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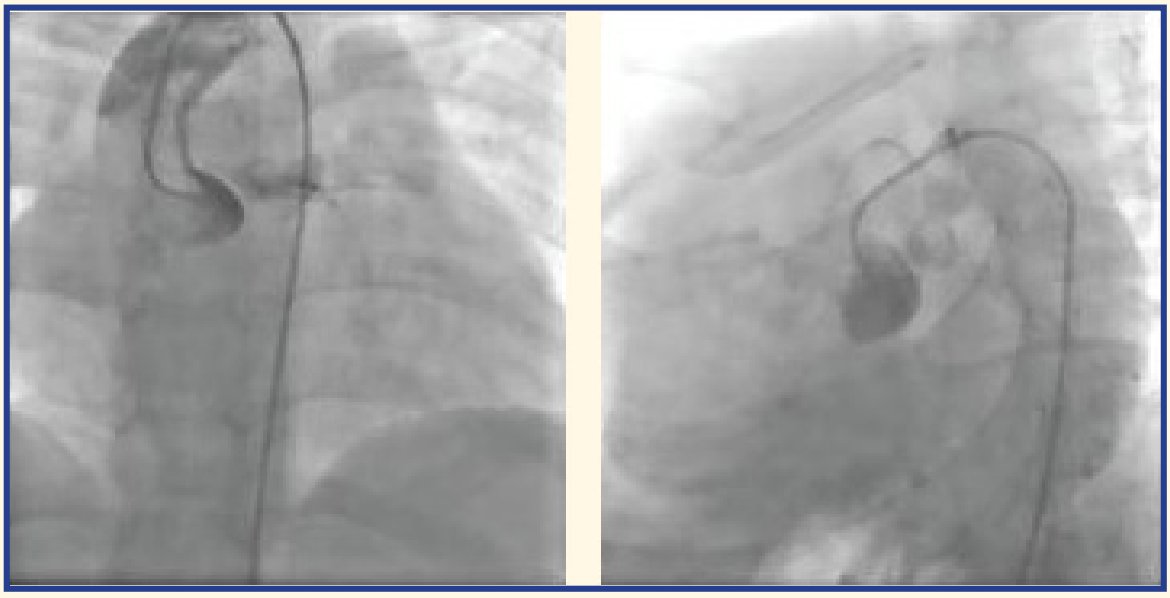

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EDITORIAL

Dear Colleagues,

We are pleased to present the second issue of 2026. This edition features original research and case reports addressing important clinical questions in pediatric medicine.

The articles in this issue span a wide range of pediatric subspecialties, including neonatology, neurology, endocrinology, nephrology, allergy and hematology. Studies exploring the use of point-of-care ultrasound for neonatal vascular access and remote diabetes education demonstrate how technological innovation and novel care models can enhance pediatric practice. Additional articles provide valuable insights into nutritional assessment in spinal muscular atrophy, genetic susceptibility to febrile seizures, predictors of renal outcomes in congenital anomalies, kidney transplantation in ciliopathy, neonatal hypoglycemia, aeroallergen sensitization, sickle cell disease, and novel otoscope in pediatric otoscopy. This issue also includes two instructive case reports that highlight the diagnostic and therapeutic challenges of incomplete Kawasaki disease with severe coronary complications and a rare cause of hemoptysis in childhood.

We sincerely thank our authors, reviewers, and editorial board members for their dedication and invaluable contributions to maintaining the scientific quality of our journal. We hope this issue provides clinicians and researchers with valuable insights, stimulates further research, and ultimately contributes to improving the health and well-being of children.

Best wishes,

Dr. Yeliz Çağan Appak

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Original Article

Point-of-care Ultrasound for Umbilical Venous and Peripherally Inserted Central Catheterization in Preterm Neonates: A Retrospective Study

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ABSTRACT

Aim: Central venous access in preterm neonates is commonly established with umbilical venous catheters (UVCs) or peripherally inserted central catheters (PICCs). However, landmark-based methods often result in malpositioning and complications. This study aimed to evaluate whether point-of-care ultrasound (POCUS) guidance improves initial tip placement accuracy and reduces subsequent clinical outcomes.

Materials and Methods: This retrospective study included preterm neonates (<37 weeks) who underwent UVC or PICC insertion between March 2023 and April 2024. The neonates were grouped by guidance modality: POCUS vs. non-POCUS (conventional landmark and length-based estimation). The primary outcome was optimal tip placement immediately after insertion [UVC: inferior vena cava (IVC)- right atrium (RA) junction; PICC: superior or IVC near the RA], verified by ultrasound or radiography. Secondary outcomes included complications occurring ≥24 hours after insertion, including malposition, infection, thrombosis, and gastrointestinal complications). Continuous and categorical variables were compared using t-tests or Mann-Whitney U tests and chi-square tests, respectively. Two-sided $p<0.05$ was considered statistically significant.

Results: Among 101 neonates (UVC n=55; PICC n=46), the overall optimal tip placement occurred in 64 cases (63.4%). Placement success was significantly higher with POCUS than with non-POCUS guidance: 29/33 (87.9%) vs. 35/68 (51.5%). UVC placement success was 84.2% in the POCUS group versus 47.2% in the non-POCUS group [odds ratio (OR): 5.96; 95% confidence interval (CI): 1.49-23.91]. PICC placement success was 92.9% versus 56.3%, respectively (OR: 10.11; 95% CI: 1.16-88.01). Total complication rates were significantly lower with POCUS for both UVC (OR: 0.24; 95% CI: 0.07-0.88) and PICC (OR: 0.13; 95% CI: 0.02-0.70), driven by low occurrences in gastrointestinal complications and infections.

Conclusion: In preterm neonates, POCUS guidance improves initial catheter tip positioning and it is associated with fewer complications. These findings support the integration of POCUS into routine neonatal vascular access workflows and warrant validation in prospective studies.

Keywords: Point-of-care ultrasound, umbilical venous catheter, peripherally inserted central catheter, preterm neonates

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Introduction

Establishing reliable intravenous access is essential in neonatal intensive care for administering medications, fluids, and parenteral nutrition. In preterm neonates, the fragility and small caliber of peripheral veins make cannulation difficult and increase the risk of extravasation, edema, tissue injury, and pain. As a result, central venous access, most often via umbilical venous catheters (UVCs) or peripherally inserted central catheters (PICCs), is commonly used to provide stable, long-term access.

UVCs provide emergency access through the umbilical stump, while PICCs enable central venous access via a peripheral vein (1,2). Both approaches reduce repeated venous punctures, minimize pain for neonates, and reduce the workload for practitioners, helping maintain stable blood oxygen levels and improving survival rates in preterm neonates (1,2).

However, determining the appropriate insertion length and achieving an optimal tip position can be challenging in small neonates. Conventional landmark-based methods are widely used, but they are prone to malpositioning and repeated repositioning, prolonged procedure durations and increased complication risks (1-4).

