic and anaerobic Gram-negative organisms, which are the predominant pathogens in perforated appendicitis. Accordingly, our empirical regimens include ampicillin/sulbactam, amikacin, and metronidazole; ceftriaxone and metronidazole; or cefotaxime and metronidazole. The choice among these combinations is influenced by local resistance patterns, surgeon experience, drug availability, and cost considerations.

In clinical practice, the attending pediatric surgeon selects the empirical regimen based on disease severity, hemodynamic status, and perceived risk of resistant organisms. However, an increase in postoperative complications in recent years has led to more frequent culture-guided antibiotic modifications.[8,10,13]

This study retrospectively evaluates intra-abdominal fluid culture and antibiogram results obtained during surgery in children with perforated appendicitis, with the aim of characterizing the microbiological profile, determining antibiotic susceptibility patterns, and assessing their impact on empirical antibiotic therapy. Our central hypothesis is that intraoperative peritoneal fluid cultures improve empirical antibiotic selection by identifying resistance to commonly used agents, thereby reducing postoperative complications.

Materials and Methods

Study design and participants

This retrospective study included 154 pediatric patients who underwent surgery for perforated appendicitis between January 2014 and December 2020 at the Pediatric Surgery Clinic of Adıyaman Training and Research Hospital. Intra-abdominal fluid samples were collected during surgery for microbiological analysis.

Exclusion criteria were the absence of intra-abdominal fluid culture, negative culture results, non-operative management, uncomplicated acute appendicitis, hospitalization within the previous three months, and preoperative antibiotic use.

This study was approved by the Ethics Committee for Non-Invasive Clinical Research at Adıyaman University Faculty of Medicine (decision number 2020/7-20, dated 21.07.2020). Written informed consent was obtained from the parents of all participants.

Diagnostic criteria

The diagnosis of perforated appendicitis was based on clinical history, physical examination, laboratory findings (white blood cell count

[WBC, $\times 10^3/\mu L$] and C-reactive protein [CRP, mg/dL]), imaging studies, and intraoperative confirmation.[2,5] Imaging modalities included ultrasonography (USG) and/or intravenous (IV) contrast-enhanced computed tomography (CT). Imaging findings suggestive of perforation included peri-appendiceal fluid, irregular or disrupted appendix wall, contaminated pericecal appearance, and free intraperitoneal air. Intraoperative confirmation included visualization of a perforated appendix wall, intra-abdominal fecaliths, or abscesses formation.[16]

Data collection

Patients' medical records were retrospectively reviewed using the KarMed Health Information Management System (Version 1.2.48.299). Data included patient age, sex, pre-antibiotic WBC and CRP levels, imaging modality, empirical antibiotic regimen, time from diagnosis to surgery, surgical technique, intra-abdominal fluid culture and antibiogram results, postoperative antibiotic modifications and indications, length of hospital stay, and postoperative complications (intra-abdominal abscess, surgical site infection [SSI]) within 30 days after surgery.

Procedures and antibiotic regimens

All patients received IV fluids and antibiotics after diagnosis. Preoperative antibiotics were administered within 1 hour of diagnosis according to institutional protocol. Empirical antibiotic therapy was selected by the attending pediatric surgeon based on clinical severity, risk of resistant organisms, local susceptibility patterns, drug availability and cost considerations. Broader regimens (Combination 1) were typically preferred for patients with more severe presentations. Empirical antibiotic therapy consisted of one of the following combinations:

Combination 1: Ampicillin/sulbactam (Sulbaksit, Tüm Ekip İlaç, 2002), metronidazole (Metrosel, OSEL İlaç, 2003), and amikacin (Amikaver, OSEL, 1999).

Combination 2: Ceftriaxone (Desefin, Deva Holding A.Ş, 2006) and metronidazole.

Combination 3: Cefotaxime (Eqitax, Tüm Ekip İlaç, 2003) and metronidazole.

Dosages were as follows: ampicillin/sulbactam 150 mg/kg/day in four doses IV, metronidazole 30 mg/kg/day in three doses IV, amikacin 15 mg/kg/day in two doses IV, ceftriaxone 100 mg/kg/day in two doses IV, and cefotaxime 100 mg/kg/day in three doses IV.

To ensure clarity and reproducibility, patients were categorized into three groups based on the empirical antibiotic regimen administered prior to surgery. Group 1 consisted of patients who received Combination 1; Group 2 included those treated with Combination 2; and Group 3 included patients who received Combination 3.

All patients underwent open appendectomy within 8 hours of diagnosis, and no laparoscopic procedures were performed. During surgery, 1-10 mL of peri-appendiceal fluid was aspirated using a sterile syringe. The abdominal cavity was irrigated with warm sterile saline until clear. A soft or Penrose drain was placed in all cases and removed on postoperative days 3–5. Samples drawn into syringes were inoculated into aerobic and anaerobic blood culture media (Pediatric blood culture vials, BD, USA) and transported to the microbiology culture laboratory. Bacterial identification and antibiotic susceptibility testing were performed using an automated system (Phoenix 100, BD, USA). Results, including minimum inhibitory concentration (MIC) values and extended-spectrum beta-lactamase (ESBL) positivity, were reported within 1-5 days.

Post-operative empirical antibiotic therapy was modified based on poor clinical progress, laboratory findings (unresolved WBC and CRP levels), culture and antibiogram results, or complications such as intra-abdominal abscesses and SSIs. Unresolved WBC and CRP levels were defined as: WBC remaining above 12 $\times 10^3/\mu L$ or increasing compared with the previous day, and/or CRP remaining failing to show a downward trend within 48–72 hours postoperatively.

Definitions

Poor clinical progress was defined as persistent fever (>38°C), abdominal pain, vomiting, diarrhea, inability to tolerate oral intake, abdominal distention, rising WBC/CRP levels, pre-operative intra-abdominal abscess, diffuse peritonitis, or severe intestinal adhesions.[3]

Post-operative patients with deteriorating general conditions, fever, abdominal pain, vomiting, diarrhea, or elevated WBC and CRP levels were evaluated for intra-abdominal abscess via USG by a radiologist. Intra-abdominal abscesses were treated with antibiotics, and when necessary, USG-guided percutaneous drainage.

Surgical site infections were defined according to the Centers for Disease Control and Prevention (CDC) criteria, including superficial, deep, or organ/space infections occurring within 30 days postoperatively.[17]

Statistical analysis

Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize demographic characteristics, laboratory values, microbiological findings, and postoperative outcomes. Continuous variables were expressed as mean ± standard deviation (SD) or median (range), depending on distribution. Categorical variables were expressed as frequencies and percentages.

Normality of distribution for continuous variables was assessed using the Shapiro–Wilk test. For comparisons Student's t-test was applied to normally distributed data, while the Mann–Whitney U test was used for non-normally distributed data. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. A p-value of <0.05 was considered statistically significant.

No formal power analysis was performed prior to the study; however, the sample size was considered adequate for descriptive and comparative analyses. Although Groups 2 and 3 had relatively small sample sizes, comparative analyses were performed across the three empirical antibiotic regimens for postoperative outcomes, including intra-abdominal abscess and surgical site infection rates. Antibiotic resistance patterns were evaluated descriptively based on culture results, without formal statistical comparison between empirical treatment groups.

A post-hoc power analysis was performed to evaluate the ability of the study to detect differences in postoperative intra-abdominal abscess and SSI rates among the three empirical antibiotic regimen groups. Given the observed effect sizes and the sample distribution (Group 1: n=97, Group 2: n=38, Group 3: n=19), the statistical power for detecting small-to-moderate differences between groups was limited (<0.60), particularly for Groups 2 and 3 due to their smaller sample sizes. Therefore, non-significant findings in these comparisons should be interpreted with caution.

Results

Between January 2014 and December 2020, 1353 cases of acute appendicitis were treated at Adıyaman Training and Research Hospital. Of these, 181 (13.4%) had perforated appendicitis. Intra-abdominal fluid cultures were obtained in 171 (94.5%) cases, and bacterial growth was detected in 154 (90.1%) cases, all of whom were included in this study (Fig. 1).

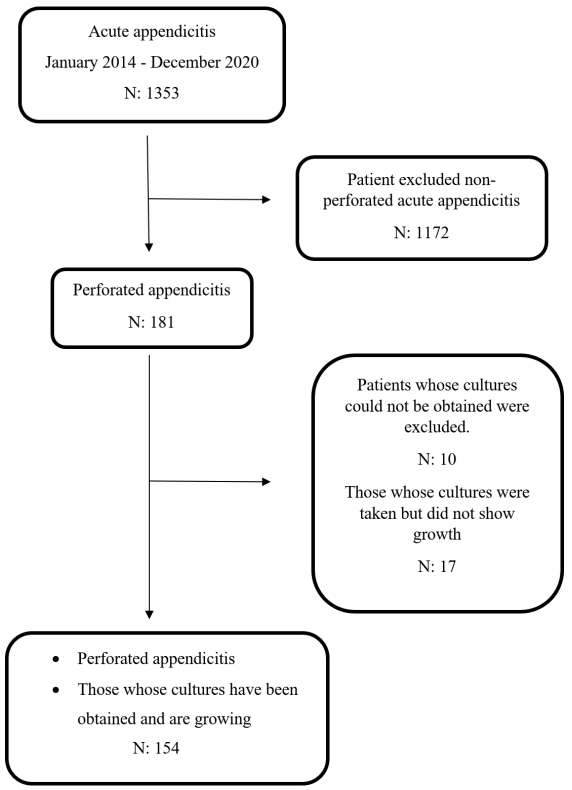

Fig. 1. Scheme of patients' inclusion

Patient characteristics

Among the 154 cases, 97 (63%) were boys and 57 (37%) were girls, with a mean age of 9.15 ± 4.08 years. The mean length of hospital stay was 9.94 ± 3.93 days. Demographic characteristics and preoperative laboratory values are summarized in Table I.

Microbiological findings

A total of 167 bacterial strains were isolated from the intra-abdominal fluid cultures. Polymicrobial growth was observed in 13 patients (8.4%). The most frequently isolated microorganisms were: *Escherichia coli* (132, 79.0%), *Pseudomonas aeruginosa* (23, 13.8%), *Klebsiella pneumoniae* (4, 2.4%), *Enterobacter cloacae* (3, 1.8%), *Enterococcus raffinosus* (4, 2.4%), *Staphylococcus hominis* (1, 0.6%) (Table I.). ESBL production was detected in 12 *E. coli* isolates (9.1%) and 1 *K. pneumoniae* isolate (25%).

Table I. Demographic, and microbiological characteristics of the patients (N=154).

Age (years), mean ± SD	9.15 ± 4.08
Sex (F/M), n (%)	57 (37%) / 97 (63%)
Preoperative WBC count (10^3/μL), mean ± SD	16,890 ± 4,934
Preoperative CRP (mg/dL), median (range)	10.6 (0.0-35.0)
Length of hospital stay (day), mean ± SD	9.94 ± 3.93
İntraabdominal abscess, n (%)	31 (20.1%)
Surgical site infection, n (%)	39(25.3%)
Distribution of microorganisms isolated in peritoneal fluid culture, n (%)	
E. coli	132 (79.0)
P. aeruginosa	23 (13.8)
K. pneumoniae	4 (2.4)
E. raffinosus	4 (2.4)
E. cloacae	3 (1.8)
S. hominis	1 (0.6)

CRP: C-reactive protein, F: female, M: male, SD: standard deviation, WBC: white blood cell.

Antibiotic susceptibility

Three empirical antibiotic combinations were used. 97 patients (63.0%): ampicillin/sulbactam, metronidazole, and amikacin, 38 patients (24.7%): ceftriaxone and metronidazole, 19 patients (12.3%): cefotaxime and metronidazole.

The susceptibility patterns of the most common isolates are shown in Table II. *E. coli* isolates demonstrated low susceptibility to ampicillin/sulbactam (23%) and ceftriaxone (60%) compared to cefotaxime (92%) and amikacin (99%). ($p < 0.001$). *P. aeruginosa* isolates demonstrated low susceptibility to ampicillin/sulbactam (8%), ceftriaxone (16%), and cefotaxime (0%) but high susceptibility to amikacin (99%), meropenem (92%), and piperacillin/tazobactam (73%). ($p < 0.001$). Susceptibility to meropenem was significantly higher than to piperacillin/tazobactam ($p < 0.05$). *K. pneumoniae* isolates demonstrated no susceptibility to ampicillin/sulbactam (0%). moderate susceptibility to ceftriaxone (75%) and cefotaxime (75%), and high susceptibility to amikacin (100%) and meropenem (100%) ($p < 0.001$). Piperacillin/tazobactam showed lower susceptibility (75%) compared to ceftriaxone and cefotaxime.

Post-operative outcomes

Empirical antibiotic therapy was modified in 102 cases (66.2%) due to resistance to at least one antibiotic in the empirical regimen, poor clinical progress, development of intra-abdominal abscesses, or SSIs (Table III).

Intra-abdominal abscess developed post-operatively in 31 cases (20.1%). The median time to abscess formation was 10 days (range 5–18). Twenty patients (64,5%) already had intra-abdominal abscess at the time of surgery. The intra-abdominal fluid cultures results among abscess cases yielded *E. coli* in 24 cases (77.4%), *P. aeruginosa* in 5 cases (16.1%), *K. pneumoniae* in 1 case (3.2%), and *E. cloacae* in 1 case (3.2%).

Table II. Antimicrobial susceptibility rates of microorganisms isolated from peritoneal fluid.

		Antimicrobial susceptibility, N (%)											
	N	**SAM**	**CRO**	**CTX**	**CAZ**	**CXA**	**AMK**	**CN**	**MEM**	**TZP**	**IPM**	**ETP**	**VA**
E. coli	132	30 (23)	79 (60)	121 (92)	90 (68)	59 (45)	130 (99)	121 (92)	129 (98)	114 (86)	130 (99)	121 (92)	-
P. aeruginosa	23	2 (8)	4 (16)	0	20 (85)	6 (25)	23 (99)	21 (91)	21 (92)	17 (73)	21 (90)	5 (20)	-
K. pneumoniae	4	0	3 (75)	3 (75)	4 (100)	2 (67)	4 (100)	3 (75)	4 (100)	3 (75)	4 (100)	4 (100)	-
E. raffinosus	4	0	1 (33)	4 (100)	4 (100)	1 (33)	4 (100)	4 (100)	3 (67)	3 (67)	4 (100)	3 (67)	4 (100)
E. cleocae	3	1 (33)	2 (67)	3 (100)	2 (67)	2 (67)	3 (100)	3 (100)	3 (100)	3 (100)	3 (100)	3 (100)	-
S. hominis	1	1 (100)	-	1 (100)	1 (100)	-	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	-	-

AMK: amikacin; CAZ: ceftazidime; CN: gentamicin; CRO: ceftriaxone; CTX: cefotaxime; CXA: cefuroxime; ETP: ertapenem; IPM: imipenem; MEM: meropenem; SAM: ampicillin-sulbactam; TZP: piperacillin-tazobactam; VA: vancomycin.

Table III. Postoperative modification of empirical antibiotic therapy and reasons for change.

Empirical regimen group	Total patients	Modification required	Resistance	Poor clinical progress	Abscess	SSI
Group 1	97	66 (68.0%)	47 (48.5%)	17 (17.5%)	17 (17.5%)	2 (2.1%)
Group 2	38	23 (60.5%)	16 (42.1%)	6 (15.8%)	6 (15.8%)	1 (2.6%)
Group 3	19	13 (68.4%)	8 (42.1%)	4 (21.0%)	4 (21.0%)	1 (5.2%)
Total	154	102 (66.2%)	71 (46.1%)	27 (17.5%)	27 (17.5%)	4 (2.6%)

Data expressed as number (percentage). SSI: surgical site infection.

Postoperative abscess formation showed no meaningful variation among the empirical antibiotic regimens, occurring in 20/97 (20.6%) of patients in Group 1, 7/38 (18.4%) in Group 2, and 4/19 (21.0%) in Group 3, with no statistically significant differences observed ($p > 0.05$). Among patients with abscesses where *E. coli* was isolated, empirical therapy included ampicillin/sulbactam, amikacin, and metronidazole in 15 cases; ceftriaxone and metronidazole in 5 cases; and cefotaxime and metronidazole in 4 cases. Resistance to empirical therapy was observed as follows: ampicillin/sulbactam (11 strains resistant, 4 susceptible), ceftriaxone (3 strains susceptible, 2 resistant), and cefotaxime (2 strains susceptible, 2 resistant). Among patients with abscesses caused by *P. aeruginosa*, all 5 cases showed resistance to empirical therapy (ampicillin/sulbactam in 3 cases, ceftriaxone in 2 cases). Resistance to ceftriaxone was noted in one case with *K. pneumoniae*. Resistance to cefotaxime was observed in one case with *E. cloacae*. Overall, 22 (71.0%) of the patients with abscesses had isolates resistant to at least one antibiotic in the empirical regimen. The frequency of resistant strains was significantly higher in patients who developed intra-abdominal abscesses ($p < 0.01$).

Antibiotic therapy was changed post-abscess development in 27 cases (87.1%). Changes included meropenem (16 cases), imipenem (3 cases), ceftriaxone (2 cases), piperacillin/tazobactam (2 cases), trimethoprim-sulfamethoxazole (2 cases), cefoperazone/sulbactam (1 case), and vancomycin + meropenem (1 case). Abscess resolution was achieved with antibiotics alone in 30 cases (96.8%), and with percutaneous drainage plus antibiotics in 1 case (3.2%).

Surgical site infections developed in 39 patients (25%). SSI rates did not differ significantly between antibiotic regimen groups ($p > 0.05$). Despite resistance to empirical antibiotic therapy in 31 SSI cases (79.5%), antibiotic modification was required in only 4 cases (10.2%). The most patients improved with daily local wound care and drainage.

Discussion

The Infectious Diseases Society of America's 2024 Clinical Practice Guideline emphasizes the importance of obtaining intra-abdominal cultures to guide antimicrobial therapy for complicated intra-abdominal infections.[18]Consistent with these recommendations, intra-abdominal fluid cultures were obtained in 94.5% of cases in our study, highlighting their routine use in clinical practice. Current guidelines advise avoiding empirical antibiotics with resistance rates exceeding 10%–20%,[3,11,19] underscoring the importance of local susceptibility data in optimizing treatment strategies.

Our study identified *E. coli* as the most frequent isolate (79%), followed by *P. aeruginosa* (13.8%), *K. pneumoniae* (2.4%), and *E. raffinosus* (2.4%), consistent with previous studies from Türkiye and Europe.[1,8,9] In Türkiye, studies from İzmir, Elazığ, Istanbul, and Adıyaman similarly report *E. coli* as the predominant pathogen, with *P. aeruginosa* ranking as the second or the third most common isolate.[8,9,20] Regional variability in ESBL positivity further highlights the need for center-specific microbiological surveillance.

Regarding antibiotic susceptibility, our study found *E. coli* to be highly resistant to ampicillin/sulbactam (23%) and moderately susceptible to ceftriaxone (60%). Antibiotics with over 90% susceptibility included cefotaxime, carbapenems, amikacin, and gentamicin. These results align with national and European data, which similarly report low activity of ampicillin/sulbactam and high effectiveness of carbapenems and aminoglycosides.[1,8,9]

The susceptibility of *P. aeruginosa* to the empirically used antibiotics was below 16%, except for amikacin (99%). Antibiotics with over 90% effectiveness against this agent were carbapenems amikacin, and gentamicin. Similar results were reported by Turel and Tartar, who found no susceptibility to ampicillin/sulbactam and >90% activity for imipenem and amikacin.[8,9] Lob et al. also reported high susceptibility

to imipenem, cefepime, ceftazidime, and amikacin.[1] Notably, piperacillin/tazobactam was less effective in our cohort (<75%) compared to other reports, emphasizing regional differences.[1,8]

K. pneumoniae isolates in our study showed ≤75% susceptibility to most empirically used antibiotics, except for amikacin (100%) and carbapenems (>90%). These results are consistent with previous studies reporting low susceptibility to ceftriaxone and cefotaxime but high susceptibility to carbapenems.[1,8] Notably, piperacillin/tazobactam susceptibility was lower in our study (<80%) compared with >90% in other reports, again emphasizing the need for continuous local surveillance.