Post-insertion imaging is essential in order to verify the catheter tip position. Radiography is widely used but offers only a static snapshot and may fail to detect catheter migration. Repeated radiographic examinations also delay clinical decision-making and expose neonates to additional radiation. Ultrasound, by contrast, allows real-time, bedside visualization of catheter advancement and tip position and also allows for the detection of catheter migration associated with neonate positioning or limb position (5-7). In recent years, point-of-care ultrasound (POCUS) has become an accessible, portable tool for procedural guidance and catheter verification. However, evidence specific to UVC and PICC placement in preterm neonates remains limited.

This study aimed to evaluate whether POCUS guidance improves the accuracy of UVC and PICC tip placement and reduces complications when compared with conventional methods in preterm neonates.

Materials and Methods

Study Design and Participants

This retrospective study included 101 preterm neonates who underwent central venous catheterization in neonatal intensive care units (NICUs) between March 2023 and April 2024. Eligible infants were <37 weeks' gestation and required UVC or PICC for clinical indications (e.g., respiratory distress, the need for prolonged parenteral nutrition, or hyperosmolar/irritant infusions). In order to allow for adequate surveillance monitoring of post-procedural complications, catheters which remained in place for <1 week were excluded. This study was approved by the review opinion of the Clinical Research Ethics Committee of Shenzhen Second People's Hospital (approval number: 2024-369-01PJ, date: 11.11.2024). Consent was waived due to the retrospective design of this study.

Neonates were grouped by catheterization method: POCUS-guided (POCUS) versus conventional (non-POCUS). Assignment to the POCUS group depended on the availability of a radiologist at the bedside when central access was required. When a radiologist was unavailable, catheterization was performed using conventional methods by NICU nurses in order to avoid delays in treatment.

Demographic variables, including sex, postnatal age, gestational age (GA), and birth weight, were retrieved from the electronic medical record. In the POCUS group, catheter placement was performed by a radiologist with over three years of experience using the MyLab seven (Esaote, Genoa, Italy) ultrasound device, equipped with a 9-12 MHz linear array probe. In the non-POCUS group, catheter insertion was performed by two NICU nurses with over two years of experience using conventional landmark- and formula-based estimation methods.

UVC and PICC Placement

For UVCs, in the POCUS group, the UVC tip was guided to the inferior vena cava (IVC) right atrial (RA) junction. If necessary, a small volume (0.5-2 mL) of normal saline was used to enhance tip visualization. In the non-POCUS group, insertion length followed the modified Shukla formula based on anatomical landmarks: (3×birth weight in kg+9)/2+1 cm (3).

For PICCs, in the POCUS group, the PICC tip was guided to the junction of the superior vena cava (SVC) or IVC near the RA junction. Similarly, normal saline was injected as needed for visualization. In the non-POCUS group, the conventional method was used, estimating insertion length based on anatomical landmarks (4).

Tip Verification

After placement, all neonates underwent ultrasound examination and thoracoabdominal radiography in order to verify the catheter tip position (Figure 1). Optimal tip positions were defined as: UVC tip at the IVC-RA junction, approximately 0.5-1.0 cm above the diaphragm; PICC tip in the SVC or IVC near the RA junction (7-11).

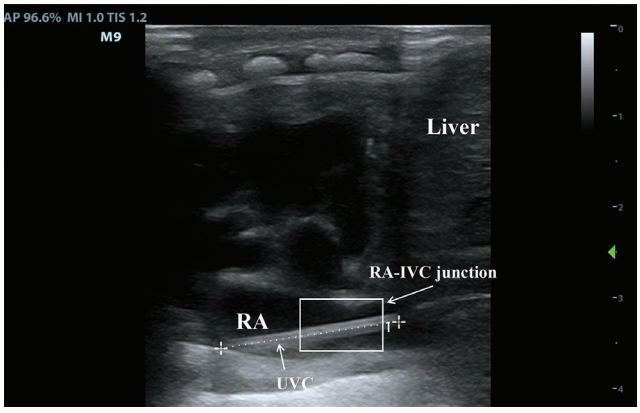

Figure 1. A POCUS scan was conducted to confirm the position of the umbilical venous catheter (UVC) tip after insertion. The tip is seen to be at the junction of the inferior vena cava (IVC) and the right atrium (RA), representing the optimal zone

Outcomes

The primary outcome was the success rate of optimal catheter tip placement immediately after insertion, as confirmed by ultrasound or radiography. Placement failure included the inability to position the catheter tip within the predefined optimal zone. Secondary outcomes were complications occurring ≥24 hours after insertion: malposition, necrotizing enterocolitis (NEC), gastrointestinal complications (e.g., bowel bleeding, distention), pleural effusion, pulmonary hemorrhage, infection, limb swelling, and venous thrombosis. NEC was diagnosed based on the modified Bell's staging, requiring at least Stage II (12). Gastrointestinal bleeding was identified by the presence of gross blood in gastric aspirates or stools, or a positive fecal occult blood test. Bowel distention was defined as a persistent increase in abdominal girth accompanied by radiographic evidence of bowel dilation (11). Infection was defined as a positive blood culture obtained from a peripheral vein or the catheter hub in a symptomatic infant, where no other source of infection was identified. Venous thrombosis was defined as the presence of an echogenic intraluminal mass in a vessel associated with the catheter confirmed by ultrasound.

Statistical Analysis

Continuous and categorical data are presented as means ± standard deviation and frequency (percentage), respectively. Normality was evaluated with the Kolmogorov-Smirnov test. Inter-group comparisons were performed using Student's t-tests or Mann-Whitney U tests for continuous variables and chi-square tests for categorical variables. In order to assess the clinical relevance and magnitude of the effect of POCUS guidance, effect sizes were expressed as odds ratios (OR). Two-sided $p<0.05$ was considered statistically significant. All analyses were performed using SPSS software (version 26, Chicago, IL).

Results

Among the 101 neonates included in this study, 55 underwent UVC insertion, and 46 underwent PICC insertion. Of the UVC cases, 19 were in the POCUS group and 36 in the non-POCUS group. Of the PICC cases, 14 were in the POCUS group and 32 in the non-POCUS group. Baseline postnatal age, GA, and birth weight did not differ significantly between groups for either UVC or PICC (Table I).

The overall success rate of optimal catheter tip placement was 63.37% (64/101). Placement success was significantly higher in the POCUS group than in the non-POCUS group: 87.9% (29/33) vs. 51.5% (35/68). Specifically, for UVC, the POCUS-guided success rate was 84.2% compared with 47.2% in the non-POCUS group [OR: 5.96; 95% confidence interval (CI): 1.49-23.91]. For PICC, the POCUS group achieved a 92.9% success rate, while the non-POCUS group had a 56.3% success rate (OR: 10.11; 95% CI: 1.16-88.01) (Table II).

After insertion, UVC malposition occurred in 22/55 (40.0%), with tips located in the RA (4/22, 18.2%), ductus venosus (8/22, 36.4%), umbilical vein (9/22, 40.9%), and

Table I. Comparison of demographic data for UVC and PICC insertions between the POCUS and non-POCUS groups

	UVC			PICC		
	POCUS group (n=19)	**Non-POCUS group (n=36)**	**p value**	**POCUS group (n=14)**	**Non-POCUS group (n=32)**	**p value**
Sex (Male), n (%)	9 (47.4)	19 (52.8)	0.78	12 (85.7)	22 (68.8)	0.40
Postnatal age (hours)	20.9±12.4	22.3±13.1	0.09	184.3±77.8	139.3±76.2	0.32
GA (days)	220.3±16.0	221.8±18.5	0.76	217.1±19.9	221.8±19.0	0.55
Birth weight (grams)	1,549.0±405.5	1,554.3±508.2	0.97	1,360.0±263.9	1,512.2±406.0	0.38

UVC: Umbilical venous catheters, PICC: Peripherally inserted central catheters, POCUS: Point of care ultrasound, GA: Gestational age

right intrahepatic portal branch (1/22, 4.5%). For PICC, malposition occurred in 15/46 (32.6%): RA 9/15 (60.0%), subclavian 3/15 (20.0%), jugular 2/15 (13.3%), and iliac 1/15 (6.7%). No instances of RA placement were observed in the POCUS group for either catheter type (Table SI).

Post-insertion complications (≥24 hours) were less frequent in the POCUS group. For UVCs, complications occurred in 23/55 (41.8%): 4/19 (21.1%) in the POCUS group versus 19/36 (52.8%) in the non-POCUS group (OR: 0.24; 95% CI: 0.07-0.88) (Table III). Significant differences were observed for gastrointestinal bleeding and bowel distention.

For PICCs, complications occurred in 20/46 (43.4%): 2/14 (14.3%) in the POCUS group versus 18/32 (56.3%) in the non-POCUS group. Although the overall complication rate showed marginal statistical significance (p=0.08), the effect size demonstrated a strong clinical protective trend (OR: 0.13; 95% CI: 0.02-0.70), indicating an 87% reduction in the odds of adverse events under ultrasound guidance. Notably, PICC-related infections occurred in five neonates in the non-POCUS group and in none of the neonates in the POCUS group (p=0.04) (Table III).

Table II. Proportion of successful and failed UVC and PICC in optimal tip placement between the POCUS and non-POCUS groups

	UVC				PICC			
Outcome	**POCUS group (n=19)**	**non-POCUS group (n=36)**	**Odds ratio (95% CI)**	**p value**	**POCUS group (n=14)**	**non-POCUS group (n=32)**	**Odds ratio (95% CI)**	**p value**
Success, n (%)	16 (84.2)	17 (47.2)	5.96 (1.49-23.91)	0.008	13 (92.9)	18 (56.3)	10.11 (1.16-88.01)	<0.001
Failure, n (%)	3 (15.8)	19 (52.8)			1 (7.1)	14 (43.8)		

UVC: Umbilical venous catheters, PICC: Peripherally inserted central catheters, POCUS: Point of care ultrasound, CI: Confidence interval

Table III. Comparison of postoperative complications following UVC insertion between POCUS and non-POCUS groups

	UVC				PICC			
Complications n (%)	**POCUS group (n=19)**	**non-POCUS group (n=36)**	**Odds ratio (95% CI)**	**p-value**	**POCUS group (n=14)**	**non-POCUS group (n=32)**	**Odds ratio (95% CI)**	**p-value**
Necrotizing enterocolitis	1 (5.3)	1 (2.8)	-	1.00	-	-		-
Gastrointestinal bleeding	2 (10.5)	13 (36.1)	0.21 (0.04-0.98)	0.043	2 (14.3)	4 (12.5)	1.17 (0.18-7.53)	0.87
Bowel distention	1 (5.3)	8 (22.2)	0.19 (0.02-0.99)	0.047	0	4 (12.5)	-	0.08
Pleural effusion	0	1 (2.8)	-	1.00	-	-	-	-
Pulmonary hemorrhage	0	1 (2.8)	-	1.00	-	-	-	-
Infection	-	-	-	-	0	5 (15.6)	-	0.04
Limb swelling	-	-	-	-	0	3 (9.4)	-	0.13
Venous thrombosis	-	-	-	-	0	2 (6.3)	-	0.22
Total complications	4 (21.1)	19 (52.8)	0.24 (0.07-0.88)	0.023	2 (14.3)	18 (56.2)	0.13 (0.02-0.70)	0.08

UVC: Umbilical venous catheters POCUS: Point of care ultrasound, PICC: Peripherally inserted central catheters, CI: Confidence interval

Discussion

In this retrospective study, POCUS guidance was associated with improvements in optimal tip placement rates for both UVCs and PICCs and reductions in post-insertion complications when compared with conventional landmark-based methods. These findings are consistent with previous studies showing that real-time ultrasound improves initial positioning accuracy and reduces the need for repositioning and repeated radiographic confirmation.

Correct catheter tip placement is clinically important as malposition can contribute to organ injury, thrombosis, feeding intolerance, and infection. Early UVC placement, ideally performed immediately after birth, has been reported to achieve a higher success rate (13). However, anatomical differences among neonates, particularly in the umbilical vein pathway and the relationship between intrahepatic vessels and the IVC, increase the risk of catheter mispositioning when performed without guidance (14). Visualization challenges in very small peripheral veins further complicate PICC placement (15).

POCUS offers real-time, radiation-free visualization during catheter advancement and tip positioning, potentially reducing repeated manipulations and radiographs (7,8,16,17). In our study, POCUS increased the UVC placement success from 47.2% to 84.2% and PICC placement success from 56.3% to 92.9%. These results are consistent with previous studies which have supported POCUS guidance for neonatal central access (7,18,19). The high success rates associated with POCUS may be attributed to its ability to provide direct visualization and real-time monitoring of catheter placement.

Post-insertion complications such as malposition, infection, NEC, bleeding, thrombosis, and pleural/pericardial effusion are common with neonatal UVC and PICC insertions (1,2,20,21). In this study, 3.6% of neonates developed NEC after UVC insertions, while Sulemanji et al. (20). reported a 1.9% rate of NEC after insertions. This discrepancy may be due to the more frequent malpositioning in the non-POCUS group, as malposition is associated with mesenteric venous ischemia and NEC development (20).

Gastrointestinal bleeding was also more frequent in the non-POCUS group than in the POCUS group (36.1% vs. 10.5%). This may be due to increased vessel wall damage during blind insertion techniques, potentially contributing to the development of thrombosis and subsequent bleeding (22-24). Bowel distention, although often regarded as a secondary manifestation rather than a primary endpoint, was also more common in the non-POCUS group in our study. Since distention can reflect downstream complications (e.g., thrombosis or malposition-related perfusion issues), prompt reassessment of the catheter position is prudent when it occurs after insertion (25-27).