Although amikacin showed 98% susceptibility to all isolated microorganisms, its use as monotherapy is limited by the polymicrobial nature of perforated appendicitis and resistance to companion agents such as ampicillin/sulbactam.[1] The guidelines by the Surgical Infection Society and the Infectious Diseases Society of America recommend gentamicin and tobramycin as part of combination therapy.[3]

Based on these findings, our center has initiated a review of empirical antibiotic protocols, with consideration of replacing ampicillin/sulbactam, metronidazole, amikacin, and ceftriaxone, metronidazole combinations with cefotaxime, metronidazole combination

Postoperative intra-abdominal abscesses occurred in 20.1% of cases, consistent with studies previously reported rates of 14%–20%.[14,21,22] Importantly, 71.0% of abscess cases involved pathogens resistant to at least one antibiotic in the empirical regimen, highlighting the clinical relevance of culture-guided therapy. Abscess rates did not differ significantly between the three empirical antibiotic groups, suggesting that resistance patterns rather than the specific empirical regimen may play a more decisive role in abscess formation.

Surgical site infections developed in 25.3% of patients, predominantly caused by *E. coli* (79.5%). Most cases were successfully managed with local wound care, and only a minority required antibiotic modification, consistent with previous studies.[8]

This retrospective single-center study has several limitations. The relatively small sample size in Groups 2 and 3 limited the statistical power of between-group comparisons. Additionally, patients with more severe clinical presentations were more likely to receive broader empirical regimens (e.g., Combination 1). This may have introduced confounding by indication. As a result, treatment failures associated with certain regimens may be overestimated. Other limitations include the absence of multivariate analysis to adjust for confounders, the lack of a matched control group (e.g., non-perforated appendicitis), and the potential influence of clinical variables such as symptom duration, timing of admission, comorbidities, drain use, and operative technique. Future multicenter prospective studies are needed to validate these findings and refine empirical antibiotic strategies.

Conclusions

The microorganisms isolated from intra-abdominal cultures in pediatric perforated appendicitis demonstrated high resistance to commonly recommended empirical agents such as ampicillin/sulbactam, ceftriaxone, and piperacillin/tazobactam. These findings underscore the necessity of regularly updating empirical antibiotic protocols based on intraoperative culture results and local resistance patterns. Tailoring postoperative antibiotic modifications according to both clinical response and antibiogram results may improve treatment effectiveness and reduce postoperative complications.

Ethical approval

The study was approved by the Ethics Committee for Non-Invasive Clinical Research at Adıyaman University Faculty of Medicine (dated 21.07.2020, decision number 2020/7-20).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: MGÖ, MA; data collection, analysis and interpretation: MGÖ, MA, MS, MSA, HÖA, MG, MİY, SA; draft manuscript preperation: MGÖ, MA. 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

Rippling muscle disease due to a *CAV3* mutation with myocarditis-like presentation in an adolescent

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ABSTRACT

Background. This case report describes a rare presentation of rippling muscle disease (RMD) due to a pathogenic *CAV3* variant, manifesting with myocarditis-like cardiac involvement in an adolescent patient. To the best of our knowledge, this represents an exceedingly rare pediatric case of RMD associated with clinically significant cardiac findings.

Case Presentation. A previously healthy 15-year-old male adolescent presented with vomiting and markedly elevated creatine kinase and troponin levels, raising suspicion of acute myocarditis. Cardiac magnetic resonance imaging (MRI) demonstrated non-ischemic myocardial fibrosis, and genetic testing identified a pathogenic de novo variant in the *CAV3* gene consistent with rippling muscle disease.

Conclusions. This case highlights the potential for myocarditis-like cardiac involvement in caveolin-3–related rippling muscle disease and underscores the importance of considering underlying genetic myopathies in adolescents presenting with unexplained elevations of serum creatine kinase (hyperCKemia) and cardiac biomarkers.

Key words: Rippling muscle disease, pediatric cardiomyopathy, caveolin-3 (*CAV3*) mutation, non-ischemic myocardial fibrosis.

Rippling muscle disease (RMD) is a myopathy caused by pathogenic variants in the *CAV3* gene encoding caveolin-3, typically inherited in an autosomal dominant manner, although rare autosomal recessive cases have also been reported.[1] The clinical spectrum ranges from asymptomatic elevation of serum creatine kinase (hyperCKemia) to muscle stiffness, mechanically induced muscle rippling, exercise intolerance, and limb-girdle muscular dystrophy phenotypes.[1] Although cardiac involvement has been described in caveolinopathies[2-4], pediatric cases remain limited.[2]

In the acute setting, adolescents presenting with chest pain or elevated troponin levels are frequently evaluated for myocarditis. However, when CK elevation is disproportionately high or persists despite supportive treatment, alternative diagnoses such as genetic myopathies must be considered.

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Here, we report a previously healthy adolescent with suspected myocarditis and persistent hyperCKemia who was ultimately diagnosed with rippling muscle disease due to a pathogenic *CAV3* variant, with cardiac magnetic resonance imaging revealing non-ischemic myocardial fibrosis.

Case Presentation

A previously healthy 15-year-old male adolescent presented to the emergency department with vomiting. He denied fever, myalgia, recent upper respiratory symptoms, exercise intolerance, or supplement use. Physical examination revealed full muscle strength (5/5) in all extremities, with mild hypertrophy of the lower-limb muscles, particularly in the calf region. The patient's weight was 105 kg (>97th percentile) and height was 165 cm (approximately 10th–25th percentile), with a body mass index of 38.6 kg/m² (>97th percentile for age and sex), consistent with severe obesity. Mild calf hypertrophy was evident on both anterior and lateral views (Fig. 1 and Fig. 2). The remainder of the systemic examination was unremarkable. Initial laboratory investigations demonstrated markedly elevated creatine kinase (CK, 8,612 U/L; reference range: <270 U/L) and troponin T (65 ng/L; reference range: 0–14 ng/L). His past medical history was unremarkable. There was no parental consanguinity and no family history of neuromuscular or cardiac disease. The electrocardiogram (ECG) demonstrated normal sinus rhythm with sinus arrhythmia, without conduction abnormalities or ectopy (Fig. 3). Transthoracic echocardiography showed prominent left ventricular trabeculations, raising suspicion for left ventricular noncompaction cardiomyopathy. The patient was admitted with a provisional diagnosis of acute myocarditis and was started on intravenous hydration and supportive management. Twenty-four-hour Holter monitoring revealed no arrhythmias.

During hospitalization, CK levels continued to rise, peaking at 32,448 U/L. By day 10 of treatment, CK decreased to 3,642 U/L and troponin T to 40 ng/L, and the patient was subsequently discharged.

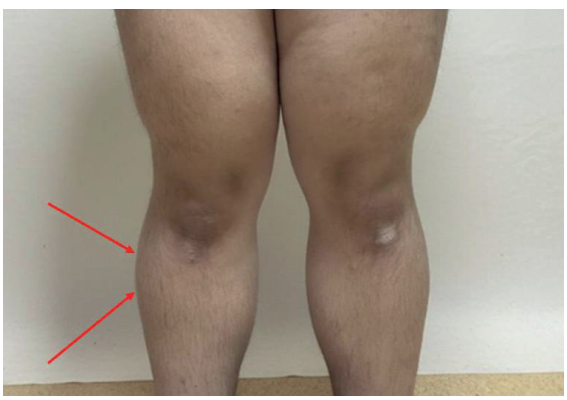

Fig. 1. Anterior view of the lower extremities in a patient with rippling muscle disease, demonstrating prominent calf musculature consistent with calf hypertrophy (arrows indicate calf muscle hypertrophy).

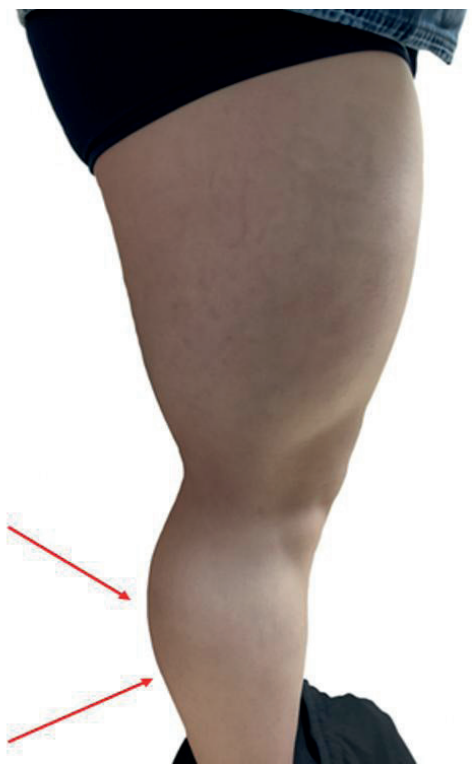

Fig. 2. Lateral view of the lower extremity in a patient with rippling muscle disease, demonstrating calf hypertrophy and increased prominence of the gastrocnemius muscle (arrows indicate calf muscle hypertrophy).

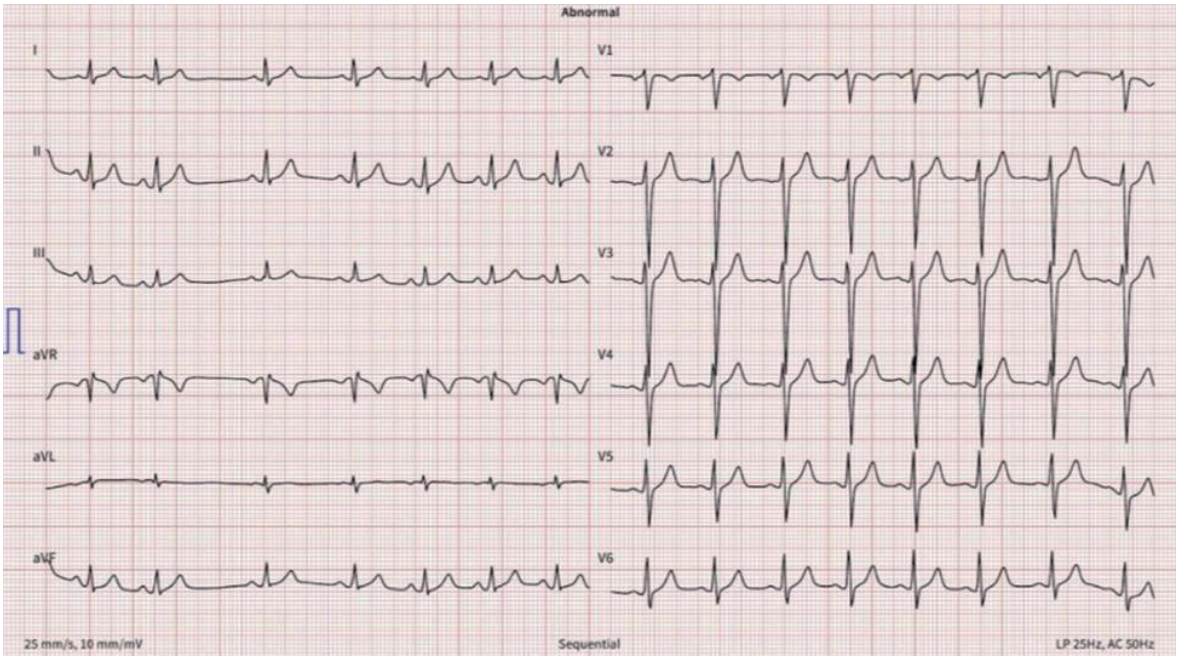

Fig. 3. Twelve-lead electrocardiogram demonstrating sinus rhythm with sinus arrhythmia, without significant conduction abnormalities.

Metabolic evaluation, including tandem mass spectrometry, plasma amino acid analysis, urine organic acid analysis, serum lactate, and ammonia levels, yielded normal results, thereby excluding relatively more common inborn errors of metabolism, including fatty acid oxidation defects, mitochondrial disorders, and organic acidemias. Targeted genetic testing panels for Duchenne muscular dystrophy and glycogen storage diseases were negative. Whole exome sequencing revealed a heterozygous variant c.80G>A, p.(Arg27Gln) in the *CAV3* (NM_033337.3) gene. This variant has been previously reported and characterized as pathogenic in the literature.[5] The variant was confirmed by Sanger sequencing. Sanger sequencing also showed that this change was not present in the parents, thus confirming a de novo occurrence in this case.

The NC/C ratio was defined as the ratio of the thickness of the noncompacted myocardial layer to the compacted myocardial layer, measured at end-diastole. An NC/C ratio >2.3 was considered diagnostic for left ventricular noncompaction. Cardiac magnetic resonance imaging demonstrated increased left ventricular trabeculation with an NC/C ratio of 11.6/2.6 = 4.46, indicating prominent trabeculation. No myocardial edema was identified on T2-weighted or T2-mapping sequences. Late gadolinium enhancement revealed subepicardial to mid-myocardial non-ischemic fibrosis involving the basal inferolateral and inferoseptal walls, as well as the mid-inferior and mid-inferoseptal segments (Fig. 4). Electromyography performed using a myasthenia protocol was unremarkable.

Based on the integration of clinical, biochemical, genetic, and imaging findings, the patient was diagnosed with caveolin-3–related rippling muscle disease with subclinical cardiac involvement. During an 18-month follow-up period, our patient remained clinically stable, with no evidence of arrhythmias or deterioration in cardiac function. Written informed consent was obtained from the patient's parents for publication of this case report and accompanying images.

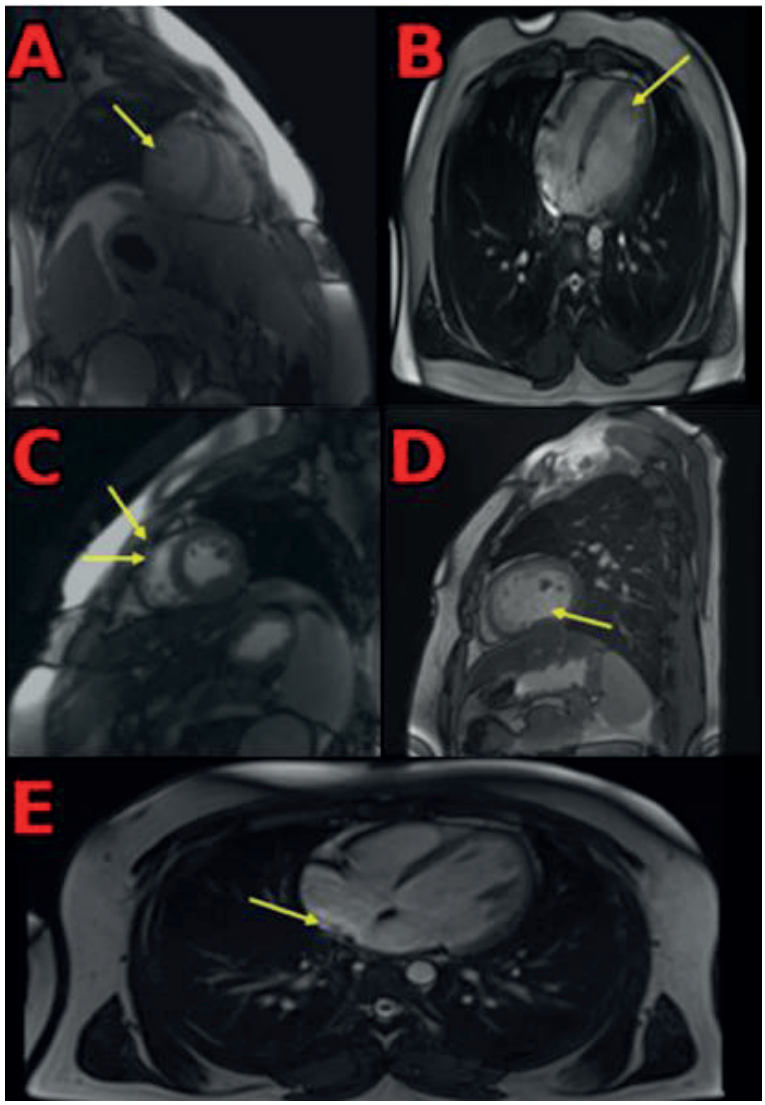

Fig. 4. Cardiac magnetic resonance imaging findings.

(A–B) Long-axis and short-axis cine images showing increased left ventricular trabeculations (arrows indicate left ventricular trabeculations). (C–D) Late gadolinium enhancement images demonstrating subepicardial to mid-myocardial non-ischemic fibrosis in the inferolateral and inferoseptal segments (arrows indicate areas of non-ischemic myocardial fibrosis). (E) Short-axis late gadolinium enhancement view highlighting myocardial fibrosis (arrow indicates focal fibrosis in the lateral wall).

Discussion

Rippling muscle disease (RMD) is a rare caveolinopathy caused by pathogenic variants in *CAV3*, which encodes the muscle-specific scaffolding protein caveolin-3. Although classically considered a skeletal-muscle disorder, caveolin-3 is also expressed in cardiomyocytes; consequently, cardiac involvement—including cardiomyopathy and arrhythmias—has been described across the caveolinopathy spectrum, with *CAV3* mutations also reported in patients with long QT syndrome, sudden infant death syndrome, and hypertrophic cardiomyopathy.[2-4] Our adolescent patient had the pathogenic c.80G>A, p.(Arg27Gln) variant and presented with marked hyperCKemia and myocarditis-like biomarker elevation. Despite a normal EMG, which has been repeatedly reported in *CAV3*-related disorders and can delay diagnosis,

cardiac MRI (CMR) demonstrated non-ischemic late gadolinium enhancement (LGE) consistent with myocardial fibrosis. These findings expand the pediatric phenotypic spectrum of caveolin-3–related disease, in which skeletal and cardiac phenotypes may occur together or separately, and the same mutation may produce variable expressivity.[6]

Mechanistically, caveolin-3 organizes caveolae and key signaling microdomains in the sarcolemma. Experimental work indicates that perturbations in caveolin-3 levels alter cardioprotective signaling and can facilitate ventricular dysfunction and arrhythmogenesis, providing a plausible substrate for the fibrosis observed on CMR.[7] Clinically, non-ischemic LGE in pediatric myopathies is increasingly recognized as a marker of early myocardial disease and adverse remodeling; while most data derive from Duchenne dystrophy cohorts, the principle that LGE heralds cardiomyopathy progression is likely generalizable to caveolinopathies and supports longitudinal surveillance.[8]

An important differential in our case is prior myocarditis, given the elevated troponin and the subepicardial/mid-myocardial LGE pattern—features that can follow viral myocarditis. However, the coexistence of a pathogenic *CAV3* variant and skeletal-muscle phenotype argues for overlapping etiologies: (i) *CAV3*-related myocardial vulnerability with early fibrosis, and/or (ii) a myocarditis episode unmasking an underlying caveolinopathy. Similar coexistence and phenotype variability have been emphasized previously, with calls for systematic cardiac screening in patients with *CAV3* variants.[8]

The trabeculation increase (NC/C 4.46) observed in this patient raises the question of left ventricular noncompaction (LVNC). While LVNC can occur in childhood and often has a genetic basis, its relationship to caveolinopathies is not fully defined and requires cautious interpretation alongside clinical context and family studies.[9] Regardless of taxonomy, our findings justify structured pediatric cardiac follow-up in *CAV3*-positive patients, including periodic ECG/Holter monitoring and interval CMR when feasible, given potential risks of conduction disease, ventricular arrhythmias, and progressive cardiomyopathy.[10]

Pathogenic variants in *CAVIN1* cause Congenital Generalized Lipodystrophy type 4, characterized by muscle rippling, elevated creatine kinase levels, arrhythmias, prominent endocrinological abnormalities (e.g., insulin resistance, hyperinsulinism, acanthosis nigricans), and gastrointestinal involvement, reflecting a multisystem disorder unlike *CAV3*-related Rippling Muscle Disease 2.

Monoallelic variants in *CAV3* are associated with a broad phenotypic spectrum beyond Rippling Muscle Disease 2, including Familial Hypertrophic Cardiomyopathy 1, isolated hyperCKemia, Long QT Syndrome 9, and Tateyama-type distal myopathy. The variant identified in our patient has previously been reported in cases with neurological involvement, particularly distal myopathy.[11,12] Additionally, *CAV3* variants have been linked to cardiovascular disorders such as long QT syndrome, atrial standstill, sudden infant death, and cardiomyopathy.[10] Given the role of caveolin-3 in cardioprotective signaling, comprehensive cardiac evaluation and neurological follow-up are recommended.

This case highlights the importance of considering caveolinopathies in pediatric patients presenting with unexplained hyperCKemia and myocardial injury markers, even when myocarditis is initially suspected and neuromuscular symptoms are absent. Clinicians should be aware that CK levels should be evaluated in patients presenting with elevated troponin levels and suspected myocarditis, as disproportionately high CK values may indicate an underlying genetic myopathy. The coexistence of a pathogenic *CAV3* mutation and non-ischemic myocardial fibrosis on CMR expands the phenotypic spectrum of caveolin-3–related myopathies

and underscores the need for early recognition, genetic counseling, and cardiac surveillance. To our knowledge, this represents one of the first reported pediatric cases from Türkiye, further expanding the limited literature on cardiac involvement in CAV3-related disease.