Catheter-related infection is another common complication of UVC and PICC insertion. We observed five infections in the non-POCUS PICC group and none in the POCUS group. This difference may reflect longer PICC usage durations and greater illness severity rather than the guidance modality alone. Oleti et al. (28), reported more cases of infection in the ultrasound-guided group compared to the conventional group. They explained that this might have been due to the longer time required for PICC insertion with ultrasound. Together, these mixed findings underscore the importance of standardized POCUS training in neonatal catheterization in order to minimize complications.

This study had several strengths, including its focus on a critical and vulnerable population of preterm neonates, explicit definitions of optimal tip positioning, and uniform post-procedure imaging. Additionally, the retrospective design allowed us to comprehensively compare outcomes between POCUS-guided and conventional catheter placement, providing valuable insights into the benefits of POCUS in clinical practice.

Study Limitations

The study also had limitations. Its retrospective design may have introduced selection bias as the choice of catheterization method was not randomized. Although baseline characteristics did not differ significantly between the groups, we cannot entirely rule out unmeasured confounding factors. Additionally, this study did not account for operator expertise, which could have influenced success rates and complication incidence rates. Future studies should compare outcomes among operators with similar levels of clinical experience to more accurately quantify the specific benefits of ultrasound guidance in neonatal vascular access. Finally, this study did not explore long-term outcomes or time-to-event endpoints (e.g., infection per 1,000 catheter-days), which could provide additional clinical context.

Conclusion

POCUS guidance for UVC and PICC placement in preterm neonates significantly improves optimal tip positioning and reduces complication rates, including gastrointestinal bleeding and infection. These findings support the integration of POCUS into routine NICU vascular access workflows, alongside structured competency-based training and standardized real-time tip verification procedures.

Future prospective studies should evaluate long-term outcomes, infection rates normalized to catheter-days, and standardized training curricula in order to optimize safety and effectiveness.

Ethics

Ethics Committee Approval: This study was approved by the review opinion of the Clinical Research Ethics Committee of Shenzhen Second People's Hospital (approval number: 2024-369-01PJ, date: 11.11.2024).

Informed Consent: Consent was waived due to the retrospective design of this study.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: H.C., J.G., R.L., Y.Z., Concept: H.C., L.P., W.Y., J.G., M.C., R.L., Y.Z., Design: H.C., L.P., W.Y., J.G., M.C., R.L., Y.Z., Data Collection or Processing: H.C., L.P., W.Y., Y.G., M.C., Analysis or Interpretation: H.C., L.P., W.Y., R.L., Y.Z., Literature Search: H.C., L.P., W.Y., J.G., M.C., Writing: H.C., R.L., Y.Z.

Conflict of Interest: The authors declare no conflict of interest.

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Supplementary Table SI Links: https://d2v96fxpocvxx.cloudfront.net/bb2eeae3-0e60-42a4-acea-81e4a349912c/content-images/d094519c-64ca-4199-8026-e7ac9bf22b2a.pdf

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Original Article

A Cross-sectional Study to Evaluate the Clinical Characteristics and Nutritional Status of Children with Spinal Muscular Atrophy

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ABSTRACT

Aim: This study aimed to evaluate the clinical characteristics, feeding features, and nutritional status of children diagnosed with spinal muscular atrophy (SMA) using multiple anthropometric indicators.

Materials and Methods: A cross-sectional observational study was conducted on 24 children (9 males, 15 females) with SMA, aged 5-192 months, in a tertiary care hospital in Türkiye. Clinical features, feeding methods, and anthropometric parameters including weight, height, body mass index, triceps skinfold thickness, and mid-upper arm circumference (MUAC) were recorded. Nutritional status was assessed using the Gomez and the Waterlow classifications, alongside MUAC z-scores based on Centers for Disease Control and Prevention growth charts.

Results: The cohort included 11 patients with SMA Type 1, 9 with Type 2, and 4 with Type 3. More than half (54.2%) were able to self-feed, while 33% were fed via percutaneous endoscopic gastrostomy. Feeding lasted longer than 15 minutes in 62.5% of cases. According to MUAC measurements, 58.3% of the patients were malnourished. Gomez classification identified 58.3% of the children as malnourished, and Waterlow classification indicated chronic malnutrition in 54.2%. A higher proportion of malnutrition was observed in those patients with SMA Type 1. MUAC measurements showed results comparable to traditional malnutrition classifications and emerged as a practical and reliable tool for nutritional assessment in SMA.

Conclusion: Malnutrition is highly prevalent among children with SMA, particularly in Type 1 patients. Comprehensive nutritional monitoring using MUAC alongside conventional anthropometric indices may improve the accuracy of malnutrition detection. A multidisciplinary approach, including early swallowing evaluations and timely nutritional interventions, is essential in order to optimize care and growth outcomes in this vulnerable population.

Keywords: Spinal muscular atrophy, malnutrition, upper arm circumference, anthropometric measurement

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Introduction

Spinal muscular atrophy (SMA) is a chronic neuromuscular disease characterized by spinal motor neuron degeneration (1). Its incidence is estimated as being between 1 in 6,000 and 1 in 10,000 live births (2).

SMA is currently divided into five subtypes: Type 0 (the most severe form with onset in the prenatal period and development of severe respiratory problems after birth), Type I (a severe form with onset before 6 months of age and the inability to sit unsupported), Type II (an intermediate form with onset before 18 months of age and the ability to sit unaided, but not to stand or walk), Type III (a mild form with onset after 18 months of age and the ability to stand and walk unaided), and Type IV (the mildest form with onset after 30 years of age) (3).

Although there have been significant improvements in the treatment of SMA, nutritional support is one of the main components in the guidelines for the standard of care in patients with SMA (4).

Common problems in SMA cases include feeding and swallowing problems such as weak sucking, limited opening of the mouth, and weak swallowing with dysfunctional airway protection (5). There is a considerable risk of morbidity from both undernutrition and obesity in children with SMA. Studies have shown that the prevalence of malnutrition is quite high, although it varies according to the type of SMA (6-8). Therefore, optimal nutritional needs, effective nutrient delivery, and reliable nutritional surveillance must be prioritized in those children with SMA.

Alongside a lack of a gold standard validated pediatric nutrition screening tool in routine clinical practice, nutritional assessment in SMA is further complicated by the challenges inherent in anthropometry in these children (8,9).

Thus, there is an ongoing effort to improve nutritional rehabilitation practice among children with SMA by using the most appropriate assessment tools in order to obtain a more accurate anthropometric profile and more realistic nutritional goals (10).

There is accumulating evidence that mid-upper arm circumference (MUAC) is the best case-detection method for pediatric malnutrition in terms of easiness, age independence, precision, accuracy, sensitivity, specificity and the lack of requirement for any special equipment, formal training or calculation (11,12).

This study aimed to assess the clinical characteristics, feeding features, and nutritional status of pediatric outpatients with SMA.

Materials and Methods

Participants

Patients had a confirmed diagnosis of SMA, were between one month and 18 years of age, and were enrolled in hospital-based clinical practices. This study was approved by Eskisehir Osmangazi University Non-Interventional Clinical Research Ethics Committee (approval no.: 28, date: 26.05.2023). Parents or legal representatives provided written, informed consent.