Ethical approval

Not applicable. Written informed consent was obtained from the patient's parents for publication of this case report and accompanying images.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: DGA, HB; data collection: DGA, HB, HD; analysis and interpretation of results: DGA, GEG, SA, MD; draft manuscript preparation: DGA, SA. All authors reviewed the results and approved the final version of the manuscript.

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Case Report

Pediatric recurrent intracranial hypertension secondary to All-Trans Retinoic Acid treatment in a patient with acute promyelocytic leukemia: value of retinal nerve fiber layer thickness in management

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ABSTRACT

Background. All-trans retinoic acid (ATRA) is an essential agent in the treatment of acute promyelocytic leukemia (APL). However, careful monitoring is required due to its potential side effects, particularly intracranial hypertension (IH).

Case Presentation. Here, we report a 15-year-old girl who presented with headache, blurred vision, vomiting, and was found to have left homonymous hemianopsia and an acute cerebral infarct. Etiological investigations revealed acute promyelocytic leukemia and treatment with ATRA was initiated. However, this treatment was complicated by repetitive episodes of IH, which improved with discontinuation of ATRA but recurred whenever reinitiation was attempted. Despite this side effect, the patient was able to complete the planned ATRA course under medical treatment of IH, guided by retinal nerve fiber layer (RNFL) thickness measured using optical coherence tomography (OCT).

Conclusions. Changes in papilledema were detected on OCT earlier than on clinical examination. This case illustrates the reversibility of IH secondary to ATRA therapy, the feasibility of completing ATRA treatment despite the side effect of IH, the importance of medical treatment for IH in combination with appropriate dose adjustments, and the accuracy and convenience of RNFL thickness as a biomarker for treatment efficiency. Managing IH in the context of a chronic systemic disorder requires a collaborative approach, close follow-up, and individualized management.

Key words: acute promyelocytic leukemia, ATRA, intracranial hypertension, papilledema, retinal nerve fiber layer thickness.

All-trans retinoic acid (ATRA), a metabolite of vitamin A, has been shown to significantly improve outcomes for patients with acute promyelocytic leukemia (APL), in which the prognosis was poor before the introduction of this agent.[1] APL's response rate to ATRA is high, but of limited duration; its combination with arsenic trioxide (ATO) and chemotherapy

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prolongs remission and results in a 10-year overall survival rate of over 85%.[1] ATRA's potential side effects include intracranial hypertension (IH), and pseudotumor cerebri syndrome, occurring in up to 13% of pediatric and 2-7% of adult patients.[2] This can lead to interruption of treatment. Studies have reported that treatment can be carried out by discontinuing ATRA and restarting it at lower doses.[3]

Early diagnosis and appropriate management of IH secondary to ATRA are critical for the success of treatment in APL. IH can present with headache, visual field defects, and cranial nerve palsies. A definitive diagnosis is made by measuring intracranial pressure via lumbar puncture (LP).[4] The IH diagnostic criteria, which provide a standardized framework for diagnosis, are provided in Supplementary Table I.[4] However, LP carries a certain risk in APL patients due to their tendency for bleeding; therefore, clinical follow-up of symptoms and opthalmological examination findings are important in practice, although the assessment of the fundus can be challenging in young children. Noninvasive imaging methods such as ocular ultrasound, fundus autofluorescence, and optical coherence tomography (OCT) are increasingly being used as complementary tools.[5]

Only a few reports have been published on the management of recurrent IH in pediatric patients under ATRA treatment. We describe the treatment details of a case with APL and recurrent IH and underline the use of retinal nerve fiber layer (RNFL) thickness as a biomarker.

Case Presentation

A 15-year-old girl presented with a one-month history of left frontal headache associated with blurred vision and relieved by vomiting. Her vision returned to baseline once the pain subsided. She reported recurrent herpes labialis infections for the previous three months, as well as loss of appetite, malaise, and a 7 kg weight loss in the month prior to presentation. The family history was positive for migraine in her aunt and grandmother. Physical and ophthalmological examination findings were unremarkable except for left homonymous hemianopsia. The patient's body mass index (BMI) was 25 kg/m^2 at the 73rd percentile. The complete blood count revealed pancytopenia (white blood cell: 1.2×10^3/μL, neutrophil count: 0.2 ×10^3/μL, hemoglobin: 8.8 g/dl, platelet count: 74 ×10^3/μL). Two atypical cells were detected on the peripheral blood smear. Brain magnetic resonance imaging (MRI) revealed an acute infarction in the territory of the right posterior cerebral artery (PCA) (Supplementary Fig. 1). MR angiography demonstrated that the right distal PCA (P2 segment) was significantly thinner and showed poorer branching compared with the left. Further laboratory investigations for autoimmune and infectious etiologies, including viral serology (herpes simplex virus, varicella zoster virus, human immunodeficiency virus, Epstein-Barr virus, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), antinuclear antibodies (ANA), anti-double-stranded DNA (anti-dsDNA), antiphospholipid antibodies, and antineutrophil cytoplasmic antibodies (ANCA), were negative. Bone marrow aspiration revealed a 95% predominance of blast cells and flow cytometric analysis was compatible with APL-M3, confirmed by cytogenetic analysis showing t(15;17). Cerebrospinal fluid (CSF) protein (23 mg/dL), glucose (86 mg/dL), and opening pressure (23 cm H_2O) were within normal ranges. CSF cytology revealed no atypical cells. Treatment with ATRA (25 mg/m^2/day) and ATO (0.15 mg/kg/day) was started. The course of the treatment and clinical parameters of the patient's follow-up are shown in Fig. 1.

On day 2 of the second course of ATRA, the patient complained of an itchy, raised maculopapular eruption on the upper limbs that quickly spread to the trunk and lower limbs, and persisted despite the administration of antihistamines and systemic steroids. Skin

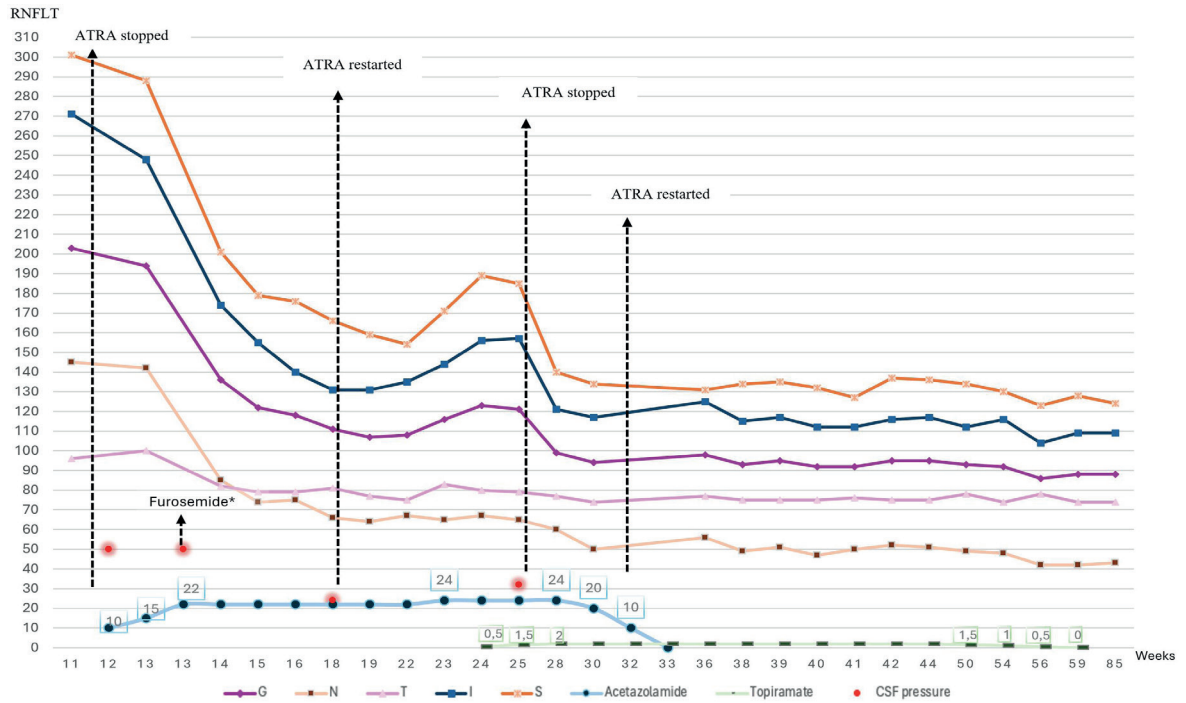

Fig. 1. Changes in average retinal nerve fiber layer thickness over time weeks and treatment.

ATRA, All-trans retinoic acid; CSF, cerebrospinal fluid; RNFLT, retinal nerve fiber layer thickness. Retinal regions for RNFLT G, Global; N, Nasal; T, Temporal; I, Inferior; S, Superior. Furosemide*: 1 mg/kg single dose. Acetazolamide and topiramate dosage units: mg/kg/day. CSF pressure unit: cmH_2O.

biopsy was compatible with drug eruption. ATRA and ATO were discontinued. The rash disappeared within 4-5 days. Desensitization was performed prior to restarting the two drugs, and treatment was restarted after 2 weeks.

At the end of the third course of ATRA treatment, she presented with headache, vomiting, a new-onset visual field defect in the right eye, and expansion of the previous visual field defect on the left side. Bone marrow aspiration was normal. Ophthalmic examination revealed grade 3 papilledema (Fig. 2) and OCT confirmed thickening of the RNFL (Fig. 3). Brain MRI and MR venography showed no significant findings except for chronic infarction. On LP, the opening pressure was too high to measure, and the closing pressure was 30 cm H_2O. CSF protein (23.7 mg/dL) and glucose (65 mg/dL) levels were normal; no atypical cells were observed on cytology. The cumulative ATRA dose was determined as 3,360 mg, based on a daily dose of 25 mg/m² for a body surface area of 1.6 m². The patient developed symptoms of intracranial hypertension at the end of the third course of ATRA intake, which may suggest the impact of cumulative toxicity of the drug on the clinical picture. Acetazolamide (10 mg/kg/day) was started, and ATRA was stopped. The headache regressed in 2 days, while metabolic acidosis that developed on day 6 was treated with oral sodium bicarbonate. Because the right-sided visual field defect did not regress and fundus findings did not improve, a therapeutic LP was performed on the 7th day of treatment, where the CSF opening pressure was again not measurable and the closing pressure was 18 cm H_2O. The dose of acetazolamide was increased to 22 mg/kg/day, and a single dose of furosemide (1 mg/kg) was given. The right sided visual field defect regressed after one week. The papilledema regressed to grade 2, and the thickness of the RNFL decreased within one week. The dose of sodium bicarbonate was increased according to the metabolic acidosis (serum HCO_3^- values). After two weeks, the

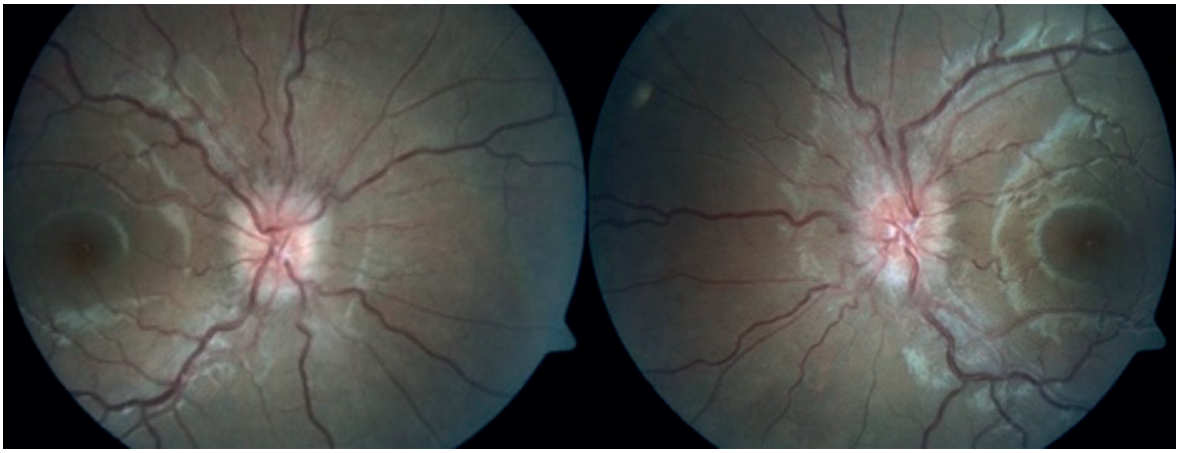

Fig. 2. Grade 3 bilateral papilledema. The optic disc margins are elevated in all quadrants. Circumferential halo is seen, some of the vessels are obscured while leaving the optic disc.

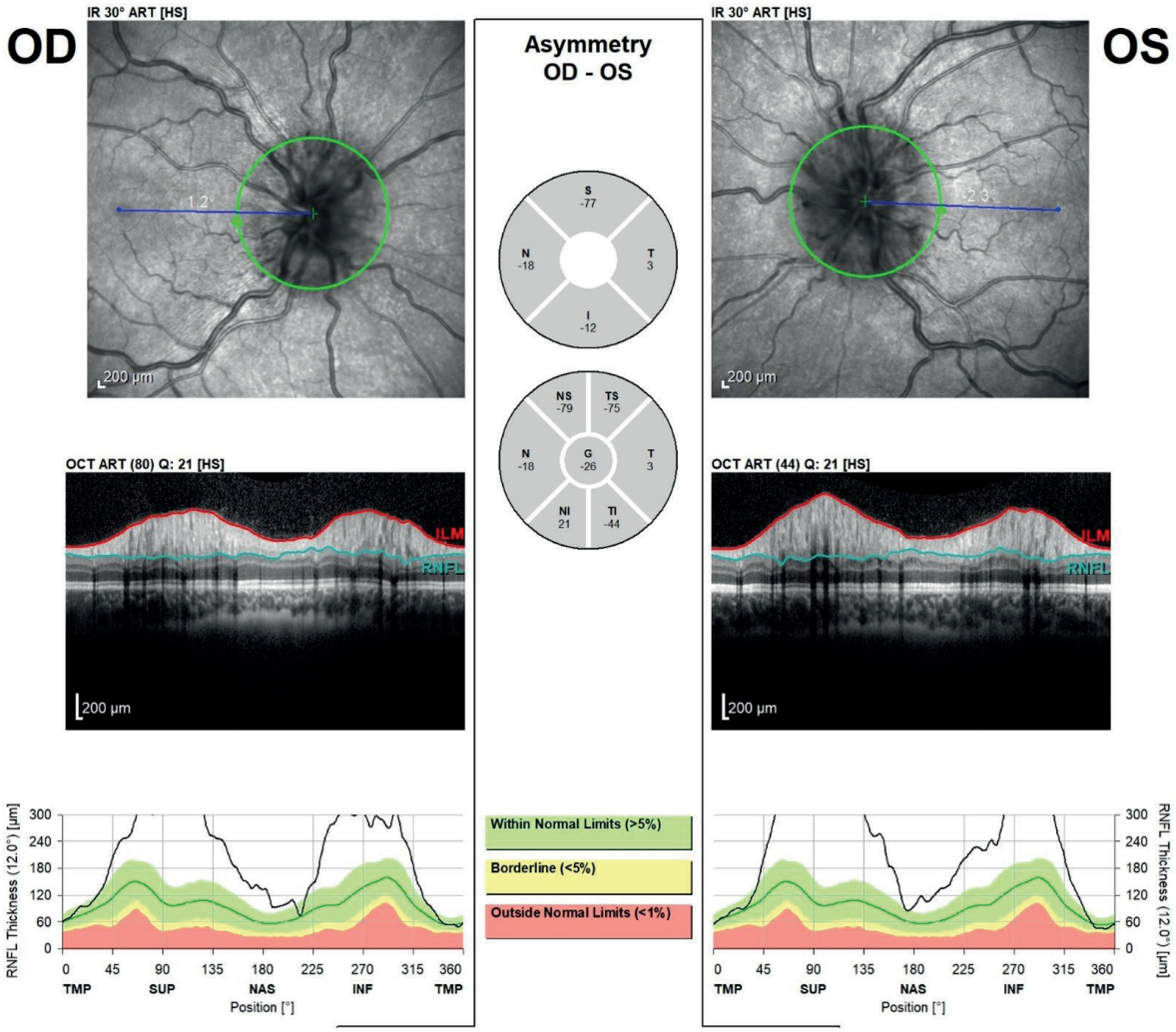

Fig. 3. Optical coherence tomography demonstrates marked thickening of the retinal nerve fiber layer (RNFL). The RNFL thickness shown in graphics is above normal limits. Green shows the normal RNFL limits. RNFL thickness below normal limits is represented with yellow (borderline) or red (outside normal limits).

papilledema regressed to grade 1-2. ATRA was restarted at half-dose and increased to the full dose after one week.

After day 12 of the current admission and before the fourth course of ATRA, bone marrow aspiration and LP were repeated to assess CNS remission and intracranial pressure. The CSF results were normal (pressure 24 cmH_2O), and ATRA was restarted at half dose, with a plan to increase to full dose after three days. One month later, the patient complained of worsening headaches and vomiting. Although no papilledema was observed, OCT findings revealed increased RNFL thickness and convolution of retinal blood vessels. Repeated brain MRI and venography were normal. Topiramate (0.5 mg/kg/day) was added to acetazolamide. A week later, grade 1-2 papilledema and increased RNFL thickness were observed. The topiramate dosage was increased. However, the ophthalmologic examination two weeks later revealed grade 2 papilledema. The opening and closing CSF pressures were 32 and 21 cm H_2O, respectively. Topiramate was increased to 1.5 mg/kg/day, ATRA was discontinued, and weekly detailed eye examinations were performed. The RNFL thickness was the first finding to show improvement (in week one), the papilledema regressed by week three, and pallor on the nasal side of the optic discs was observed by week four. ATRA treatment was restarted.

After two months, optic disc pallor was more marked, but RNFL thickness was normal. Acetazolamide was tapered off over five weeks. Topiramate was given for one more month after the last ATRA treatment and discontinued within two months during follow-up.

The patient's planned 7-month, seven-course chemotherapy was completed without other complications over a total of 11 months. There was no relapse of IH and APL during a 2 year-follow-up.

Informed consent was obtained for publication.

Discussion

Acute promyelocytic leukemia is a unique subtype of acute myeloid leukemia (AML) in which the ATRA/ATO combination has transformed a frequently fatal disease into one with a high cure rate. IH is a known complication of ATRA and was reported to be 18% in a single-center study from our country.[1,6] There are few reported cases of recurrent IH after reinitiation of ATRA in the literature.[2] Montesinos et al.[2] found an incidence of IH of 3.1% in all age groups and recurrence of IH despite discontinuation of ATRA in 28% of cases. APL accounts for 5-10% of pediatric AML cases.[1] IH risk has been found to be high in pediatric patients, especially during the first 2-3 weeks of APL induction therapy regimens.[7] According to the literature, cessation of ATRA is sufficient to resolve IH in approximately 30% of patients.[2] In others, drugs such as acetazolamide or topiramate or therapeutic LP may relieve the signs and symptoms, as in our patient.[1] The treatment should be tailored according to the patient's presentation, but reliable parameters are needed for follow-up. Papilledema can last up to 3 months, and treatments like acetazolamide may require adjustments for up to 6 months in IH.[8-10] As in our patient, recurrent LP or add-on treatment may be necessary. With improvement in symptoms, ATRA treatment can be resumed. Previously reported pediatric IH cases and their characteristics, as well as the distribution of IH in APL case series are shown in Table I.

A recent study[11] reported that vitamin A derivatives were responsible for 16.2% of cases of drug-induced IH, which is mostly caused by acne medications. These findings indicate that caution should be exercised with regard to IH when using vitamin A and its derivatives for any purpose.

This case illustrates the challenge faced in managing IH in a malignant disease requiring ATRA treatment. Our patient had multiple problems due to her disease: the presentation

of APL with ischemic infarction is very rare.[12] In our patient, the cerebrovascular complication of APL resulted in visual field defects observed at the time of diagnosis. Their presence complicated the distinction of visual impairment caused by IH. Although APL is a disease prone to thrombosis, the IH due to ATRA is not the result of venous thrombosis. ATRA increases the production of CSF and alters the lipid structure of the arachnoid villi, resulting in impaired CSF reabsorption.[1] On the other hand, IH secondary to intracranial leukemic infiltration has also been reported under ATRA treatment.[13] Therefore, differential diagnosis is important for treatment and follow-up.