Study Design

This observational, cross-sectional study was conducted in a tertiary hospital in Türkiye.

Data Collection

In a single visit, information was gathered on the patients' anthropometric measurements, the results of their nutritional status assessment (using the Gomez and Waterlow classifications), date of birth, age at SMA diagnosis, etiology and their type of SMA. Information regarding disease-modifying therapy (nusinersen) was also recorded. All patients included in this study were receiving nusinersen treatment.

Nutritional Management

All of the patients received routine clinical care, including nutritional follow-up, as part of standard practice. Nutritional support and feeding methods [oral or percutaneous endoscopic gastrostomy (PEG)] were determined based on the clinical condition and needs of each patient. However, detailed data regarding specific nutritional interventions (such as caloric adjustments, dietary composition, or standardized dietitian-guided protocols) were not systematically recorded or analyzed within the scope of this study.

SMA Classification

SMA was clinically categorized into Types 1, 2, and 3 according to the established clinical criteria.

Anthropometrics

Anthropometric measurements included height (cm), body weight (kg), body mass index (BMI; kg/m^2), triceps skinfold thickness and MUAC along with estimations of mean z-scores and percentiles for weight-for-age (WFA), height-for-age (HFA), and weight-for-height (WFH) and these were then analyzed relative to the reference values established by Centers for Disease Control and Prevention (CDC) Growth Charts. MUAC z-scores were

calculated using MUAC z-score reference standards. These standards were developed in order to assess pediatric malnutrition (13). Height measurements were obtained using standard clinical methods. In those patients with limited mobility or postural deformities, measurements were performed as accurately as possible under clinical conditions; however, alternative segmental measurements were not systematically applied. MUAC z-scores were calculated using the established reference data for pediatric populations based on age-appropriate standards. MUAC has been previously validated as a practical tool for assessing malnutrition in children, particularly in those with physical limitations.

Definition of Malnutrition

Malnutrition was defined according to the data of percentiles in the Gomez and Waterlow Classifications using CDC standard growth charts.

Gomez Classification

Based on WFA percentiles, the Gomez categorization scheme divides nutritional status into four categories: normal (≥90.00th percentile), first-degree/mild malnutrition (76th-90th percentiles), second-degree/moderate malnutrition (61st-75th percentiles), and third-degree/severe malnutrition (≤60th percentile) (14,15).

Waterlow Classification

The Waterlow categorization distinguishes between two types of malnutrition: "wasting," which is based on acute malnutrition and WFH, and "stunting," which is based on chronic malnutrition and height for age. Both the degree of stunting (the percentage of projected HFA) and wasting (the percentage of expected WFH) were calculated using the Waterlow Classification system. The severity of malnutrition cases was further classified using the WFH [overweight/obesity (≥110%), normal (≥90%), mild (80-89%), moderate (70-79%), severe (≤70%)] and HFA [normal (≥95%), mild (90-94%), moderate (85-89%), severe (≤85%)] parameters (14,15).

Statistical Analysis

The statistical analyses were performed using the Statistical Package for the Social Sciences SPSS version 11.0 (SPSS Inc., Chicago, IL, USA), which was available in our institutional system. Due to the relatively small sample size, particularly within the SMA subtype groups, inferential statistical analyses were not performed, and the results are presented descriptively.

Results

Demographic Parameters and Clinical Features of the Patients

This study was conducted with 24 (9 males, 15 females) children with SMA. The mean age of the patients was 90.67±50.72 months (5-192). Eleven children were diagnosed as SMA Type 1 thus representing the most severe form of SMA.

Hammersmith Functional Motor Scale (HFMS) data were available for 24 patients, whereas Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) data were available for 15 patients. The mean HFMS and CHOP-INTEND scores were 36.18±17.08 and 37.85±21.21, respectively. The types of children with SMA are summarized in Table I.

More than half of the study group were able to self-feed (54.2%). Sixteen children had had a tracheostomy. These patients were under respiratory support as part of their clinical management; however, detailed data regarding the type and duration of ventilation were not analyzed in this study. The PEG was the route of feeding in 33.3% of cases (Table II). The distribution of PEG feeding varied across the SMA subtypes, with a higher frequency observed in the more severe forms; however, due to the limited sample size, subgroup comparisons were not performed. All of the patients included in this study were under nusinersen treatment at the time of evaluation.

Anthropometrics and Nutritional Status of the Study Population

The anthropometric measurements of the study group are presented in Table III.

The results of the MUAC measurements revealed that 14 (58.3%) children had malnutrition and one patient was overweight. The results of the MUAC measurements are presented in Table IV.

In general, the Gomez classification (WFA) revealed that malnutrition was evident in 58.3% of the children with SMA based on the CDC growth charts. According to the Waterlow (stunting) classification of HFA based on the CDC growth charts, 54.2% of the patients were chronically malnourished (Table V).

Table I. Clinical characteristics of study group

Type of SMA	SMA patients, n (%)
Type 1	11 (45.8)
Type 2	9 (37.5)
Type 3	4 (16.7)

SMA: Spinal muscular atrophy

Table II. Feeding features of children with SMA	
Feeding-related characteristics	**SMA patients, n (%)**
Duration of feeding	
<15 min	9 (37.5)
15-30 min	13 (54.2)
>30 min	2 (8.3)
Self-feeding ability	
Self-fed	13 (54.2)
By caregiver	11 (45.8)
Feeding method	
Orally	16 (66.6)
PEG feeding	8 (33.3)
Feeding duration data were collected for all patients in the study cohort, regardless of feeding method. PEG: Percutaneous endoscopic gastrostomy, SMA: Spinal muscular atrophy	

Table III. The anthropometric measurements of patients				
Anthropometric variables	**All SMA Types**	**SMA Type 1**	**SMA Type 2**	**SMA Type 3**
Mean Age				
Mean	90.67	47.18	117.78	149.25
Median	80.00	25.00	130.00	164.50
Std.	59.72	35.97	49.92	51.71
Min.	5	5	41.00	76
Max.	192	107	182.00	192
Height				
Mean	114.50	95.73	123.78	145.25
Median	114.00	85.00	117.00	149.50
Std.	30.08	22.56	25.42	26.61
Min.	64	64	85	109
Max.	173	133	162	173
Height Z Score				
Mean	-1.25	-0.55	-2.11	-1.08
Median	-1.20	-0.50	-2.05	-1.31
Std.	1.43	1.18	1.54	0.74
Min.	-4.33	-2.23	-4.28	-1.65
Max.	1.46	1.54	0.08	-0.07
Weight				
Mean	24.68	13.44	30.51	42.50
Median	19.50	12.00	22.00	47.50
Std.	16.69	6.34	16.36	17.33
Min.	5.0	5.0	10	18.0
Max.	57.0	26.0	52	57.0
Weight Z Score				
Mean	-1.73	-1.88	-1.55	-0.46
Median	-1.59	-1.43	-0.02	-0.26
Std.	2.35	1.46	3.29	0.62
Min.	-9.72	-5.29	-9.28	-1.37
Max.	1.19	-0.16	1.23	0.04