Monitoring of IH is particularly important in cases with recurrent IH. Ophthalmological examination, a practical and non-invasive method, is essential.[5] Imaging findings are not sensitive to IH: as in our patient, MRI may be normal and does not reflect changes in IH immediately.[14] Measurement of CSF pressure is accurate but requires an invasive procedure. Therefore, sensitive and reliable biomarkers are needed for the detection of IH. In our patient, relying only on symptoms and papilledema only would not have given the chance of adequate and timely treatment, and complications of IH could have developed. According to our experience, measuring RNFL thickness by OCT provides early and objective information.[5] In the future OCT may also be used to measure three-dimensional optic nerve head parameters to distinguish IH from other optic neuropathies.[14]

In our country, OCT is available in training hospitals and university hospitals.

Conclusion

Children with APL treated with ATRA need close follow-up for IH. OCT is helpful in diagnosis, follow-up, and treatment decisions. IH can be resolved, and vision can be preserved by adjusting ATRA doses and administering appropriate drug treatment for IH within an individualized approach.

Supplementary materials

Supplementary materials for this article are available online at https://doi.org/10.24953/turkjpediatr.2026.6693.

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Ethical approval

Since this is a case study, ethical committee approval has not been obtained. Informed consent has been obtained from the family.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: PY, DY, GH; data collection: PY, GFY, SA; analysis and interpretation of results: PY, GFY, ŞÜC, GH; draft manuscript preparation: PY, DY, GH. 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.

Table I. All-Trans retinoic acid induced intracranial hypertension in pediatric acute promyelocytic leukemia: case characteristics and series distribution

References	IH	LP	Age (y)	ATRA dose mg/m^2	Days¶	ATRA treatment during IH	Treatment for IH	Outcome
Smith et al.[15]	Definite	+	6	80	7-10	i+r	NA	CR
Mahmoud et al.[16]	NA	NA	NA	45	3	c	NA	CR
	NA	NA	NA	45	3	c	NA	Died
	NA	NA	NA	45	3	d	NA	CR
	NA	NA	NA	45	13	d	NA	CR
	NA	NA	NA	45	17	d	NA	CR
Varadi et al.[17]	Definite	+	17	45	NA	d	Acetazolamide	CR (BMT)
Visani et al.[18]	Definite	+	16	45	31	d	Acetazolamide	CR
Decaudin et al.[19]	Definite	+	16	45	20	c	Serial LP	CR
Sano et al.[20]	Definite	+	18	45	23	d	Glycerin	CR
Chen et al.[21]	NA	NA	17	NA	42	NA	NA	NA
Tallman et al.[22]	NA	NA	4	45	13	NA	Dexamethasone	Died
Schroeter et al.[23]	Probable (Intracranial pressure unknown	+	8	25	65	d	Steroid, mannitol Acetazolamide	CR
Guirgis et al.[24]	Definite	+	16	50 mg‡	57	c	Acetazolamide	CR
	Probable	-	17	90mg‡	21	c	Acetazolamide	CR
Vanier et al.[25]	Probable (a leak in the manometer)	+	4	45	27	i+r	Fluconazole discontinued	NA
Naithani et al.[26]	NA	NA	9	45	12	i+r	Acetazolamide Mannitol	CR
Labrador et al.[27]	Definite	+	15	25	35	i	Acetazolamide	CR

¶ The day of ATRA treatment, on which IH developed, #total number of patients with IH, ‡mg per day, *during induction, * *during consolidation
ATRA, all-trans retinoic acid; BMT, bone marrow transplant; c, continuation; CR, complete remission; d, discontinuation; IH, intracranial hypertension; i, interruption; LP, lumbar puncture (and high CSF pressure was documented); r, dose reduction; y, years

Table I. Continued.

References	IH	LP	Age (y)	ATRA dose mg/m²	Days¶	ATRA treatment during IH	Treatment for IH	Outcome
Rasul et al.[28]	Definite	+	16	NA	21	d	Serial LP Dexamethasone Lumbar shunt	NA
Abla et al.[29]	Definite	+	13	25	4	i+r	Acetazolamide	CR
Coombs et al.[30]	Probable	-	8	45	4	r	Dexamethasone	CR
	Probable	+	11	45	13	c	NA	CR
	Probable (No papilledema)	+	15	45	47	i+r	NA	CR
Schwartz et al.[31]	Definite	+	10	25	NA	i or d	Dexamethasone	CR
Shirai et al.[32]	Definite	+	11	45	46	c	Acetazolamide, prednisolone	CR
Molinaro et al.[33]	NA	NA	12	NA	NA	i	Acetazolamide, dexamethasone	CR
Our case	Definite	+	15	25	90	i	Dexamethasone, acetazolamide, furosemide (single dose), topiramate, serial LP	CR

IH distribution in APL case series

	IH	Patients# (PTC incidence)	Age (y)	ATRA dose mg/m²	IH treatment
Warrell et al.[34]	Definite Probable	2 (18.1%)	9-75	45	Dexamethasone, serial LP, analgesics
Frankel et al.[35]	NA	2 or 3 (NA)	9-75	45	Dexamethasone, LP
Tallman et al.[36]	NA	at least 4 (2.3%)	1-81	45	Unknown
Bapna et al.[37]	NA	2 (13.3%)	3.5-15	45-90	Dexamethasone
Mandelli et al.[38]	NA	5 (2%)	2.2-73.9	45	Unknown

¶ The day of ATRA treatment, on which IH developed, #total number of patients with IH, ‡mg per day, *during induction, * *during consolidation
ATRA, all-trans retinoic acid; BMT, bone marrow transplant; c, continuation; CR, complete remission; d, discontinuation; IH, intracranial hypertension; i, interruption; LP, lumbar puncture (and high CSF pressure was documented); r, dose reduction; y, years

Table I. Continued.

References	IH	LP	Age (y)	ATRA dose mg/m²	Days¶	ATRA treatment during IH	Treatment for IH	Outcome
IH distribution in APL case series								
	IH	Patients# (PTC incidence)	Age (y)	ATRA dose mg/m²			IH treatment	
Douer et al.[39]	Definite	4 (5.8%)	5-82	90 (liposomal)			Unknown	
Mann et al.[40]	NA	1 (5%)	1.8-16.3	15-45			Unknown	
Testi et al.[41]	NA	10 (8.1%)	1-18	25			ATRA discontinuation (1/10)	
Ortega et al.[42]	NA	4 (6%)	2-17	25			Interruption and re-starting ATRA at reduced dose (2/4), ATRA discontinuation (2/4)	
Montesinos et al.[2]	NA	30*+ 2** (in total 3.1%) (in pediatric 13%)	NA	25 (in pediatric age)			ATRA interruption (9/32 had recurrent PTC)	
Gregory et al.[43]	Definite	3 (11%)	1-18	45			Unknown	
Imaizumi et al.[44]	NA	5 (8.6%)	0.9-16	45			Unknown	
Jeddi et al.[45]	NA	1 (2.6%)	4-64	25 (≤20 years)			Unknown	
Avvisati et al.[46]	NA	16 (2%) (in 10/16 <18 years)	1.4-74.7	25			Analgesics, furosemide, dexamethasone, ATRA discontinuation	
Dorantes-Acosta et al.[47]	NA	1 (9.1%)	1.4-12.7	45			Dexamethasone	
Testi et al.[48]	NA	15 (5.8%)	1-21	25			Analgesics, diuretics, temporary ATRA discontinuation	
Aksu et al.[6]	Definite	3 (18%)	1.5-17	25			Serial LP, acetazolamide, dexamethasone, topiramate (in 1/3)	
Kutny et al.[49]	NA	At least 5 (6%)	<18	45			Interruption and re-starting ATRA, Dexamethasone	

¶ The day of ATRA treatment, on which IH developed, #total number of patients with IH, ‡mg per day, *during induction, * *during consolidation
ATRA, all-trans retinoic acid; BMT, bone marrow transplant; c, continuation; CR, complete remission; d, discontinuation; IH, intracranial hypertension; i, interruption; LP, lumbar puncture (and high CSF pressure was documented); r, dose reduction; y, years

Table I. Continued.

References	IH	LP	Age (y)	ATRA dose mg/m^2	Days¶	ATRA treatment during IH	Treatment for IH	Outcome
IH distribution in APL case series								
	IH	Patients# (PTC incidence)	Age (y)	ATRA dose mg/m^2			IH treatment	
Strocchio et al.[50]	NA	2 (11.1%)	4.8-17.5	25			Interruption and re-starting ATRA	
Zhang et al.[51]	NA	3 (4.3%)	1-17	25			Unknown	
Spezza et al.[52]	NA	3 (14.3%)	1-16	25			Unknown	
Breviglieri et al.[53]	Probable	6 (19%)	1-17	45 (≥14 years) 25 (<14 years)			Acetazolamide	
Khan et al.[54]	NA Probable	3 (15%)	3-13	25			Dexamethasone, Mannitol, ATRA discontinuation Dexamethasone, ATRA discontinuation or interruption	
Kutny et al.[55]	NA	12* (7.8%) 7** (4.6%)	1.1-21.7	25			Unknown	
Testi et al.[56]	NA	5 (4.6%)	1.1-14.4	25			ATRA interruption	
Vaid et al.[57]	Probable	11 (17.2%)	5-60	25 (in pediatric age)			Acetazolamide, ATRA dose reduction (in 6/11)	
Roy et al.[58]	NA	3 (4.8%)	0.9-12.2	26±3.7			Unknown	
Javed et al.[59]	NA	6 (11.7%)	12-58	25			Unknown	
Singh et al.[60]	NA	12 (6.6%)	12-66	25-45			Unknown	
Maldonado et al.[61]	NA	4* (18.2%)	2-18	45			Continued ATRA	

¶ The day of ATRA treatment, on which IH developed, #total number of patients with IH, ǂmg per day, *during induction, * *during consolidation
ATRA, all-trans retinoic acid; BMT, bone marrow transplant; c, continuation; CR, complete remission; d, discontinuation; IH, intracranial hypertension; i, interruption; LP, lumbar puncture (and high CSF pressure was documented); r, dose reduction; y, years

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Case Report

A rare case of bilateral axillary accessory breast tissue coexisting with prolactinoma in an adolescent girl

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ABSTRACT

Background. Unlike polythelia, which is typically identified at birth by the presence of an areola or nipple, accessory axillary breast tissue is rarely observed in children and adolescents. Nevertheless, it can affect this age group and should be considered in the differential diagnosis of an axillary mass.

Case Presentation. A 15-year-old girl with a diagnosed prolactinoma, receiving cabergoline treatment, presented with a week's history of tender, bilateral axillary masses. Ultrasonographic evaluation and subsequent surgical excision confirmed the diagnosis of bilateral accessory axillary breast tissue. To the best of our knowledge, this is the first reported case of co-existing bilateral accessory axillary breast tissue and prolactinoma in an adolescent girl.

Conclusion. This case highlights the importance of thorough physical examination in adolescents with prolactinomas. Accessory breast tissue may become more prominent during puberty or in hyperprolactinemic states, and it may be misdiagnosed. Recognizing this rare occurrence is key to avoiding unnecessary investigations or interventions.

Key words: accessory breast tissue, polymastia, prolactinoma.

Accessory breast tissue consists of normal breast tissue located outside the breast. This ectopic breast tissue can develop anywhere along the mammary ridges due to incomplete involution (the 'milk line'). It includes a range of conditions characterized by the presence of glandular tissue (polymastia), supernumerary nipples without breast tissue (polythelia), areolas, or combinations of these features.[1] Kajava proposed a classification system in 1915 that remains widely used today (Table I). Polythelia is most often found on the chest, upper abdomen, or just below the normally positioned breast, whereas the most common site of accessory breast tissue is the axilla, where it may occur unilaterally or bilaterally.[2] Some forms of accessory breast tissue are present at birth, whereas others may become apparent later in life during periods of hormonal change such as pregnancy or menstruation.[3] It affects between 0.4% and 6.0% of the general population.[3] The diagnosis of accessory axillary breast tissue is rare in children and adolescents, with only a few detailed cases in these groups reported in the literature.[3-5]

Prolactin (PRL) plays a key role in the development of mammary glands within breast tissue and in milk production. Prolactinomas are the most common organic cause of hyperprolactinemia and represent the most prevalent type of pituitary adenoma in children and adolescents.[6] The clinical manifestations of

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prolactinomas vary according to the patient's sex and age at onset, as well as tumor size. Where emergency surgery is not indicated, the first-line treatment for prolactinoma is dopamine agonists, which both normalize PRL levels and reduce tumor size.[7]

Hyperprolactinemia, particularly when caused by prolactinomas, can stimulate mammary gland development and milk production. However, only a few well-documented cases of bilateral accessory breast tissue in adults with prolactinoma have been reported in the literature.[8] Hyperprolactinemia, particularly when caused by prolactinomas, can stimulate mammary gland development and milk production. Existing evidence is limited to isolated adult case reports, and prior publications have not conclusively clarified whether prolactin exerts a direct proliferative effect on accessory axillary breast tissue.[8,9] The absence of pediatric data and the lack of mechanistic evidence in adult studies underscore the current gaps in the literature.Here, we describe a case involving an adolescent girl diagnosed with a prolactinoma and bilateral axillary accessory breasts, with the aim of providing clinicians with additional diagnostic and treatment experience. Reports of accessory axillary breast tissue in the pediatric population are scarce, and, to the best of our knowledge, coexistence with prolactinoma has not been previously described in an adolescent.

Case Presentation

A 15-year-old girl presented with heavy menstrual bleeding. The patient experienced menarche at the age of 12. During the first year following menarche, her menstrual cycles occurred approximately every two months, after which they became regular on a monthly basis. The amount of menstrual bleeding had not previously been excessive, typically not exceeding four sanitary pads per day. On laboratory evaluation, her hemoglobin was 8.6 g/dL (normal [N]: 11.7-15), ferritin 3.9 μg/L (N: 12-140), luteinizing hormone (LH) 2.8 IU/L (N: 2.4-12.6), follicle-stimulating hormone (FSH) 7.2 IU/L (N: 3.5-12.5), estradiol (E2) 32.2 ng/L (N: 22-341), and total testosterone 30 ng/dL (N: 20-38). Her PRL level was 78 ng/mL (N: 5-20 ng/ml) in tests conducted prior to the initiation of combined oral contraceptive treatment. Magnetic resonance imaging (MRI) revealed a pituitary microadenoma measuring 7.5 × 6.0 × 7.0 mm. Evaluation of the other pituitary hormones revealed an adrenocorticotropic hormone (ACTH) level of 27.5 pg/mL (N: 7.2-63), a cortisol level of 11.3 μg/dL (N: 4.8-19), and an insulin-like growth factor (IGF)-1 level of 229 ng/mL (N: 151-485). According to her medical history, other than asthma treatment administered prior to puberty, she had no exposure to medications associated with hyperprolactinemia or abnormal uterine bleeding. Following acute management of heavy menstrual bleeding, the patient was monitored while receiving cabergoline 0.5 mg/week. The PRL level normalized (7 ng/mL) within the first month, with an MRI at six months showing initial adenoma shrinkage, and one-year follow-up imaging confirming a reduction in size to 3.8 × 2.7 mm. A PRL level below 20 ng/mL was maintained. At an outpatient visit, the patient reported bilateral axillary swelling that had developed over the preceding week, following a month of irregular medication use. This episode occurred during the first year of prolactinoma treatment, when her PRL level had increased to 29 ng/mL. On examination, painful swellings were present beneath both axillae, without erythema, ulceration, or palpable fluctuation (Fig. 1). No galactorrhea was observed. She had no history of tuberculosis, cat-scratch disease, or other systemic infection. There was no evidence of pathological lymphadenopathy or organomegaly. Laboratory tests showed a PRL level of 28 ng/mL and a negative β-hCG result. At the time the axillary swelling developed, the patient was menstruating. Gonadotropin levels (LH and FSH) were not measured during this episode. No palpable masses were found in either breast. Bilateral mammary gland tissue was detected on axillary ultrasound, with the accessory tissue more prominent on the right side. The accessory breast observed in this

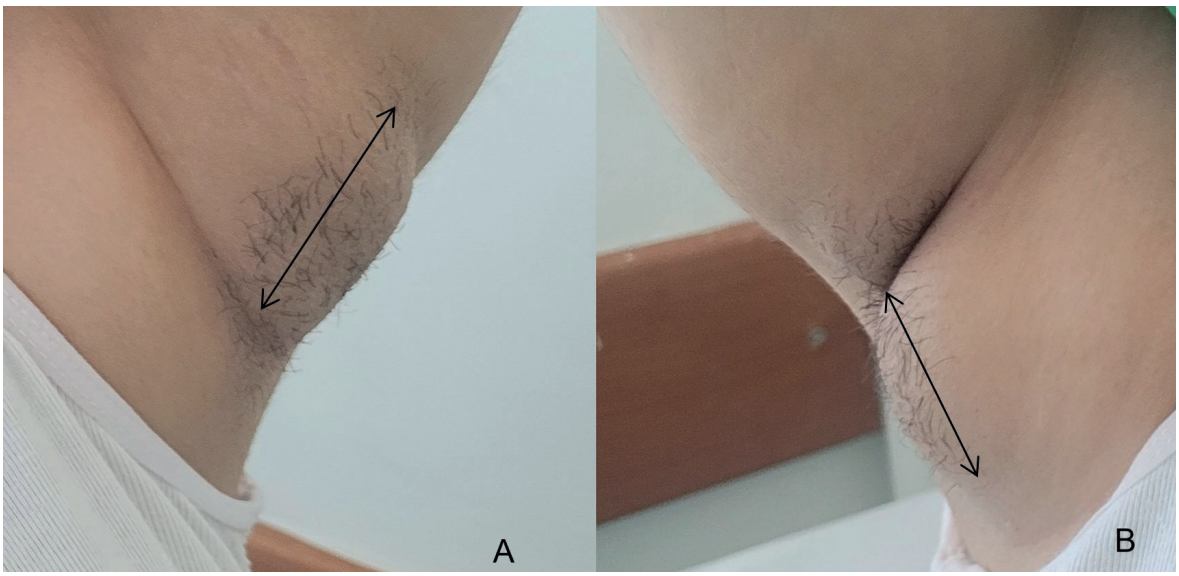

Fig. 1. Patient's left (A) and right axilla (B) and left axilla at the time presentation, both displaying a tense swelling, measuring 6 × 5 cm, without erythema.

patient corresponded to Class IV in Kajava's classification system (Table I). There was no reported family history of a similar condition.

The cabergoline dose was increased to 1 mg/week. Echocardiography was normal. An abdominal ultrasound performed to check for associated anomalies revealed no abnormalities in the kidneys or other organs. The patient was referred to surgery with a pre-diagnosis of bilateral axillary breast tissue, and the pediatric surgeon recommended elective excision (Fig. 2). Histopathological findings revealed normal mammary tissue without atypia in the bilateral accessory breast tissues, confirming the diagnosis of bilateral accessory axillary breast tissue (Fig. 3). The incision healed well, and no recurrence was observed during the 3-month follow-up period. Written informed consent for publication of the case details and accompanying images was obtained from the patient and her legal guardian.

Discussion

To the best of our knowledge, this is the first reported adolescent patient with co-existing bilateral accessory axillary breast tissue and

Table I. Classification of accessory breast tissue as proposed by Kajava in1915[3].