Table III. Continued

Anthropometric variables	All SMA Types	SMA Type 1	SMA Type 2	SMA Type 3
BMI				
Mean	16.51	14.07	18.64	19.16
Median	15.63	13.51	19.02	19.34
Std.	4.65	2.48	5.74	3.14
Min.	8.77	10.16	8.90	15.15
Max.	28.40	18.67	28.40	22.82
BMI Z Score				
Mean	-1.08	-1.69	-0.64	0.09
Median	0.23	-0.45	0.35	0.09
Std.	3.09	2.34	3.79	0.62
Min.	-10.65	-5.93	-10.18	-0.60
Max.	2.58	0.18	2.50	0.81
MUAC				
Mean	17.87	15.11	19.80	22.25
Median	18.00	15.00	22.00	24.00
Std.	4.49	2.05	5.64	4.19
Min.	10.00	13.0	10.00	16
Max.	25.0	18.0	25.00	25
TSFT				
Mean	11.04	10.82	11.33	11.00
Median	12	12.00	12.00	11.50
Std.	3.65	2.78	5.26	1.41
Min.	2	4	2	9
Max.	18	13	18	12

Std: Standard deviation, Min: Minimum, Max: Maximum, BMI: Body mass index, MUAC: Mid-upper arm circumference, TSFT: Triceps skinfold thickness

Table IV. The results of z-score of bands MUAC and other anthropometric measurements

Anthropometric measurements	+2 to +1	+1 to 0	0 to -1	-1 to -2	-2 to - 3	-3 to -4
MUAC Z Score						
All types	1	1	8	8	3	3
Type 1	0	0	5	2	3	1
Type 2	1	1	2	2	0	2
Type 3	0	0	1	3	0	0
Weight Z Score						
All types	1	4	7	5	4	3
Type 1	0	0	3	3	4	1
Type 2	1	3	2	1	0	2
Type 3	0	1	2	1	0	0
Height Z score						
All types	1	4	7	6	4	2
Type 1	1	3	3	3	1	0
Type 2	0	1	2	1	3	2
Type 3	0	0	2	2	0	0
BMI Z score						
All types	2	9	4	1	1	3
Type 1	0	3	1	0	1	2
Type 2	2	4	1	1	0	1
Type 3	0	2	2	0	0	0

Totals may not correspond to subgroup sizes in all categories because complete anthropometric data were not available for all patients.
MUAC: Mid-upper arm circumference, BMI: Body mass index

Table V. Assessment of nutritional status of the study group

SMA All Types	**Nutritional status**	**Gomez Classification WFA CDC percentile**	**Waterlow Classification WFH CDC percentile**	**Waterlow Classification HFA CDC percentile**	**MUAC**
		n	**n**	**n**	**n**
	Normal/Overweight	10	15	11	10
	Malnourished	14	4	13	14
	1st degree (n) **2nd degree (n)** **3rd degree (n)**	7 5 2	2 1 1	5 5 3	8 3 3
	Total	24	19	24	24
SMA Type 1	**Nutritional status**	**Gomez Classification WFA CDC percentile**	**Waterlow Classification WFH CDC percentile**	**Waterlow Classification HFA CDC percentile**	**MUAC**
		n	**n**	**n**	**n**
	Normal/Overweight	4	4	7	5
	Malnourished	7	2	4	6
	1st degree (n) **2nd degree (n)** **3rd degree (n)**	3 3 1	1 1 0	2 1 1	2 3 1
	Total	11	11	11	11
SMA Type 2	**Nutritional status**	**Gomez Classification WFA CDC percentile**	**Waterlow Classification WFH CDC percentile**	**Waterlow Classification HFA CDC percentile**	**MUAC**
		n	**n**	**n**	**n**
	Normal/Overweight	5	2	3	4
	Malnourished	4	7	6	5
	1st degree (n) **2nd degree (n)** **3rd degree (n)**	1 2 1	5 1 1	0 4 2	3 0 2
	Total	9	9	9	9
SMA Type 3	**Nutritional status**	**Gomez Classification WFA CDC percentile**	**Waterlow Classification WFH CDC percentile**	**Waterlow Classification HFA CDC percentile**	**MUAC**
		n	**n**	**n**	**n**
	Normal/Overweight	1	1	1	1
	Malnourished	3	3	3	3
	1st degree (n) **2nd degree (n)** **3rd degree (n)**	3 0 0	3 0 0	3 0 0	3 0 0
	Total	4	4	4	4

Waterlow classification based on WFH was calculated only for patients with available WFH measurements (n=19). Therefore, totals in this column do not correspond to the full cohort size (n=24).
MUAC: Mid-upper arm circumference, WFA: Weight-for-age, HFA: Height-for-age, WFH: Weight-for-height, CDC: Centers for disease control and prevention

Discussion

SMA affects multiple systems, despite it being primarily a chronic neurological condition (16). Therefore, the treatment of SMA must be planned in a multidisciplinary manner. Nutritional support is one of the main components of the guidelines for the standard of care in patients with SMA (4). This study presents a cross-sectional evaluation of the clinical features and nutritional status of children diagnosed with SMA, emphasizing the high prevalence of malnutrition and the factors influencing nutritional health in this population. According to the Gomez classification based on WFA, 58.3% of the patients in this study were malnourished. Similarly, the Waterlow classification using HFA indicated chronic malnutrition in 54.2% of the cohort.

The consistency across these different methods highlights this issue and underlines the importance and urgency of addressing malnutrition in children with SMA. A higher proportion of malnutrition was observed in those patients with SMA Type 1, the most severe phenotype in our study, suggesting a possible association between disease severity and nutritional status. MUAC z-score analysis also identified 58.3% of the children as being malnourished. De Amicis et al. (9) conducted a study with Type 1 and Type 2 cases which revealed that mean weight was significantly lower in SMA patients than in healthy controls, while supine length was more variable. They also present a set of disease-specific percentile curves of BW, SL (supine length), and BMI-for-age for girls and boys with SMA Type 1 and SMA Type 2. However, these specific curves had not yet been approved by ESPGAN as of the time of writing. During follow-up, SMA patients should be monitored in terms of their nutritional status. A retrospective study carried out with sixty cases reported that weight z-scores had decreased in 23% of patients. This ratio was 47% in terms of BMI (17).

Feeding and swallowing problems are one of the most important complications of SMA. Dysphagia in SMA Type 1 is described as disturbed and weak sucking, problems with handling oral secretions, weak swallowing with dysfunctional airway protection, and gastroesophageal reflux. Dysphagia in SMA Type 1 may also lead to other problems such as poor weight gain, discomfort and risk of aspiration pneumonia. Choking and sweating during feeding were reported as being 91% and 55% in SMA patients, respectively. It has been reported that 72% of patients had to interrupt feeding due to coughing attacks and sweating (18). As a result, the duration of feeding is prolonged. In our study, 62.5% of the participants reported feeding durations of longer than 15 minutes. PEG is an alternative for children with feeding difficulties. The present study revealed that only eight cases were feeding via PEG. This result was lower than has been reported in the literature (19). This difference may be influenced by several factors, including clinical decision-making processes, parental preferences, and the timing of PEG recommendations in routine practice. This point might be one of the reasons why the prevalence of malnutrition was high in present research (20).

Standard anthropometric measurements can be challenging in children with SMA due to spinal deformities (e.g., scoliosis), joint contractures, and altered body composition. In this context, MUAC stands out as a practical and reliable tool for nutritional assessment. In our study, MUAC showed comparable results with traditional malnutrition classification systems and offered significant advantages in terms of its usability, age independence, and minimal technical requirements. Prior studies have similarly highlighted MUAC as an effective screening tool for pediatric malnutrition, especially in populations with physical limitations (21,22). Additionally, the use of standard CDC growth charts may overestimate malnutrition in children with SMA, as reduced muscle mass and altered body composition may not necessarily reflect true caloric deficiencies.

In recent years, dramatic and promising developments have occurred in the treatment of SMA. Although some studies have reported improvements in dysphagia, it is not dramatic as motor functions (6,18). When considering nusinersen, which is the most commonly used drug, studies have suggested that this drug may have less effect on the brainstem than on other parts of the spinal cord (23-25).

Study Limitations

In the present study, all of the cases were being treated with nusinersen. However, detailed treatment-related variables (e.g., duration of therapy, dosing intervals) were not analyzed, which may be considered a limitation. This study had several limitations. The small sample size and single-center design may limit the generalizability of the findings. Moreover, the cross-sectional nature of this study precludes analysis of longitudinal changes in nutritional status or the effects of interventions over time. The lack of detailed data on nutritional interventions may be considered as another limitation of this study. In addition, the inclusion of different SMA types in a single analysis may also be considered as a limitation, as clinical severity and functional status vary significantly between SMA types, which may have influenced the nutritional findings and their interpretation. Nevertheless, the use of multiple anthropometric indicators and validated classification systems strengthens the credibility of our findings. In addition, the lack of inferential statistical analyses may be considered as a limitation of this study. Additionally, anthropometric measurements such as height may be affected by postural deformities, including scoliosis and joint contractures, which are common in SMA. Furthermore, standard MUAC reference values may not fully reflect body composition in children with SMA due to their reduced muscle mass. Additionally, potential differences in the nutritional statuses between PEG-fed and orally fed patients were not analyzed. An analysis of these differences in nutritional statuses in future studies may provide further insight into the issues affecting this population.

Conclusion

In conclusion, the management of nutrition in SMA should not be limited to dietitians. A multidisciplinary approach involving pediatric neurologists, gastroenterologists, rehabilitation specialists, and speech and swallowing therapists is essential. Early swallowing evaluations and a timely transition to enteral feeding in at-risk children can prevent further nutritional decline. Periodic reassessment using multiple anthropometric tools and functional indicators can help personalize interventions and improve outcomes. Further large-scale, prospective studies are warranted in order to evaluate the long-term progression of nutritional status in SMA patients and to assess the effectiveness of targeted nutritional interventions in improving both growth and functional outcomes.

Ethics

Ethics Committee Approval: This study was approved by Eskisehir Osmangazi University Non-Interventional Clinical Research Ethics Committee (approval no.: 28, date: 26.05.2023).

Informed Consent: Parents or legal representatives provided written, informed consent.

Footnotes

Authorship Contributions

Surgical and Medical Practices: K.B.Ç., A.D.Y.Ş., Concept: K.B.Ç., A.D.Y.Ş., Design: K.B.Ç., A.D.Y.Ş., Data Collection or Processing: A.D.Y.Ş., G.K.Y., Ö.U., C.Y., Analysis or Interpretation: E.A., Literature Search: K.B.Ç., Writing: K.B.Ç.

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Original Article

From Febrile Seizures to Epilepsy: *IL-1β (-511)* and *IL-10 (-1082)* Gene Polymorphisms

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ABSTRACT

Aim: The etiology of febrile seizures (FS) is multifactorial, including genetic, immunological, and inflammatory components. The primary objective of this research was to assess the relationship between *IL-1β* (*-511*) and *IL-10* (*-1082*) gene polymorphisms and the likelihood of recurrent FS and subsequent epilepsy in pediatric patients.

Materials and Methods: In this study, we retrospectively reviewed data from 44 patients diagnosed with FS. We employed restriction fragment length polymorphism-polymerase chain reaction (PCR) and amplification refractory mutation system-PCR techniques in order to detect genetic variations in the IL-1β (-511) and IL-10 (-1082) loci. The study population underwent long-term follow-up for an average of 13±5 years to evaluate the correlations between these polymorphisms and clinical prognoses, specifically FS recurrence and the onset of epilepsy.

Results: In the IL-1β (-511) region, no significant association was found between G/A, A/A, or G/G polymorphisms and FS recurrence (p=0.131) or epilepsy development (p=0.407). Likewise, the G allele at the IL-10 (-1082) position showed no meaningful correlation with epilepsy risk (p=0.378). However, the presence of the A allele at the locus in question was found to be significantly associated with the development of epilepsy (p=0.002). Carriers of the A allele exhibited a 10.8-fold increased risk of epilepsy compared to non-carriers (odds ratio=10.8; 95% confidence interval: 2.04-57).

Conclusion: Our data indicate that the IL-10 (-1082) A allele serves as a significant predictor for epilepsy susceptibility after FS. These results highlight the potential role of cytokine gene variations, especially IL-10, in determining the long-term neurological prognosis of children with FS.

Keywords: Febrile seizures, genetic polymorphism, interleukin-1 beta, interleukin-10

Introduction

Febrile seizures (FS) constitute a common pediatric neurological emergency with a male predominance; although typically benign, their underlying pathogenesis remains incompletely understood (1,2). FS are generalized seizures which occur with a fever (>38 °C) in children between 6 months and 5 years of age and are not caused by central nervous system (CNS) infection or metabolic imbalance (3). Approximately half of children with FS manifest their initial episode between 12-30 months of age, whereas only 6-15% experience seizure onset beyond four years of age. Typical symptoms include altered consciousness, limb movements and ocular signs (4).

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FS are among the most prevalent neurological disorders in childhood, with an incidence ranging from 2% to 5% (3,5). FS are the most common convulsive disorder of childhood, with a recurrence probability of 33% (6). High recurrence rates and incidence are commonly associated with early age of onset, prolonged seizure duration, positive family history, and convulsions occurring at lower body temperatures (6,7). Furthermore, several factors such as a family history of FS and early age at onset have been identified as significant risk factors for recurrence in the Turkish pediatric population (6). Moreover, studies have indicated a familial predisposition to FS, with 20-33% of patients reporting a family history of the condition (8). Reported recurrence rates after the first seizure range widely from 15% to 70%, whereas approximately 5.4% of these children eventually develop epilepsy (9). FS evaluation primarily consists of the characterization of its type (either simple FS or complex FS) (10).