Clinical category	Alternative name	Definition
Class I	Polymastia	A complete breast including glandular tissue, nipple, and areola
Class II	Polymastia, supernumerary breast without areola	Only glandular tissue and nipple, without areola
Class III	Polymastia, supernumerary breast without nipple	Only glandular tissue and areola, without nipple
Class IV	Mamma aberrata	Glandular tissue only
Class V	Pseudomamma	Nipple and areola but without glandular tissue (replaced by fat)
Class VI	Polythelia	Nipple only
Class VII	Polythelia areolaris	Areola only
Class VIII	Polythelia pilosa	Patch of hair only

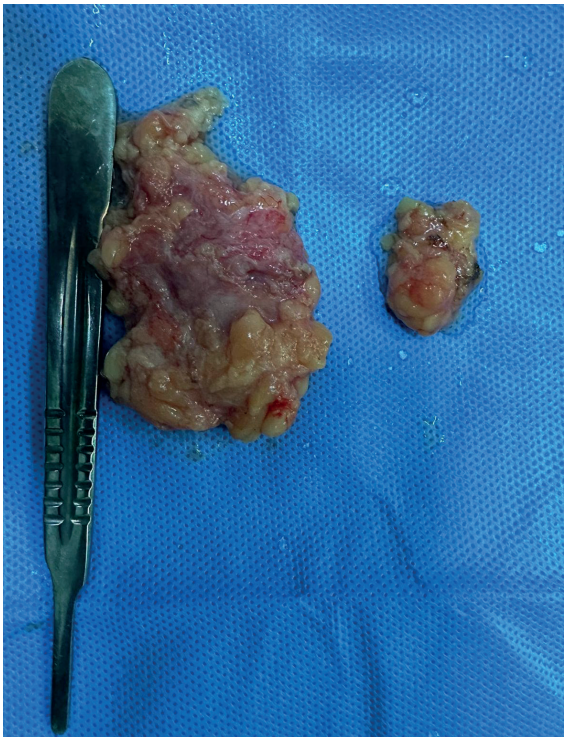

Fig. 2. The specimen dissected from the right axilla, approximately 6.5 x 4.0 cm in size.

prolactinoma. Although numerous cases of accessory axillary breast tissue have been reported in adults, only a few have been described in children and adolescents.[3,5,10] In one case series of 11 adolescents with axillary accessory breast tissue, the youngest patient was 13 years old.[3] Another case report described a 9-year-old prepubertal girl with bilateral axillary accessory breasts.[5]

The relatively small number of reported cases in children may be due to the condition going unnoticedeither because accessory axillary breast tissue only becomes apparent and symptomatic after hormonal stimulation, or because the patient's body shape obscures it. Hormonal changes (e.g. menstruation, pregnancy, and lactation) can cause the masses to become tender and fluctuate in size.[11]

In this case, no complaints were reported at the time of prolactinoma diagnosis, and no axillary mass was palpable during the initial physical examination. The findings only

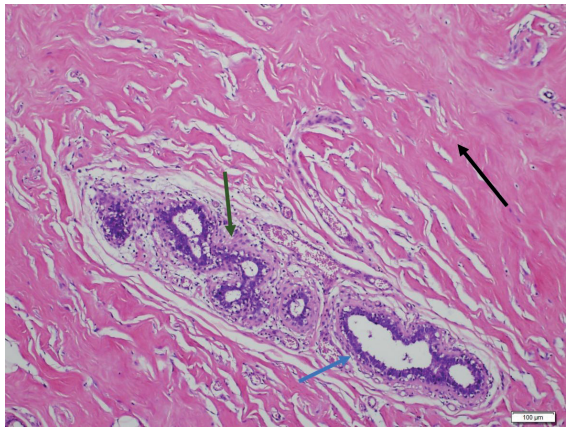

Fig. 3. Histopathology of the specimen excised from the right axilla, demonstrating findings of benign breast parenchyma (green arrow), including mammary ducts (blue arrow) and stroma (black arrow) (H&E staining, original magnification x100).

became apparent during the menstrual cycle in the first year of treatment. This situation can be explained as follows. Hyperprolactinemia can lead to menstrual irregularity, estrogen deficiency, and testosterone deficiency. [7]In our patient, treatment with cabergoline improved gonadal function, and the accessory breast tissue may have become more prominent as estrogen levels returned to normal. PRL promotes the growth of mammary alveoli and stimulates breast alveolar epithelial cells to synthesize milk components [6]. At the same time, the effects of PRL on breast tissue may render accessory breast tissue more noticeable. Our case is noteworthy due to the delayed presentation of accessory breast tissue following a period of irregular cabergoline use, despite the patient having previously achieved target PRL levels. A plausible explanation is that normalization of PRL may have permitted reactivation of the hypothalamic–pituitary–gonadal axis, leading to increased gonadotropin secretion; however, the exact underlying mechanism remains unclear. Accessory breast tissue originates during embryological development and typically becomes clinically apparent during periods of hormonal fluctuation such as puberty, menstruation, pregnancy, or lactation.[3] In this patient, the transient rise in PRL or associated hormonal imbalances may have triggered an

earlier or more pronounced manifestation of the accessory breast tissue.

Ultrasonography is the recommended imaging method for children and adolescents suspected of having accessory breast tissue. However, histopathological examination is required to confirm the diagnosis and to demonstrate histological features characteristic of normal breast tissue.[2,3]

Polythelia often does not require surgery. By contrast, surgical excision of axillary breast tissue enables confirmation of the diagnosis, relief of pain, and improvement of cosmetic appearance.[12,13]Accessory breast tissue is subject to the same benign and malignant pathologies as normal breast tissue, including pain, swelling, lactation, mastopathy, fibroadenoma, fibrocystic change, and carcinoma.[14-16]

Accessory breasts can be inherited as an autosomal dominant trait with incomplete penetrance, although they are more often sporadic.[3] In our case, there was no family history of accessory axillary breast tissue. The literature describes familial incidence, as well as associations with cardiovascular or renal anomalies and trisomy 21, but none of these anomalies were present in our patient.[10]

The classical syndrome is characterized by cyclic pain during menstruation, accompanied by symptoms such as swelling, tenderness, restricted shoulder mobility, and irritation from clothing. [10]

Possible differential diagnoses include lymphadenopathy, hidradenitis suppurativa, lipoma, malignancy, sebaceous cyst, plexiform neurofibroma, neuroma, follicular cyst, slack skin with granulomatous inflammation, and vascular malformation.[10-12,17]

Ultrasonography is the initial diagnostic tool, typically revealing hypoechoic breast tissue similar to orthotopic tissue. Bilateral ultrasonography is recommended to rule out contralateral involvement. Histopathological examination is required to confirm the diagnosis.[2] The risk of incision-site infection and recurrence can be reduced by complete excision of the lesion along with the surrounding skin.[3]

However, there is some controversy in the literature regarding the optimal timing of surgery. Many authors argue that the best time is before pregnancy because the reoperation rate is lower and patients are more satisfied when the procedure is carried out at a young age.[18]Monitoring and reducing serum PRL levels may lessen disease severity, shorten the treatment period, lower the risk of recurrence, and help prevent or manage endocrine disorders associated with hyperprolactinemia.

Children and adolescents with a supernumerary nipple or areola should be made aware of the possibility of underlying breast tissue. Consequently, follow-up is recommended until the end of puberty.[3]Although accessory breasts are often asymptomatic, they may cause anxiety, cosmetic concerns, pain, and restricted arm movement. According to the literature, excision of accessory axillary breast tissue has also been associated with notable adverse effects.[3,4] In the present case bilateral surgical excision was performed because of persistent pain, cosmetic concerns, and the need for definitive histopathological confirmation. In the context of the underlying hyperprolactinemic state and the bilateral symptomatic presentation, surgical management was deemed the most appropriate approach to ensure symptom relief and diagnostic certainty.

Gonadotropin levels (LH and FSH) were not assessed at the time of detection of bilateral axillary breast tissue; although such measurements could have provided additional insight into the hormonal milieu, they were not obtained at that time. An important limitation of this case is the relatively short postoperative follow-up period of three months, which is insufficient to thoroughly assess recurrence risk or long-term cosmetic outcomes. An extended follow-up would be necessary to better characterize the long-term course and overall surgical success.

Conclusion

We have presented what we believe to be the first case report of the co-existence of accessory axillary breast tissue and prolactinoma in an adolescent girl. Axillary accessory breast tissue should be considered in the differential diagnosis of axillary masses in pediatric patients. Symptoms may arise before pregnancy and prior to the end of puberty. The most common are axillary swelling and cyclic pain coinciding with menstruation. Bilateral ultrasonography is widely recommended for diagnosis. Surgical management is safe and effective in children and adolescents. This case contributes to the limited literature on the association between prolactinomas and bilateral axillary accessory breast tissue in adolescence.

Ethical approval

Written informed consent was obtained from the patient's guardian for the publication of the case details and images.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: TKÇ, SSB; data collection: TKÇ, SSB; analysis and interpretation of results: TKÇ, medikal and surgeal practice: TKÇ, SSB, draft manuscript preparation: TKÇ. 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

From osteolytic lesions to hungry bone syndrome: a rare case of primary hyperparathyroidism in childhood

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ABSTRACT

Background. Primary hyperparathyroidism (PHPT) is a rare endocrine disorder in childhood, most commonly associated with a single parathyroid adenoma. Compared to adults, pediatric cases often present with more pronounced clinical manifestations and may lead to severe skeletal complications. This report presents a symptomatic case of PHPT complicated by extensive skeletal involvement, brown tumors, and postoperative hungry bone syndrome (HBS).

Case presentation. A 16-year-old female was admitted with progressive leg pain and weight loss. Laboratory evaluation revealed marked hypercalcemia, severely elevated parathyroid hormone, hypophosphatemia, and vitamin D deficiency. Imaging findings were consistent with a parathyroid adenoma; however, the initial surgical attempt failed to localize the adenoma. Subsequent advanced imaging with four-dimensional computed tomography (4D-CT) and interventional radiology-guided localization enabled successful resection. Postoperatively, the patient developed profound and prolonged hypocalcemia with concomitant hypophosphatemia and hypomagnesemia, consistent with HBS, requiring intensive intravenous and oral calcium, calcitriol, phosphate, and magnesium replacement. Radiological and histopathological evaluations demonstrated diffuse skeletal involvement with multiple brown tumors.

Conclusions. This case highlights that although rare, PHPT should be considered in the differential diagnosis of children presenting with refractory bone pain and hypercalcemia. Accurate preoperative localization of parathyroid adenomas requires advanced imaging techniques and a multidisciplinary approach. Furthermore, in patients with markedly elevated parathyroid hormone and alkaline phosphatase levels, vitamin D deficiency, and long-standing skeletal involvement, the risk of developing HBS should be anticipated and management strategies tailored accordingly.

Key words: primary hyperparathyroidism, parathyroid adenoma, hypercalcemia, brown tumors, hungry bone syndrome.

Primary hyperparathyroidism (PHPT) is a condition characterized by hypercalcemia due to excessive secretion of parathyroid hormone (PTH) from the parathyroid glands, accompanied by inappropriately normal or elevated serum PTH levels. While PHPT is more common in adults, it is rare in childhood and adolescence, with an incidence of 2–5 cases per 100,000 individuals.[1,2] The most common cause of PHPT in childhood and adolescence is a single parathyroid adenoma, accounting for 70–80% of cases. Multiglandular adenomas

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or multiple adenomas, are less common, accounting for approximately 15–20% of cases. Adenomas are usually sporadic, and some cases may develop with multiple endocrine neoplasia (MEN) type 1 and 2A syndromes or familial isolated hyperparathyroidism.[3]

Symptoms of hyperparathyroidism include constipation, bone pain, fatigue, and depression. Severe hypercalcemia can cause shortening of the QT interval (the time from the Q wave of the QRS complex to the end of the T wave) on the ECG, ventricular tachycardia, and even fatal arrhythmias such as ventricular fibrillation. Hypercalcemic patients with hyperparathyroidism may experience nephrolithiasis, osteopenia, osteoporosis, bone fractures, pancreatitis, peptic ulcer disease, and hypertension. Symptomatic disease is more common in children with primary hyperparathyroidism than in adults (79%–90%), and 44% of organ involvement (e.g., nephrolithiasis, nephrocalcinosis, and bone involvement) can be definitively treated with surgery. Pediatric case reports demonstrate a wide range of nonspecific features.[4,5]

Brown tumors are rare focal giant cell lesions that arise from hypercalcemia resulting from excessive PTH secretion from the parathyroid glands. These lesions are caused by the direct effect of PTH on bone tissue in patients with hyperparathyroidism. In normal physiology, the parathyroid glands continuously monitor serum calcium levels and increase PTH secretion in response to hypocalcemia. Elevated PTH levels increase serum calcium levels by increasing calcium reabsorption in the kidneys and bone resorption. However, in pathological conditions, this mechanism operates uncontrolled, leading to aggressive osteoclastic activity in bone tissue and the development of localized lytic lesions. Histologically, these lesions exhibit a characteristic "brown" color due to vascularity, hemorrhage, and hemosiderin deposition. Although nonneoplastic, they can be locally destructive.[6,7]

Hungry bone syndrome (HBS) is a clinical condition characterized by pronounced and prolonged hypocalcemia that develops due to a sudden decrease in PTH levels in patients who underwent parathyroidectomy for PHPT and had high preoperative bone turnover. This condition is frequently accompanied by hypophosphatemia and hypomagnesemia. Increased calcium transfer into bone tissue as a result of sudden PTH suppression is proposed as the primary pathophysiological mechanism, and this is associated with a decrease in bone remodeling processes. Although HBS is rare after parathyroidectomy, it is a complication that can lead to serious clinical consequences.[8,9] Although current literature data is limited, it is estimated that approximately 13% of patients undergoing parathyroidectomy may develop HBS. Risk factors that may influence the development of HBS include young age at the time of surgery, elevated PTH and alkaline phosphatase (ALP) levels, low serum albumin and magnesium levels, and skeletal pathologies such as subperiosteal erosions, lytic bone lesions, and brown tumors.[10]

This report aims to present an exceptionally rare and severe case of pediatric primary hyperparathyroidism characterized by extensive skeletal destruction, multiple brown tumors, and postoperative hungry bone syndrome, and to underscore the critical importance of timely diagnosis, precise preoperative localization, and proactive postoperative management in this vulnerable age group.

Case Presentation

We present the case of a 16-year-old female who had been initially admitted to another health center with complaints of progressively worsening diffuse leg pain and weight loss over the past two months. Initial evaluation revealed a serum calcium level of 12.9 mg/dL (8.4-10.2), an ALP level of 983 U/L (50-117), and a PTH level of 1127 pg/mL (15-65). Despite intravenous (IV) hydration and furosemide therapy for hypercalcemia, serum calcium levels persisted,

leading to the plan to begin pamidronate therapy. An allergic reaction developed during the pamidronate infusion, and treatment was discontinued. Neck ultrasonography (USG) revealed a hypoechoic, 20x30 mm solid lesion adjacent to the inferior left thyroid pole, demonstrating vascularization, and was diagnosed as a parathyroid adenoma. A lower extremity magnetic resonance imaging (MRI) was performed due to widespread persistent lower extremity bone pain, which revealed widespread heterogeneous signal intensities in the proximal and mid-portions of both tibias, focal sclerotic areas in the left epiphyseal-metaphyseal region, and an infiltrative lesion (Fig. 1). The preliminary diagnosis was Langerhans cell histiocytosis or brown tumor. The patient was referred to our center for further evaluation by the pediatric endocrinology, oncology, and surgery departments. The patient's history did not include any prenatal, natal, or postnatal features. She had no known chronic disease or regular medication use. There was no family history of consanguinity between the mother and father. It was learned that the mother was under treatment for hyperthyroidism, and the father and a sister were under treatment for systemic sclerosis. On physical examination, her body weight was 43 kg (−2.17 SDS), height was 155 cm (−1.19 SDS), and body mass index was 17.9 kg/m^2 (−1.61 SDS). Pubertal development was consistent with Tanner stage 5. Systemic examination findings were normal. Laboratory findings revealed a serum calcium level of 13 mg/dL (8.4-10.2), serum phosphate was 2.2 mg/dL (2.8-4.8), serum magnesium was 2.01 mg/dL (1.7-2.2), serum ALP was 938 U/L (50-117), urine calcium/creatinine ratio was 0.7 mg/mg, serum intact PTH level was 1127 pg/mL (15-65), and there was severe vitamin D deficiency (serum 25-OH-D_3 level was 4.77 ng/mL). Diffuse radiolucent areas on whole-body plain radiographs were interpreted as brown tumors (Fig. 2). On the 16th day of hospitalization, while the patient was undergoing preoperative preparation for hyperparathyroidism due to a parathyroid adenoma, a spontaneous subtrochanteric femoral fracture occurred. Dual-energy X-ray absorptiometry (DXA) revealed a lumbar spine (L1–L4) bone mineral density Z-score of −3.5. Based on the presence of a femoral fracture and markedly reduced bone mineral density, the patient was diagnosed with secondary pediatric osteoporosis. Calcitonin levels (screened for MEN 2A), urinary catecholamine and metabolite levels (screened for pheochromocytoma / MEN 2A), and the anterior pituitary hormone profile (screened for MEN 1) were all within normal limits. Parathyroid scintigraphy revealed activity uptake in the lower pole of the left thyroid lobe consistent with a parathyroid adenoma. The patient, diagnosed with PHPT and symptomatic hypercalcemia due to a parathyroid adenoma, was operated on by a pediatric surgeon based on the current ultrasound and scintigraphy imaging findings.

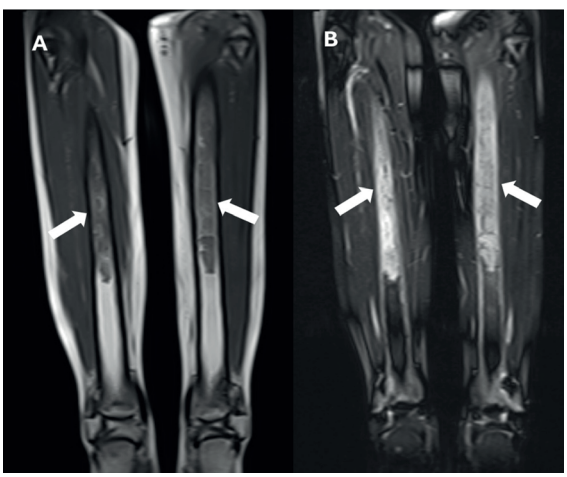

Fig. 1. Magnetic resonance imaging of the lower extremities. Coronal T1-weighted images demonstrate hypointense areas (A), while coronal T2-weighted fat-suppressed images (B) show corresponding hyperintense areas in both tibiae (arrows). In the setting of hyperparathyroidism associated with a parathyroid adenoma, these findings are consistent with lytic and sclerotic bone changes secondary to metabolic bone disease.

The patient with persistent postoperative hypercalcemia and elevated serum PTH levels underwent dynamic computed tomography (4D-CT) of the neck and thorax. Imaging demonstrated a mass lesion situated

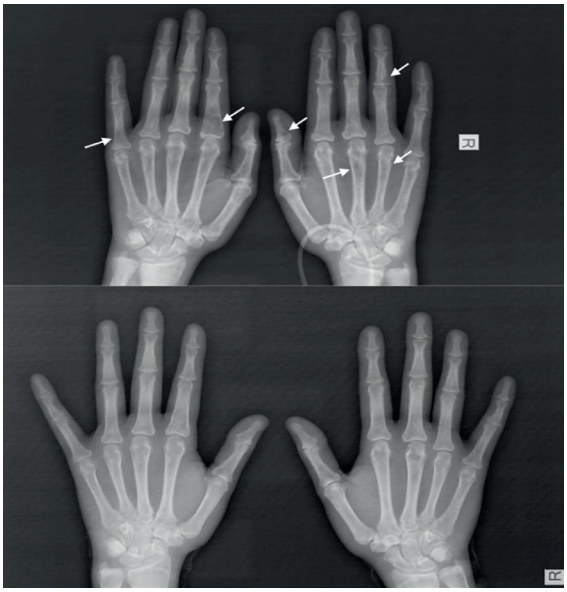

Fig. 2. Plain radiographs of the hands and wrists. Initial radiograph (top) demonstrates diffuse cortical thinning and subperiosteal lytic lesions in the phalanges of both hands, findings consistent with typical subperiosteal bone resorption associated with hyperparathyroidism secondary to hypercalcemia (white arrows). Follow-up radiograph (bottom) obtained one year later shows partial regression of some lesions and complete resolution of others.

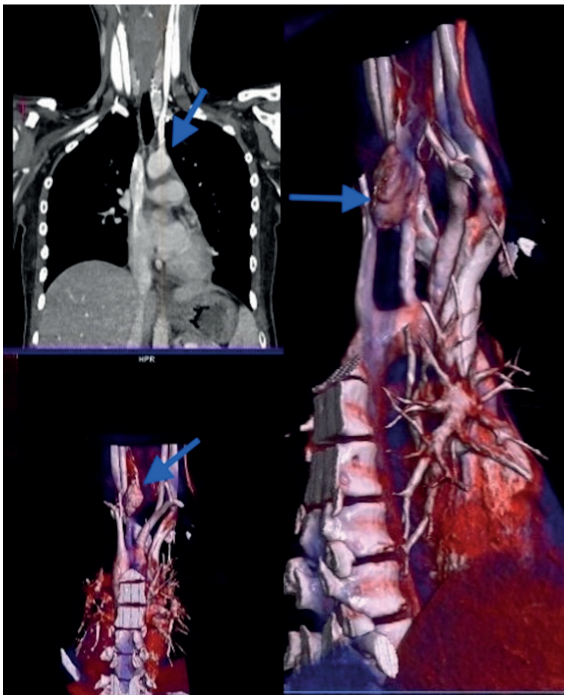

Fig. 3. Contrast-enhanced coronal computed tomography (top left) and 3D reconstruction images (right, bottom left) show a well-defined, expansile mass located in the paratracheal region with intense contrast enhancement (blue arrows). This appearance is consistent with a parathyroid adenoma, which was confirmed histopathologically.

posterolateral to the trachea and mediolateral to the left common carotid artery (Fig. 3). Diffuse sclerotic bone changes were noted in the vertebral column, ribs, humerus, clavicle, and scapula. Furthermore, a heterogeneous mass measuring 30 × 35 × 30 mm, containing sclerotic components, was identified along the posteromedial wall of the left maxillary sinus (Fig. 4). Histopathological examination of a biopsy specimen obtained from the maxillary lesion revealed findings consistent with a brown tumor.

Before the planned second operation, interventional radiology marked the adenoma location. The surgical team accessed the lesion with a guidewire and successfully excised the adenoma. In the postoperative period, the patient developed marked hypocalcemia accompanied by low parathyroid hormone levels (serum calcium: 5.2 mg/dL; PTH: 14.8 pg/mL). The clinical presentation was considered consistent with transient postoperative hypoparathyroidism and hungry bone syndrome. Accordingly, treatment was intensified with intravenous calcium gluconate (2.4 g/day), oral calcium carbonate (6 g/day), and calcitriol at a dose of 3 μg/day. During this period, hypophosphatemia and hypomagnesemia accompanying hypocalcemia were also detected; therefore, oral phosphate solution and magnesium supplementation were added to the treatment regimen. Stabilization of serum calcium, phosphorus, and magnesium levels was achieved by the third postoperative week. Subsequently, therapy was transitioned to an oral regimen consisting of calcium carbonate 3 g/day, calcitriol 2 μg/day, and magnesium 365 mg administered three times daily, and the patient was discharged on this treatment.

During the follow-up period, no clinical symptoms related to hypocalcemia, bone pain,

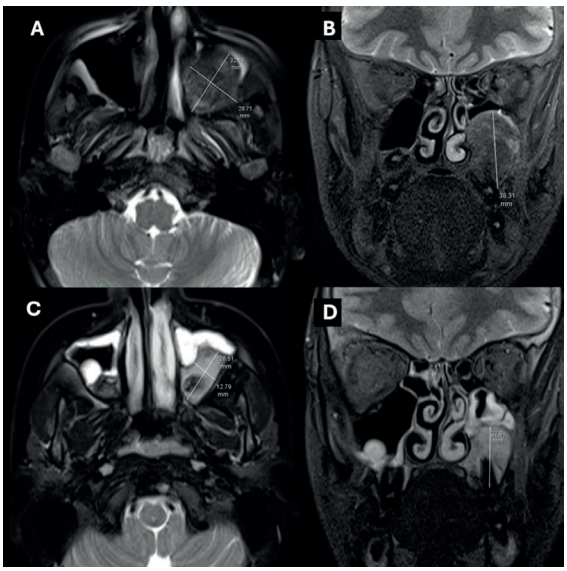

Fig. 4. Brown tumor. Pre-treatment axial (A) and coronal (B) T2-weighted magnetic resonance (MR) images demonstrate a lesion originating from the posteromedial wall of the left maxillary sinus. The lesion measured 29 × 33 × 38 mm at this time point, and the imaging findings were considered consistent with a brown tumor. Axial (C) and coronal (D) T2-weighted MR images obtained at the postoperative 8th month reveal a lesion at the same location with reduced dimensions of 13 × 27 × 27 mm. Post-treatment measurements indicate an approximately 60% reduction in lesion volume.

or new fractures were observed. Treatment doses were gradually tapered based on serial serum calcium and magnesium levels, as well as the urinary calcium-to-creatinine ratio. At the first postoperative month, biochemical evaluation revealed normalization of serum calcium and parathyroid hormone levels, and the transient hypoparathyroid state was considered resolved. Given the persistently low bone mineral density, calcium, magnesium, and calcitriol supplementation were continued. With stepwise dose reduction, all treatments except 25-hydroxyvitamin D were discontinued by the eighth postoperative month. One month after cessation of therapy, biochemical assessment demonstrated a serum calcium of 9.6 mg/dL, phosphorus of 3.3 mg/dL, magnesium of 1.9 mg/dL, parathyroid hormone of 24 pg/mL, and 25-hydroxyvitamin D of 28 ng/mL. Consequently, maintenance therapy was continued with 25-hydroxyvitamin D prophylaxis at a daily dose of 600 IU.

Physical therapy was initiated to support the skeletal system in the patient, who was considered osteoporotic based on bone mineral density assessment. At the first-year postoperative follow-up, bone mineral densitometry revealed an age-adjusted lumbar spine (L1–L4) Z-score of −0.6 SDS. The patient was also followed by the orthopedic team, and removal of the femoral implant placed intraoperatively for the subtrochanteric femoral fracture was planned at three months.

Informed consent was obtained from the patient and her parents for this publication.

Discussion

This case demonstrates a symptomatic and complicated presentation of PHPT, a rare condition in childhood. PHPT is an endocrine disorder relatively rare in children compared to adults, with a reported incidence of 2–5 per 100,000. PHPT generally presents with distinct symptoms at diagnosis in the pediatric age group and can lead to systemic complications. As in the case presented here, musculoskeletal pain, anorexia, and weight loss due to hypercalcemia are common presentations in children. Our patient, who began with complaints of widespread leg pain and weight loss, was diagnosed with hyperparathyroidism due to severe hypercalcemia detected during biochemical evaluation, along with markedly elevated serum PTH levels. One of the key diagnostic factors in our patient was the coexistence of elevated PTH, low phosphorus levels, high ALP, and vitamin D deficiency. This biochemical profile helps exclude benign differentials, particularly familial hypocalciuric hypercalcemia (FHH). Furthermore, the patient's urine calcium/creatinine ratio, as high as 0.7, also excludes FHH.[11] The absence of pathological findings in genetic and hormonal screening for MEN syndromes, along with the

ultrasound findings, supports the diagnosis of sporadic adenoma-induced PHPT.

The literature has reported a higher rate of symptomatic presentation in childhood PHPT cases compared to adults, with musculoskeletal findings being particularly prominent.[4,11] The symptoms and distinct radiological findings of bone involvement in our patient demonstrate the destructive effects of long-term PTH exposure on the skeletal system.

MRI and CT revealed widespread heterogeneous signal changes and sclerotic areas in both tibias, the vertebral columns, ribs, humerus, and maxillary sinuses, consistent with advanced bone involvement and a mass in the maxillary sinus, suggesting a diagnosis of brown tumor. These lesions are non-neoplastic giant cell foci that develop secondary to hyperparathyroidism and exhibit pronounced osteoclastic activity. In cases of brown tumor reported by Guedes et al., the lesions, which presented with lytic and destructive appearances in bone, were histopathologically reported to be giant cell structures with hemosiderin-laden, vascular stroma.[6] In our case, radiological findings, a bone mineral density z-score of -3.5, and widespread skeletal involvement support the diagnosis of brown tumor. Although such lesions are histologically benign, they can be locally aggressive and cause severe structural deformities if diagnosis is delayed. In the differential diagnosis of brown tumor, it is important to distinguish them from giant cell bone tumors and infiltrative bone diseases such as Langerhans cell histiocytosis; however, the most critical differentiating factors are the presence of concomitant marked PTH elevation and hypercalcemia.[6,7] The literature has reported that brown tumors are more common in cases of long-standing hyperparathyroidism, in postmenopausal women, and after the age of 50, while they are extremely rare before puberty.[6] In this context, the development of diffuse brown tumor that we described in our 16-year-old female patient is one of the rare conditions described in the literature; this can be explained by the fact that the disease progresses with advanced bone involvement, meaning that it remains undiagnosed for a long time. Bone lesions associated with brown tumors typically show regression following parathyroidectomy in the majority of cases. Effective and appropriate treatment of hyperparathyroidism leads to suppression of osteoclastic activity and is accompanied by the emergence of new bone formation.[6] Consistent with the literature, follow-up brain magnetic resonance imaging performed at the eighth postoperative month in our patient demonstrated a 60% reduction in the maxillary mass lesion (Fig. 4). Furthermore, follow-up plain radiographs obtained at the twelfth month revealed a decrease in sclerotic changes in the bones, with complete resolution observed in some lesions (Fig. 2).

Another notable aspect of our case is the difficulty in localizing the adenoma and the failure of the initial surgical attempt. Preoperative accurate localization of a parathyroid adenoma is crucial, especially when minimally invasive parathyroidectomy is planned. Cervical USG and 99mTc-sestamibi parathyroid scintigraphy are traditionally the first-line imaging methods. In adult series, both methods have a sensitivity of approximately 70–85% in cases of PHPT with a single adenoma, and diagnostic accuracy increases when used together.[12,13] Imaging methods can be inadequate in pediatric patients due to the small size of the glands, potential ectopic location, and unclear boundaries with the thyroid tissue. Ultrasound and Tc-99m sestamibi scintigraphy, in particular, can lead to false-negative results even in experienced hands. In such cases, advanced imaging techniques such as 4D-CT or intraoperative localization with accurate marking are critical for successful surgery.[13] The adenoma was not detected in our patient's first operation. Subsequently, 4D-CT localized the adenoma, and interventional radiology-guided localization allowed a successful resection in the second attempt. This case highlights the importance of a multidisciplinary approach and, when necessary, the use of advanced

imaging techniques in PHPT, a rare condition in childhood.

The severe hypocalcemia that developed in our patient following adenoma excision was found to be consistent with hungry bone syndrome. This syndrome is a clinically significant condition characterized by increased bone resorption and turnover due to long-term PTH administration due to hyperparathyroidism. This syndrome results from the rapid absorption of calcium from the circulation by the bones following surgical excision of the adenoma. The literature reports that the incidence of HBS ranges from 25% to 90% in patients with skeletal involvement, while this rate is significantly lower at 0% to 6% in those without skeletal involvement.[8,9] Particularly in the preoperative period, severe vitamin D deficiency, the presence of a widespread brown tumor, and high ALP levels placed our patient at high risk for HBS. Despite active vitamin D therapy and high-dose oral and intravenous calcium replacement therapy for hypocalcemia, which began early after surgery, hypocalcemia persisted, accompanied by concurrent hypophosphatemia and hypomagnesemia. Because magnesium deficiency suppresses PTH secretion and weakens the calcium response, ensuring appropriate doses of magnesium replacement is critical for treatment. In our patient, stabilization of serum calcium levels was achieved after approximately 10 days of intensive intravenous and oral calcium therapy. While the duration of HBS varies from patient to patient, some cases may require weeks of intravenous supplemental therapy. Therefore, risk factors for the development of HBS should be identified preoperatively, and treatable risk factors, such as vitamin D deficiency, should be corrected before surgery. Due to osteoporosis secondary to long-term hypercalcemia, our patient received physical therapy support after discharge. Due to significant osteoporosis, bisphosphonate therapy was planned to support skeletal reconstruction. Children with parathyroid adenomas who carry this level of metabolic burden after surgery require follow-up by a multidisciplinary team consisting of pediatric endocrinology, surgery, interventional radiology, and physical therapy.

Conclusion

The patient we present is a remarkably rare case, demonstrating both the diagnostic challenges and systemic complications of PHPT in the pediatric age group. Although rarely seen in children presenting with widespread bone pain, PHPT should be considered in the differential diagnosis. In patients with parathyroid adenoma, accurate preoperative localization of the adenoma, along with assessment of risk factors for complications such as hungry bone syndrome—including age, elevated PTH and ALP levels, and low vitamin D status—and appropriate postoperative management of hypoparathyroidism and bone reconstruction directly influence treatment success and the recovery process.

Ethical approval

Informed consent was obtained from the patient and her parents for this publication.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: AFY, MB; data collection: AFY, NÇ, MÖ; analysis and interpretation of results: AFY, FÖÇ, İÇ; draft manuscript preparation: AFY. 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 rare cause of congenital diarrhea: a homozygous *AGR2* frameshift variant in an infant

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ABSTRACT

Background. Congenital diarrheal disorders and enteropathies (CODE) are rare genetic conditions presenting with severe diarrhea and growth failure beginning in infancy. Biallelic variants in the anterior gradient 2 (*AGR2*) gene have recently been associated with a cystic fibrosis–like disorder characterized by multisystem involvement, including gastrointestinal and respiratory manifestations.

Case Presentation. We report a male infant born to consanguineous parents, who presented with severe congenital secretory diarrhea starting in the neonatal period, failure to thrive, dehydration, and metabolic acidosis. The diarrhea was refractory to bowel rest, suggesting a secretory mechanism. Stool studies, fecal elastase, sweat chloride testing, and *CFTR* gene analysis were normal. Endoscopic evaluation revealed antral gastritis, bulbitis, and duodenitis, with duodenal biopsies showing villous flattening. The patient developed recurrent hyponatremia requiring prolonged oral sodium supplementation and experienced a single episode of bronchiolitis, which may represent either a possible early respiratory manifestation or a coincidental common infantile infection. Whole exome sequencing identified a homozygous frameshift variant in the *AGR2* gene (c.247_250del; p.His83ValfsTer4), and parental testing confirmed autosomal recessive inheritance.

Conclusion. This case expands the clinical spectrum of AGR2-related disease by highlighting a predominantly gastrointestinal presentation with severe congenital secretory diarrhea, failure to thrive, electrolyte imbalance, and a possible early respiratory manifestation. Given the rarity of this condition, AGR2 deficiency may be considered in selected infants presenting with severe congenital diarrhea and failure to thrive, particularly in the setting of consanguinity, even in the absence of definite pulmonary involvement.

Key words: *AGR2*, congenital diarrhea, failure to thrive, infant, mucus barrier.

Congenital diarrheal disorders and enteropathies (CODE) are a group of rare diseases that primarily affect intestinal epithelial cell function, leading to diarrhea and impaired growth beginning in infancy. Affected patients often require lifelong fluid and nutritional support.[1] As most cases of CODE are associated with single-gene defects, their prevalence is increased in populations in which consanguineous marriages are common. Next-generation sequencing has been used increasingly in recent years as a powerful tool to identify known and novel pathogenic variants causing congenital diarrhea.[1,2]

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AGR2, encoded by the anterior gradient 2 (*AGR2*; MIM *606358) gene, is an endoplasmic reticulum resident-protein disulfide isomerase that catalyzes disulfide bond formation between cysteine residues during protein folding.[3] AGR2 is highly expressed in mucus-secreting tissues, including the lungs and gastrointestinal tract. Secreted mucins, the main components of mucus, are high–molecular-weight glycoproteins containing numerous cysteine residues that facilitate proper folding and multimerization through disulfide bond formation, and AGR2 is required for the correct processing of gel-forming mucins.[3,4] Biallelic *AGR2* variants have recently been identified as the cause of a cystic fibrosis–like disorder characterized by recurrent respiratory infections and failure to thrive, with or without diarrhea (RIFTD; MIM #620233).[3,5] To date, only a very limited number of patients with AGR2-related disease have been reported, highlighting the rarity of this condition and the need for further clinical descriptions.

In this case report, we report an infant from consanguineous parents, who presented with early-onset congenital diarrhea and failure to thrive, in whom exome sequencing identified a homozygous frameshift variant in the *AGR2* gene.

Case Presentation

The patient was a male infant born at 38 weeks of gestation with a birth weight of 2850 g to consanguineous parents (first-degree cousins) of Syrian origin. There was no family history of chronic diarrhea, recurrent infections, or other known genetic disorders. He was referred to our hospital at 2 months of age with persistent diarrhea and failure to thrive that had started on postnatal day 15. On admission, his weight was 3100 g. Physical examination revealed dehydration, abdominal distension, and severe diaper dermatitis. He was being fed standard infant formula and had watery diarrhea 10–15 times per day. Initial laboratory investigations showed urea 15 mg/dL, creatinine 0.76 mg/dL, AST 36 U/L, ALT 19 U/L, total protein 44 g/L, albumin 28 g/L, sodium 133 mEq/L, chloride 112 mEq/L , potassium 4.2 mEq/L, calcium 8.5 mg/dL, phosphorus 3.5 mg/dL, C-reactive protein 96.3 mg/L, white blood cell count 38,250/μL, hemoglobin 8.6 g/dL, mean corpuscular volume 92.6 fL, and platelet count 386,000/μL. Venous blood gas analysis revealed severe metabolic acidosis (pH 7.14, bicarbonate 10.7 mmol/L, base excess −17.5 mmol/L). Stool microscopy, rotavirus and adenovirus antigen tests, stool cultures and stool reducing substances were negative. Stool electrolyte analysis could not be performed. Fecal elastase level was normal (286 μg/g), and sweat chloride test results were within the normal range. Comprehensive metabolic and immunologic evaluations were unremarkable, including acylcarnitine profile, plasma and urine amino acids, urine organic acids, serum immunoglobulin levels, and lymphocyte subset analysis. *CFTR* gene analysis was normal. Broad-spectrum antibiotic therapy and intravenous hydration were initiated. *Klebsiella pneumoniae* was detected in the blood cultures, and the patient was treated for culture-proven sepsis. The elevated inflammatory markers were transient and resolved with supportive treatment, and no evidence of recurrent or persistent systemic inflammatory response was observed during follow-up. As diarrhea did not improve with bowel rest, secretory diarrhea was suspected. Total parenteral nutrition was initiated, and feeding was switched to an amino acid–based formula. Upper gastrointestinal endoscopy and colonoscopy were performed. Endoscopy revealed antral gastritis, bulbitis and duodenitis (Fig. 1), whereas colonoscopy findings were normal. Histopathological examination of gastric biopsies demonstrated Helicobacter pylori–negative chronic gastritis of moderate severity. Duodenal biopsies showed widespread villous flattening with an intraepithelial lymphocyte count of 8 per 100 epithelial cells (Fig. 2). Colonic biopsies revealed normal mucosa. During follow-up, the patient developed recurrent hyponatremia, with sodium levels decreasing to as low as 128 mmol/L, necessitating intravenous

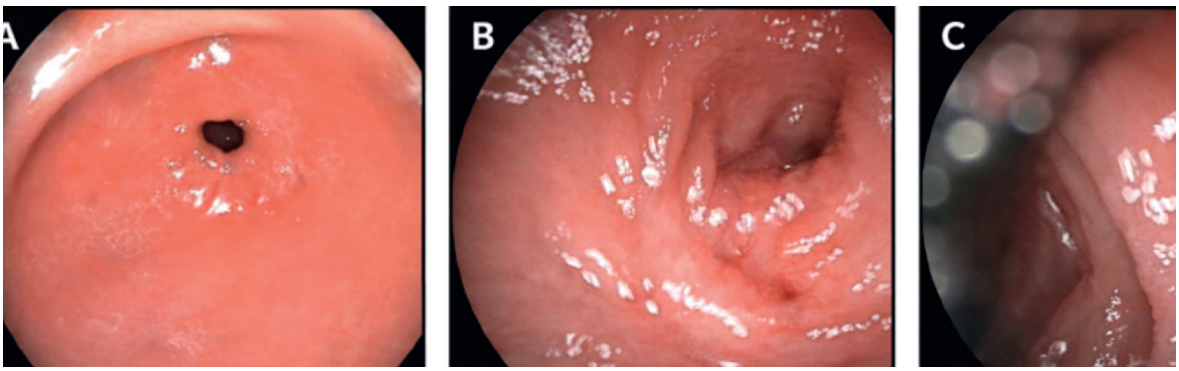

Fig. 1. Upper gastrointestinal endoscopy findings.
(A) Antral mucosa showing diffuse mucosal hyperemia, consistent with antral gastritis. **(B)** Duodenal bulb demonstrating mucosal hyperemia and edema, compatible with bulbitis. **(C)** Second portion of the duodenum showing mucosal edema, consistent with duodenitis.

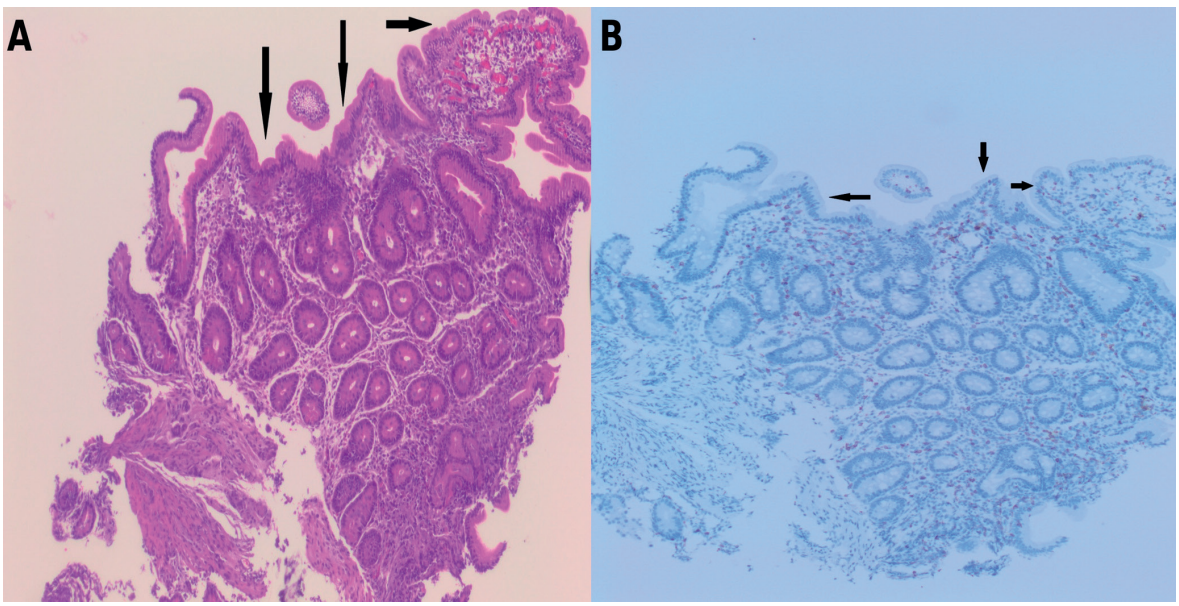

Fig. 2. Histopathological findings of the duodenal biopsies.
(A) Hematoxylin and eosin–stained section of the duodenal mucosa showing marked villous atrophy and villous flattening (black arrows). Original magnification ×200. **(B)** CD3 immunohistochemical staining demonstrating increased intraepithelial lymphocytes, with an approximate count of 8 intraepithelial lymphocytes per 100 enterocytes (black arrows). Original magnification ×200.

correction followed by ongoing oral sodium supplementation, which is still required. Currently, he is fed with an amino acid–based formula, receiving nutrition orally and via intermittent nasogastric tube feeding, and continues oral sodium supplementation. From the age of 4 months onward, the frequency of diarrhea gradually decreased, and bowel movements normalized to 1–2 times per day. However, intermittent abdominal distension and vomiting persisted, necessitating continued partial nasogastric feeding.

At the most recent evaluation at 6 months and 18 days of age, his weight was 6.6 kg (SDS −1.91), length 63 cm (SDS −2.56), and body mass index 16.6 kg/m² (SDS −0.51). Weight-for-length was preserved (SDS −0.33). At 6.5 months of age, he was hospitalized once for bronchiolitis. Whole exome sequencing identified a homozygous

Table I. Individual *AGR2* variants and associated clinical features reported in the literature and in the present case.

Study		Homozygous *AGR2* variant (NM_006408.4)	Age at onset	Gastrointestinal manifestations	Respiratory involvement	Failure to thrive	Clinical course/ outcome (age at last follow-up)
Bertoli-Avella et al.[5] (9 families, 13 patients)	**Patient 1**	c.211C>A (p.Pro71Thr) exon 4	2 wk	None	Chronic cough, exertional dyspnea, mild bronchiectasis	Yes, weight below 5th percentile	Childhood
	Patient 2	c.211C>A (p.Pro71Thr) exon 4	6 mo	None	Chronic cough, mild bronchiectasis	Yes, weight below 5th percentile, height at 10th percentile	Childhood
	Patient 3	c.211C>A (p.Pro71Thr) exon 4	1 wk	None	Chronic cough, recurrent wheezing episodes, dyspnea	Yes, weight below 5th percentile	Childhood
	Patient 4	c.349C>T (p.His117Tyr) exon 6	Birth	Acute gastroenteritis, vomiting, severe gastroesophageal reflux, chronic diarrhea	Chronic cough, pneumonia, hyperactive airway disease	Yes	Childhood
	Patient 5	c.349C>T (p.His117Tyr) exon 6	2 d	Chronic diarrhea, episodic vomiting	Mild respiratory tract infections	Yes, weight and height below 5th percentile	Infancy
	Patient 6	c.349C>T (p.His117Tyr) exon 6	1 yr	None	Chronic cough, severe pneumonia	Yes	Childhood
	Patient 7	c.330+1G>T, intron 5	8 mo	Hepatomegaly	Interstitial lung disease	Yes	Deceased
	Patient 8	c.330+1G>T, intron 5	10 d	Choking, vomiting, chronic diarrhea, hepatomegaly	Recurrent wheezing episodes, patch areas of ground glass appearance and scattered consolidations in both lungs	Yes	Childhood

GI: gastrointestinal.

Table I. Continued.

Study		Homozygous *AGR2* variant (NM_006408.4)	Age at onset	Gastrointestinal manifestations	Respiratory involvement	Failure to thrive	Clinical course/ outcome (age at last follow-up)
	Patient 9	Large deletion (exon 1-7 chr7:16834456-16918247)	6 mo	None	Bronchiectasis, chronic cough	Yes	Childhood
	Patient 10	c.349C>T (p.His117Tyr) exon 6	Birth	Chronic diarrhea (improved after 2 yr), hepatomegaly	Chronic cough, pleural effusion, hilar lymphadenopathy, bronchiectasis	Yes, weight below 3rd percentile	Childhood
	Patient 11	c.349C>T (p.His117Tyr) exon 6	Birth	Chronic diarrhea	Chronic cough, hilar lymphadenopathy	Yes, weight below 3rd percentile	Early childhood
	Patient 12	c.330+1del, intron 5	2 yr	Persistent vomiting, hepatomegaly, persistent cholestasis	Bronchiectasis, chronic cough	Yes	Childhood
	Patient 13	c.428G>A (p.Gly143Glu) exon 7	3 d	Chronic diarrhea, abdominal distention with prominent veins	Subsegmental atelectasis	Yes, weight and height below 5th percentile	Early childhood
Al-Shaibi et al.[7]	**Patient 14**	c.349C>T (p.His117Tyr)	Birth	Chronic diarrhea, upper and lower GI mixed chronic and active cellularity inflammation with clear goblet cell depletion and apoptosis	Bilateral upper chest infiltration with left lower atelectasis	Yes, weight below 3rd percentile	Early childhood
	Patient 15	c.349C>T (p.His117Tyr)	Birth	Chronic diarrhea, vomiting, upper and lower GI mixed chronic and active cellularity inflammation with clear goblet cell depletion and apoptosis	Reactive airway disease	Yes	Early childhood

GI: gastrointestinal.

Table I. Continued.

Study		Homozygous *AGR2* variant (NM_006408.4)	Age at onset	Gastrointestinal manifestations	Respiratory involvement	Failure to thrive	Clinical course/ outcome (age at last follow-up)
Takada et al.[3]	**Patient 16**	c.250A>C (p.Ser84Arg)	4 mo	Gastroesophageal reflux, chronic esophagitis and gastritis, colon biopsy showing crypt distortion, cryptitis, patchy lymphoplasmacytic inflammation, and decreased goblet cells, suggesting ulcerative colitis	Recurrent sinusitis and upper respiratory infections, Bronchiectasis	No	Adolescence
	Patient 17	c.250A>C (p.Ser84Arg)	3 mo	Esophagitis, gastric ulcers and atrophy, and severe pyloric stenosis	Progressive respiratory failure requiring a bi-pulmonary transplantation	Yes, height below 3rd percentile	Adolescence
Present case	Present case	c.247_250del (p.His83ValfsTer4)	15 d	Chronic diarrhea (improved after 4 mo), vomiting, Upper GI endoscopy showing antral gastritis, bulbitis, and duodenitis, with duodenal biopsies showing villous flattening.	A single bronchiolitis attack	Yes, weight and height below 3rd percentile	Infancy

GI: gastrointestinal.

frameshift variant in *AGR2* (NM_006408.4): c.247_250del (p.His83ValfsTer4). The American College of Medical Genetics and Genomics (ACMG) criteria classifies this variant as likely pathogenic, based on PVS1 and PM2 criteria. Parental testing confirmed heterozygous carrier status for the same variant in both parents, consistent with autosomal recessive inheritance. A heterozygous variant of uncertain significance (VUS) in *GUCY2C*, which encodes guanylate cyclase C, a receptor involved in intestinal fluid and electrolyte secretion, was also detected in the patient and his asymptomatic father. Although gain-of-function variants in *GUCY2C* have been associated with autosomal dominant forms of early-onset chronic diarrhea[6], its presence in an asymptomatic parent supported its classification as a secondary finding unlikely to explain the clinical phenotype. The clinical features of the patient in comparison with previously reported AGR2-related cases are summarized in Table I. Written informed consent was obtained from the patient's parents for the publication of this case report.

Discussion

Congenital diarrheal disorders and enteropathies (CODE) arise from structural and functional defects of absorptive, enteroendocrine, or inflammatory cells within the intestinal epithelium. These defects are determined by mutations in genes expressed throughout the gastrointestinal tract and are most commonly inherited in an autosomal recessive manner. In the first weeks of life, patients affected by CODE typically present with severe diarrhea that can lead to life-threatening dehydration and metabolic acidosis.[7] Advances in genomic sequencing have enabled the identification of novel genetic etiologies; however, AGR2-related disease remains extremely rare, with only a limited number of patients reported to date.

Goblet cells express AGR2, a protein disulfide isomerase that is essential for mucus production, which coats the intestinal epithelium and provides protection against infectious and toxic agents.[4] The mucus barrier plays a critical role in preventing bacterial invasion and shielding epithelial cells from luminal aggressors, including gastric acid. Mucin 2 (MUC2) is the major gel-forming mucin in the intestine and defective processing or loss of MUC2 leads to impaired mucus barrier integrity and promotes intestinal inflammation.[8] While MUC2 is the predominant gel-forming mucin in the intestine, Mucin 5AC (MUC5AC) and Mucin 6 (MUC6) are the principal gel-forming mucins in the stomach, whereas MUC5AC and Mucin 5B (MUC5B) are primarily expressed in the respiratory tract.[3,8,9] Recurrent respiratory infections and failure to thrive, with or without diarrhea (RIFTD) results from impaired mucus biosynthesis, and different AGR2 variants affect distinct types of mucus.[3,5]

Previous studies have highlighted the multisystem nature of AGR2-related disease. Bertoli-Avella et al. reported 13 patients from nine unrelated families with a previously undescribed genetic disorder characterized by recurrent lower respiratory infections, chronic diarrhea, and failure to thrive, a clinical phenotype closely resembling cystic fibrosis. This seminal study provided the first comprehensive evidence linking biallelic AGR2 variants to a cystic fibrosis–like multisystem disorder.[5] In another study, Al-Shaibi et al.

investigated siblings with congenital diarrhea who developed severe infantile inflammatory bowel disease due to AGR2 deficiency. Histopathological examination revealed infantile enteropathy, patchy lymphocytic infiltration in the gastric mucosa and extensive intestinal metaplasia characterized by absence of parietal cells and the presence of eosinophilic Paneth-like cells, underscoring the broad gastrointestinal involvement associated with AGR2 dysfunction.[8]

Our patient exhibited a predominantly gastrointestinal phenotype, characterized by severe congenital secretory diarrhea, failure to thrive, electrolyte imbalance, together with a

single episode of bronchiolitis, which cannot be definitively attributed to AGR2-related pulmonary disease but may represent either an early respiratory manifestation or a coincidental common infection of infancy. Longitudinal follow-up and the occurrence of recurrent or persistent respiratory symptoms would be required to establish definite pulmonary involvement in AGR2-related disease in this patient. While gastric biopsies in our case demonstrated Helicobacter pylori–negative chronic gastritis without intestinal metaplasia, duodenal biopsies showed widespread villous flattening, supporting the presence of congenital enteropathy. Although stool electrolyte analysis could not be performed, the persistence of diarrhea despite bowel rest and total parenteral nutrition strongly supported a secretory mechanism in this patient. Notably, diarrhea gradually improved with age, suggesting partial intestinal adaptation, a feature that has been variably reported in previously described patients.[5] These findings further support the concept that AGR2-related disease represents a clinical spectrum, in which the predominant organ involvement and disease severity may vary according to the specific AGR2 variant and the affected mucus subtype. The clinical and genetic characteristics of previously reported AGR2-related cases and the present patient are summarized in Table I, highlighting the phenotypic variability of AGR2-related disease.

A notable clinical feature in our patient was recurrent hyponatremia requiring prolonged oral sodium supplementation, despite normal sweat chloride test results and the absence of *CFTR* mutations. In contrast to cystic fibrosis, in which electrolyte imbalance results from impaired salt reabsorption in sweat glands, we considered that hyponatremia in AGR2-related disease primarily arises from intestinal sodium loss secondary to chronic secretory diarrhea and impaired epithelial barrier function.

The identified homozygous frameshift variant in the *AGR2* gene (c.247_250del; p.His83ValfsTer4) is predicted to result in a premature termination codon and subsequent loss of protein function, consistent with the established loss-of-function pathogenic mechanism of biallelic *AGR2* variants. Parental carrier testing confirmed autosomal recessive inheritance, further supporting the causal role of this variant in the observed clinical phenotype. The absence of alternative genetic explanations for congenital diarrhea in our patient strengthens the genotype–phenotype correlation.

This case report has several limitations. First, functional studies assessing the direct impact of the identified *AGR2* variant on mucus biosynthesis and epithelial barrier function could not be performed. Second, stool electrolyte analysis was not available, which would have provided biochemical confirmation of secretory diarrhea.

In conclusion, this case expands the clinical spectrum of AGR2-related disease by demonstrating a predominantly gastrointestinal presentation characterized by severe congenital secretory diarrhea and electrolyte imbalance requiring prolonged sodium supplementation. Partial clinical improvement over time suggests phenotypic variability and possible intestinal adaptation. Given the rarity of this condition, AGR2 deficiency may be considered in selected infants presenting with severe congenital diarrhea, failure to thrive, electrolyte imbalance, particularly in the setting of consanguinity, even without definite pulmonary involvement.

Ethical approval

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

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: MA; data collection: ACE, HNK, HTÇ, MA; analysis and interpretation of results: EÖ, HNK, MA; draft manuscript preparation: MA. 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

Post-transplant autoimmunity in a child: a lupus-like syndrome emerging in the context of chronic graft-versus-host disease

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ABSTRACT

Background. Autoimmune manifestations are increasingly recognized as late complications following hematopoietic stem cell transplantation (HSCT), particularly in association with chronic graft-versus-host disease (cGvHD). However, the occurrence of systemic lupus erythematosus (SLE)-like features remains extremely rare, especially in pediatric patients. Understanding the mechanisms underlying such manifestations, including the role of mixed chimerism, is important for early recognition and management.

Case Presentation. We report the case of a girl with thalassemia major who underwent HSCT from a fully matched unrelated donor at the age of six years. Her early post-transplant course was complicated by gastrointestinal cGvHD, followed by autoimmune hemolytic anemia and arthritis, which responded to corticosteroids and methotrexate. Four years post-HSCT, she developed a lupus-like syndrome characterized by malar rash, serositis, cytopenias, arthritis, high-titer antinuclear antibodies (ANA), elevated anti-double-stranded DNA (anti-dsDNA) antibodies, and low complement levels, fulfilling the American College of Rheumatology classification criteria for SLE. At the time of symptom onset, mixed chimerism was documented, with a notable proportion of recipient-derived lymphocytes. Treatment with mycophenolate mofetil and hydroxychloroquine led to rapid clinical and laboratory improvement.

Conclusion. This case illustrates the evolving nature of post-transplant immune dysregulation and suggests that declining donor chimerism may contribute to the reactivation of autoreactive lymphocytes, leading to atypical autoimmune manifestations. In pediatric patients presenting with unusual post-transplant symptoms, careful clinical assessment and immune monitoring may aid in timely diagnosis. Individualized immunosuppressive therapy can facilitate symptom control and support favorable long-term outcomes.

Key words: autoimmune diseases, graft vs host disease, hematopoietic stem cell transplantation, systemic lupus erythematosus.

Autoimmune complications are increasingly recognized as a late effect of hematopoietic stem cell transplantation (HSCT), and they can arise following transplantation for both malignant and non-malignant hematologic conditions. The most commonly encountered autoimmune complications are immune-mediated cytopenias, including autoimmune hemolytic anemia, immune thrombocytopenia, and neutropenia.[1] These manifestations are thought to arise from

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a breakdown of central and peripheral immune tolerance mechanisms. While dysfunction of regulatory T cells (Tregs), which normally suppress autoreactive lymphocytes, plays a central role, additional mechanisms have also been implicated, including impaired thymic reconstitution, dysregulated B-cell homeostasis with autoantibody production, aberrant cytokine signaling, and delayed immune reconstitution following HSCT.[2-4] Disruption of these tightly regulated processes may ultimately lead to unrestrained autoreactivity and the development of autoimmune disease.

Chronic graft-versus-host disease (cGvHD) remains a significant and often debilitating complication of allogeneic HSCT, with incidence rates reported between 30% and 70%, depending on various transplant-related factors.[5] The disease is marked by a wide spectrum of clinical presentations and may closely resemble classical autoimmune disorders, including systemic sclerosis, primary biliary cholangitis, and Sjögren's syndrome.[6,7]

Chimerism represents a key immunological factor implicated in the development of post-transplant autoimmunity. It refers to the coexistence of donor- and recipient-derived hematopoietic cells following HSCT and is typically classified as full donor chimerism or mixed chimerism. In the setting of mixed chimerism, the persistence of recipient immune cells alongside donor cells may contribute to immune dysregulation through impaired immune tolerance, altered antigen presentation, and ongoing immune activation.[8] Accumulating evidence indicates that mixed chimerism may predispose patients to autoimmune phenomena after HSCT, underscoring the importance of regular chimerism monitoring during long-term follow-up.

Although autoimmune features are frequently observed in cGvHD, lupus-like presentations remain exceedingly rare and are only sporadically reported. In this report, we present an unusual case of cGvHD that manifested with clinical and serological features strongly suggestive of systemic lupus erythematosus (SLE).

Case Presentation

A female infant was diagnosed with thalassemia major at six months of age during the evaluation of anemia. From early infancy, she required regular red blood cell transfusions. Due to the chronic transfusion burden, her serum ferritin level was measured at 1082 ng/mL (normal range: 10-290 ng/mL) prior to transplantation to assess iron overload. At six years of age, she underwent a fully HLA-matched (10/10) allogeneic HSCT from a matched unrelated donor (MUD). The myeloablative conditioning regimen, which included treosulfan, fludarabine, cyclophosphamide, thiotepa, and antithymocyte globulin (ATG), was followed by GvHD prophylaxis with cyclosporine and low-dose methotrexate. Early post-transplant chimerism analysis revealed 99% donor cell engraftment. Following transplantation, a post-HSCT ferritin level was measured at 678 ng/mL.

On day +42 post-HSCT, the patient presented with fever, diarrhea, and vomiting, prompting a colonoscopy which revealed diffuse mucosal edema and aphthous ulcerations. The histopathological analysis was consistent with grade 3 gastrointestinal GvHD, showing prominent apoptosis, crypt loss, and crypt abscesses. Treatment with methylprednisolone (2 mg/kg/day) resulted in rapid clinical improvement. Full donor chimerism was maintained, and corticosteroids were tapered and discontinued by six months post-transplantation. Around one year after transplantation, the patient developed autoimmune hemolytic anemia, evidenced by a hemoglobin level of 7 g/dL and a positive direct Coombs test. There was no associated GvHD or infectious trigger. Treatment with oral corticosteroids led to prompt clinical improvement and was continued for four months before successful discontinuation without relapse, while cyclosporine was ceased at 17 months post-HSCT.

Approximately three years after HSCT, the patient presented to the pediatric rheumatology clinic with an eight-month history of bilateral knee and wrist pain, associated with morning stiffness lasting approximately one hour. At that time, she maintained mixed chimerism (51%), remained transfusion-independent, and had no clinical evidence of ongoing GvHD. On physical examination, arthritis involving bilateral wrists, knees, and temporomandibular joints was observed. Laboratory testing revealed anemia (hemoglobin: 8.2 g/dL) and a positive direct Coombs test, while ANA, anti-dsDNA, and rheumatoid factor were negative. Complement levels (C3, C4) were within normal limits. The clinical presentation was suggestive of juvenile idiopathic arthritis (JIA) and autoimmune hemolytic anemia, prompting initiation of therapy with methotrexate and methylprednisolone, which led to clinical improvement. However, mild to moderate anemia persisted despite treatment. Corticosteroids were gradually tapered and successfully discontinued by the third month.

At four years post-transplant, and one year following the diagnosis of JIA, the patient presented with malar rash, fatigue, hair loss, and recurrence of joint symptoms, despite ongoing methotrexate therapy. Physical examination confirmed the presence of malar rash and arthritis of the wrists. Laboratory tests revealed cytopenias: hemoglobin 8 g/dL, neutropenia (550/μL), lymphopenia (1,300/μL), and a normal platelet count. Bone marrow biopsy demonstrated preserved trilineage hematopoiesis. Screening for viral infections was negative, and there was no proteinuria. Erythrocyte sedimentation rate (ESR) was elevated at 96 mm/h. Direct Coombs test remained positive. Autoimmune workup revealed high-titer ANA (1:3200, homogeneous pattern), elevated anti-dsDNA (171 IU/L (normal range: <100 IU/ml). Complement analysis showed a decreased C4 level (<10.06 mg/dL; normal: 12–36 mg/dL), while C3 was within the normal range (89.6 mg/dL; normal: 85–160 mg/dL). Liver function tests were within normal limits (AST: 28 U/L [normal: 5–40], ALT: 32 U/L [normal: 10–40]), and kidney function was normal (serum creatinine: 0.44 mg/dL, urea: 19 mg/dL [normal: 19–49]). Urinalysis was unremarkable, and the urinary protein-to-creatinine ratio was 0.2, indicating no significant proteinuria. Extended immunological evaluation revealed normal serum immunoglobulin levels (IgG, IgA, and IgM), normal lymphocyte subsets, and negative extended autoimmune serology, including extractable nuclear antigen (ENA) panel and antiphospholipid antibodies. Transthoracic echocardiography revealed pericardial effusion. At the time of lupus-like disease onset, chimerism analysis demonstrated 25% recipient-derived T cells and 51% recipient-derived B cells.

This constellation of findings fulfilled the classification criteria for SLE according to the American College of Rheumatology (ACR), the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR), and the Systemic Lupus International Collaborating Clinics (SLICC), including: serositis, arthritis, malar rash, Coombs-positive hemolytic anemia, leukopenia, positive ANA, and anti-dsDNA antibodies. The diagnosis was therefore revised to SLE-like disease following HSCT. Treatment with mycophenolate mofetil and hydroxychloroquine was initiated, resulting in complete clinical and laboratory remission within the first month. Fig. 1 outlines the timeline of major clinical events and treatments. She has been followed up for six months with no signs of disease activation. At the most recent visit, complement levels were within the normal range, ANA was positive at a titer of 1:160, and anti-dsDNA was negative.

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

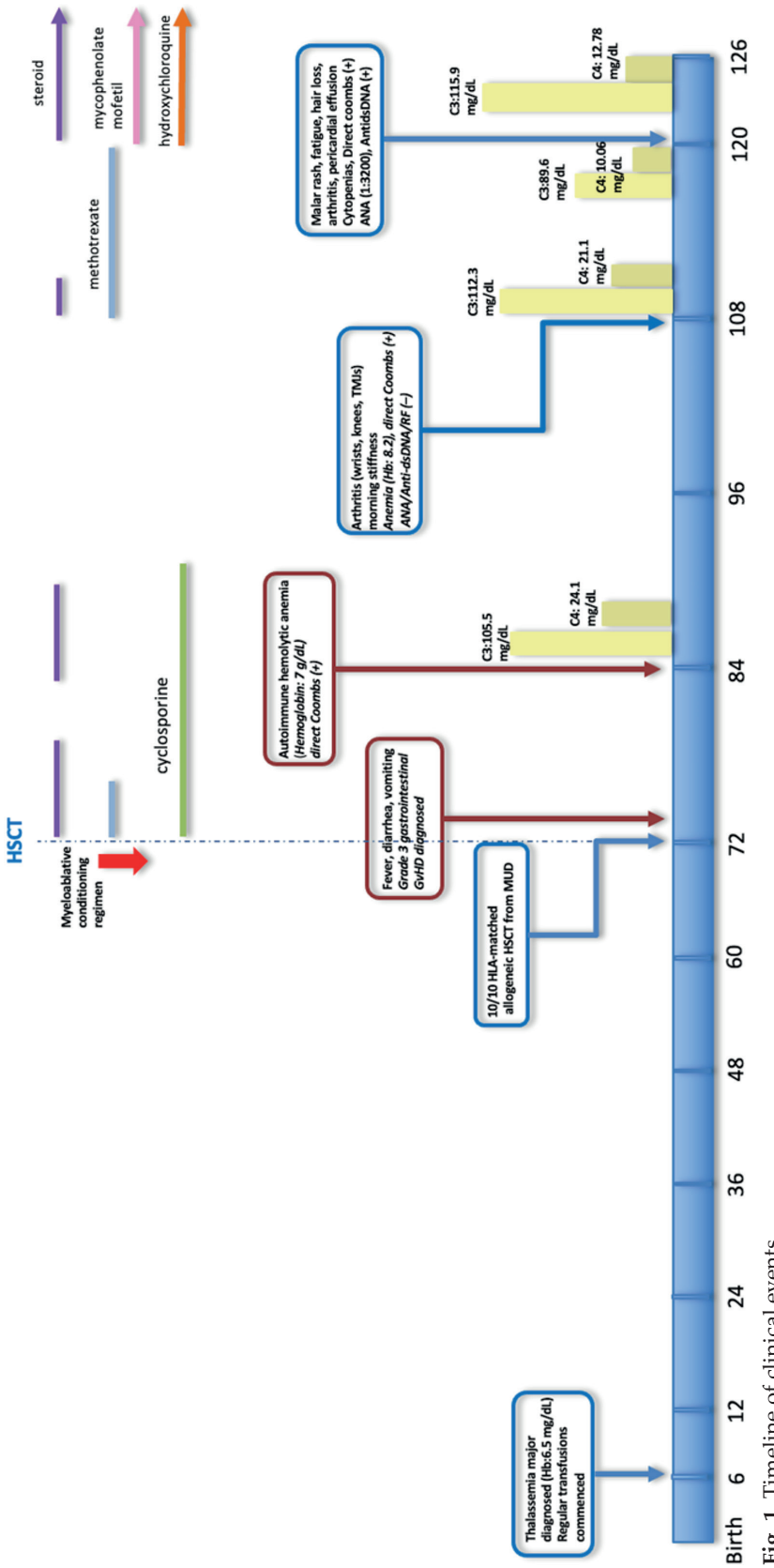

Fig. 1. Timeline of clinical events.

The x-axis represents age in months. Vertical blue and red arrows with inset boxes represent different events in the disease timeline. Horizontal arrows above the timeline indicate immunosuppressive treatments. Vertical yellow bars represent complement C3 and C4 levels. (Normal reference ranges: C3: 85–160 mg/dL; C4: 12–36 mg/dL).

ANA, antinuclear antibody; anti-dsDNA, anti–double-stranded DNA antibody; GvHD, graft-versus-host disease; Hb, hemoglobin; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; MUD, matched unrelated donor; RF, rheumatoid factor; TMJ, temporomandibular joint

Discussion

A growing range of autoimmune phenomena has been recognized as late complications of allogeneic HSCT. Although post-transplant immune dysregulation may resemble several autoimmune diseases, the manifestation of SLE-like features that meet established classification criteria is exceedingly uncommon.

The present case demonstrates a complex and evolving autoimmune course in a pediatric patient who developed a lupus-like syndrome with overlapping features of chronic GvHD and de novo autoimmunity four years after HSCT. This observation raises important questions regarding the immunopathogenesis underlying post-HSCT autoimmunity and how it differs from classical cGvHD.

One proposed mechanism involves reconstitution of a dysregulated immune system, in which impaired central and peripheral tolerance allows autoreactive T and B lymphocytes to survive and expand.[9] Recovery of Tregs following HSCT may be incomplete, or they may be functionally impaired, particularly in the context of prior GvHD and prolonged immunosuppressive therapy. Furthermore, as observed in our patient, mixed chimerism may indicate incomplete immune replacement, with persistence of autoreactive recipient-derived lymphocytes potentially contributing to autoimmunity through impaired tolerance, altered antigen presentation, and ongoing immune activation.[10] The chronological progression from initial gastrointestinal GvHD to the subsequent development of juvenile idiopathic arthritis and, eventually, a lupus-like phenotype raises the possibility that post-transplant immune dysregulation potentially driven by declining donor chimerism may underlie this evolving autoimmune spectrum, allowing reactivation of autoreactive immune cells and breakdown of tolerance. Chimerism monitoring may therefore serve not only as a marker of graft stability but also as a clinically relevant immunologic indicator in patients who develop late autoimmune manifestations. In particular, declining donor chimerism or lineage specific recipient predominance (e.g., T- or B-cell fractions) may reflect incomplete immune replacement and impaired tolerance reestablishment.[11] While evidence remains limited, our case supports the practice of regular, lineage specific chimerism assessment in long term follow-up, especially when new autoimmune symptoms or atypical inflammatory findings emerge.

Although the prevalence of cGvHD is lower in pediatric patients than in adults (approximately 20–50% vs. 60–70% in most series), it remains a clinically important complication in children, particularly as the use of peripheral blood stem cells and unrelated donors becomes more widespread.[12,13] Acute GvHD typically involves the skin, liver, and gastrointestinal tract, whereas chronic GvHD has a broader spectrum and may affect almost any organ. The updated 2020 National Institutes of Health (NIH) diagnostic criteria expanded the definition of cGvHD to include atypical features such as serositis, nephrotic syndrome, and cytopenias; these features were previously excluded under the classical definitions.[14] Autoimmune phenomena, including cytopenias and arthritis, are now increasingly recognized in the context of cGvHD.

Systemic lupus erythematosus–like after HSCT has been reported only sporadically, mostly as isolated case reports. Stylianou et al. described a lupus-like syndrome with renal involvement after allogeneic HSCT in the context of cGvHD, highlighting the clinical resemblance yet potential immunologic distinctiveness of post-transplant autoimmunity.[15] A pediatric case of SLE occurring years after unrelated cord blood transplantation has also been reported, underscoring that lupus phenotypes may emerge late in the post-transplant period.[16] These reports, together with our case, suggest that lupus-like phenotypes can occur across age groups and transplant settings, often with complex overlaps between alloimmune injury (cGvHD) and de novo autoimmunity.

There is a need for treatment guidelines specific to atypical forms of cGvHD, particularly those with autoimmune overlap, as therapeutic approaches often differ from classic cGvHD and remain limited. This need was emphasized in the 2025 NIH Chronic Graft-versus-Host Disease Consensus Conference update.[17] Chronic GvHD is typically managed with corticosteroids, either as monotherapy or in combination with other immunosuppressive agents (tacrolimus, methotrexate, cyclosporine, mycophenolate mofetil), achieving a complete remission rate of 63.5%.[18] While literature remains limited, a previously reported case of lupus-like syndrome presenting with immune complex-mediated diffuse proliferative glomerulonephritis following HSCT responded well to treatment with corticosteroids, cyclophosphamide, and mycophenolate mofetil.[19] Complete clinical and laboratory remission was achieved with the combination of corticosteroids and mycophenolate mofetil in our patient.

Beyond the post-transplant setting, chimerism/microchimerism has long been investigated as a potential contributor to autoimmunity. Microchimerism refers to the presence of a small population of genetically distinct cells (most commonly maternal–fetal) within an individual and has been described in association with autoimmune diseases, including SLE.[20] Studies evaluating maternal microchimerism in SLE have reported variable results, reflecting heterogeneity in detection methods and clinical phenotypes.[21] In juvenile inflammatory myopathies, including juvenile dermatomyositis, microchimeric cells have also been investigated; available data do not consistently support a direct pathogenic role, but they reinforce the concept that chimerism related immune tolerance mechanisms may intersect with pediatric autoimmunity.[22] Although microchimerism differs biologically from post-HSCT mixed hematopoietic chimerism, both phenomena underscore the broader principle that the coexistence of genetically distinct immune cell populations may influence immune tolerance and autoimmunity.

In conclusion, this case underscores the multifaceted and evolving nature of immune dysregulation in pediatric recipients of hematopoietic stem cell transplantation and highlights the critical importance of long-term immunologic surveillance, including serial chimerism analysis. Although the patient is currently in clinical remission, this status should be interpreted with caution, as the duration of follow-up following the onset of lupus-like disease remains limited. Given the dynamic immune reconstitution after HSCT and the presence of mixed chimerism, the risk of disease relapse or progression toward a more systemic autoimmune phenotype cannot be excluded. Therefore, prolonged, and comprehensive follow-up is warranted to monitor for potential reactivation of autoimmune manifestations or the emergence of additional systemic features over time.

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: BM, NAA; data collection: BM, SDA; analysis and interpretation of results: BM, SG,DT; draft manuscript preparation: BM, ZK, NAA. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

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Clarifying the statistical reporting in the multivariate analysis of retinopathy of prematurity biomarkers

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Dear Editor,

I read with interest the article by Liu and colleagues, "Predictive value of serum hsa_circ_0061346, hsa_circ_0000095, and hsa_circ_0068606 expression levels on the severity of retinopathy of prematurity," published in The Turkish Journal of Pediatrics.[1]

However, I would like to point out an apparent inconsistency in the statistical reporting

in Table V that may affect the interpretation of the multivariate model. For "Gestational age," the authors report $\beta = -0.015$ and SE = 0.079, together with Wald $\chi^2 = 13.436$ and $p = 0.851$.[1] When $z = \beta/SE$ is calculated from the reported β and SE, the Wald chi-square statistic is obtained as z^2 (df = 1).[2] Using the values given in the table, $z \approx -0.19$ and $z^2 \approx 0.036$, which is compatible with $p \approx 0.85$ rather than a Wald χ^2 of 13.436. This suggests that the Wald χ^2 value may have been inadvertently misreported (e.g., transcription or cell-shift error), and clarification or correction would be helpful for readers.

Beyond a typographical issue, this discrepancy has important interpretive implications. If the reported p value ($p = 0.851$) is correct, gestational age—one of the most established determinants of ROP—would appear to have no independent association in the multivariable model.[1] This contrasts with the univariable analysis (Table IV: $p < 0.0001$).[1] Such a reversal could arise from strong collinearity with closely related covariates (e.g., birth weight), overadjustment, coding/scaling choices, or other model-specification decisions.[2] Reporting how gestational age was entered into the model and providing basic collinearity diagnostics (e.g., variance inflation factors or correlation structure) would help readers interpret whether the circRNA markers retain independent predictive value beyond prematurity.

In addition, Table II indicates a marked imbalance in key baseline characteristics between the ROP and control groups. The mean gestational age is 30.57 ± 3.16 weeks in the ROP group versus 34.97 ± 1.74 weeks in the control group ($p < 0.0001$), and birth weight also differs substantially (1.56 ± 0.54 kg vs 2.38 ± 0.55 kg; $p < 0.0001$).[1] Given that gestational age is a dominant determinant of ROP risk, differences of this magnitude raise the possibility that observed circRNA expression differences may, at least in part, reflect physiological maturation rather than disease-specific processes. A brief clarification on how these imbalances were handled (and whether additional sensitivity analyses were performed) would strengthen the interpretation of the biomarker findings.

For these reasons, I believe that confirming the Table V values against the original regression output and issuing a correction would be valuable for the scientific record.

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Author contribution

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Source of funding

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Conflict of interest

The authors declare that there is no conflict of interest.

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Response to "Clarifying the statistical reporting in the multivariate analysis of retinopathy of prematurity biomarkers"

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Dear Editor,

We sincerely thank the reader for the careful review of our article and for the valuable comments regarding the statistical reporting and interpretation of the multivariable analysis.[1,2]

After re-examining the original regression output, we confirm that the values of β (−0.015) and SE (0.079) reported for gestational age are correct. According to the Wald test formula (Wald $\chi^2 = [\beta/SE]^2$), the corresponding Wald χ^2 should be approximately 0.036, which is consistent with the reported p value (p = 0.851). Therefore, the Wald χ^2 value of 13.436 presented in Table V resulted from an inadvertent transcription error during manuscript preparation. We appreciate the reader for identifying this issue, and a formal correction will be submitted to ensure the accuracy of the published record.[3]

We agree that gestational age and birth weight are closely related indicators of prematurity and may influence the interpretation of multivariable regression models when included simultaneously. Multivariable adjustment was performed to reduce potential confounding; however, we acknowledge that additional analytical approaches, such as matched or stratified analyses, may further strengthen future studies.

In addition, in the original article, the difference in gestational age between the groups was already stated as a limitation of the study in the Discussion section.

Author contribution

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

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Rethinking gender differences in social media–related eating behaviors

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I read the recent article by Başar Gökcen and Varol entitled *"Problematic social media use and eating behaviors in adolescence: gender-based differences"* with great interest.[1] The study highlights important gender-specific patterns in the associations between problematic social media use, appearance-related social media consciousness, and eating behaviors among adolescents.

While I appreciate the authors' contribution, several methodological and conceptual considerations may help clarify the interpretation of the findings. Although the cross-sectional design is acknowledged as a limitation, some interpretations appear to suggest causal relationships. Given the lack of temporal data, it remains unclear whether problematic social media use leads to unhealthy eating behaviors or whether pre-existing eating patterns and body image concerns drive greater engagement with appearance-focused content. Therefore, this bidirectional possibility should be more explicitly considered when interpreting the reported associations.

In addition, the absence of key potential confounders may have influenced the observed relationships. Factors such as mental health status, socioeconomic background, sleep patterns, and physical activity are closely associated with both social media use and eating behaviors. Previous research indicates that adolescents with mental health difficulties tend to engage more intensively with social media and exhibit higher levels of social comparison[2], while lifestyle factors such as sleep and physical activity are part of broader behavioral clusters that are also linked to dietary patterns.[3] Therefore, without accounting for these variables, the reported associations may partly reflect shared underlying determinants rather than independent effects.

Another important consideration is that the use of mediation analysis in a cross-sectional framework warrants cautious interpretation. Mediation models assume a temporal sequence in which the exposure influences the mediator, which in turn affects the outcome[4]; however, such temporal ordering cannot be established in cross-sectional studies.[5] As a result, the observed indirect effects through the proposed mediator, appearance-related social media consciousness (ASMC), may reflect statistical associations rather than true causal pathways. Therefore, these findings should be interpreted with caution when considered as evidence of mediation.

Finally, the assessment of eating behaviors using instruments such as the Eating Habits Questionnaire for Adolescents (EHQA) may not fully capture male-specific patterns related to muscularity-oriented eating behaviors. Evidence suggests that adolescent boys are more likely to engage in muscle-enhancing practices, including high protein intake, supplement use,

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anabolic steroid use, and intensive exercise.[6] These behaviors, often driven by muscularity-oriented body image concerns, represent a distinct dimension of eating and body-related risk that may not be adequately reflected in traditional measures of unhealthy eating. This may lead to a potential underestimation of maladaptive eating-related behaviors in males and, consequently, may influence the observed gender differences.

Despite these limitations, this study makes an important contribution to the literature on the association between social media and adolescent health behaviors. Future research employing longitudinal designs, objective measures of digital behavior, and more comprehensive, gender-sensitive assessments of eating-related practices will be essential to better understand the complexity of these relationships.

Author contribution

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

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Corrigendum

Author Correction to: "Predictive value of serum hsa_circ_0061346, hsa_circ_0000095, and hsa_circ_0068606 expression levels on the severity of retinopathy of prematurity." [Turk J Pediatr 2025; 67: 798-807.]

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Correction to: Turk J Pediatr 10.24953/turkjpediatr.2025.6725 (published December 30, 2025).

The authors would like to notify that a transcription error occurred during manuscript preparation in Table V of the original article. The Wald χ^2 value for gestational age was incorrectly reported as 13.436, whereas the correct value should be approximately 0.036 based on the reported β and SE values. The original article has been corrected accordingly. The authors would like to apologize for any inconvenience this may have caused.

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