A prolonged FS (more than 5 minutes) may eventually lead to febrile status epilepticus (FSE). FSE accounts for 25-52% of pediatric status epilepticus (11). Securing intravenous access represents an essential intervention during prolonged FS in order to facilitate the administration of rescue anticonvulsants and maintain adequate hydration status (3). Multiple factors confer elevated risk for epileptogenesis in children, including atypical seizure semiology, persistent electroencephalographic abnormalities, neurodevelopmental impairment, and positive familial epilepsy burden (5). Brief FS rarely induce neuronal injury, with prolonged events showing minimal neuropathological correlation in most pediatric cases. Core prevention relies on timely fever mitigation (10).

The pathogenesis of FS involves a complex interaction of genetic, immune, and inflammatory factors (12,13) Inflammatory processes are primarily triggered by fever, where pro-inflammatory cytokines such as interleukin-1 beta (*IL-1β*), IL-6, and tumor necrosis factor-alpha are produced within the brain and play a central role in seizure generation (12). These cytokines stimulate prostaglandin E2 synthesis in the hypothalamus, elevating the thermal set-point. Crucially, the susceptibility to FS is determined by the balance between these pro-inflammatory mediators and anti-inflammatory cytokines, including *IL-10* and IL-1 receptor antagonists (*IL-1Ra*) (13). Genetic variations in these cytokine genes may alter an individual's inflammatory response to infection, thereby influencing the neuronal excitability threshold (13). Furthermore, biochemical alterations such as decreased serum zinc levels during febrile episodes have been proposed as contributing to the underlying mechanisms of convulsions (12). Additionally, ion channel variations and the resulting neuronal hyperexcitability further complicate the etiopathogenesis of FS (14).

This study aimed to investigate the associations between cytokine gene polymorphisms and the risk of recurrence of FS and epilepsy development in those patients with FS who presented with *IL-1β* (*-511*) and *IL-10* (*-1082*) gene polymorphisms.

Materials and Methods

Ethical approval for this research was granted by the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee (approval no.: 749, date: 31.10.2018), and this study was performed in compliance with the STROBE statement. Written informed consent was obtained from the parents or legal guardians of all of the pediatric participants included in this study. All procedures were conducted in accordance with the principles of the Declaration of Helsinki, ensuring data privacy and confidentiality throughout the 13-year follow-up period.

This cohort study is based on an article published in 2012 by Nur et al. (15). This retrospective analysis included 92 pediatric cases presenting with their initial FS episode at the Pediatric Emergency Service and Pediatric Neurology Outpatient Clinic of Akdeniz University Faculty of Medicine Hospital. For genetic evaluation, the IL-1β (-511) polymorphism was identified via restriction fragment length polymorphism-polymerase chain reaction (RFLP-PCR), while the IL-10 (-1082) region was analyzed using the amplification refractory mutation system-PCR technique. A new study was created from the original study which stemmed from the previous study by Nur et al. (15) The new cohort included 44 pediatric patients selected retrospectively from electronic medical records, all of whom had been diagnosed with FS and who carried *IL-1β* (*-511*) and *IL-10* (*-1082*) gene polymorphisms.

Participants were included in this study if they met the following criteria:

(1) they had experienced one or more FS and had received a diagnosis of FS,

(2) they had undergone genotyping for IL-1β (-511) and IL-10 (-1082) variants,

(3) they had been followed up for at least three years, and

(4) they had experienced their first FS episode between 6 and 60 months of age.

Patients who met any of the following criteria were not included in this study.

(1) the presence of other neurological disorders which could cause seizures, such as CNS infections, intoxication, or acute electrolyte imbalances;

(2) inadequate clinical or genetic data in the electronic medical records;

(3) a follow-up duration of less than three years; or

(4) a lack of genetic analysis for *IL-1β* (*-511*) and *IL-10* (*-1082*) gene polymorphisms.

Statistical Analysis

Statistical processing was conducted using IBM SPSS Statistics for Windows, version 23.0 (SPSS Inc., Chicago, IL, United States). The normality of data distribution was assessed via the Kolmogorov-Smirnov test, while Levene's test was utilized to verify the homogeneity of variances. Continuous variables following a normal distribution are expressed as mean ± standard deviation, whereas non-normally distributed data are presented as medians (minimum-maximum). Categorical variables are reported as frequencies and percentages (n, %). In order to examine differences between independent groups, the Student's t-test was used for data meeting parametric assumptions, while the Mann-Whitney U test was applied for data not meeting these assumptions. Categorical data were compared using either the Pearson chi-square test or Fisher's exact test. Relationships between variables were assessed with Pearson or Spearman correlation analyses, according to the distribution characteristics. Statistical significance was set at $p<0.05$.

The distribution of IL-1β (-511) and IL-10 (-1082) genotypes was tested for Hardy-Weinberg equilibrium using the chi-square test in order to ensure the representativeness of the study population.

Results

A total of 44 patients with FS were evaluated for this study. Table I summarizes the demographic and clinical findings of the cases.

In the whole cohort, for the IL-1β (-511) region, G/A polymorphism was detected in 31 patients (70%), A/A polymorphism in 6 (14%), and G/G polymorphism in 7 (16%). In the IL-10 (-1082) region, G/A polymorphism was identified in 22 patients (50%), A/A polymorphism in 6 (14%), and G/G polymorphism in 16 (36%).

In the group with recurrent FS, in the IL-1β (-511) region, polymorphism frequencies were 77% for G/A, 9% for A/A, and 15% for G/G. In the G/A region, FS recurrence occurred in 84% of those patients with G/A polymorphism, 50% of those with A/A polymorphism, and 71% of patients with G/G polymorphism. However, there was no statistically significant difference between FS recurrence and the presence of polymorphisms in the IL-1β (-511) region (p=0.131).

In the subgroup analysis of those patients with recurrent FS, the distribution of genotypes in the IL-10 (-1082) region was as follows: 56% carried the G/A genotype, 15% carried the A/A genotype, and 29% carried the G/G genotype. Statistical analysis revealed no significant correlation between the occurrence of FS recurrence and the presence of these specific polymorphisms at the IL-10 (-1082) locus (p=0.219).

A statistically significant difference was identified between epilepsy risk and IL-10 (-1082) polymorphisms (G/A, A/A, and G/G). Bonferroni correction indicated that G/A and A/A polymorphisms yielded a higher probability of developing epilepsy compared to G/G polymorphism (Table II).

The associations between genetic polymorphisms in the IL-1β (-511) and IL-10 (-1082) regions and the development of epilepsy following FS are detailed in Table II.

Table I. Demographic and clinical characteristics of patients with FS (n=44)

Characteristic	**n (%)**
Total cases	44 (100)
Age	
≤18 months	25 (57)
>18 months	19 (43)
Male	25 (57)
Female	19 (43)
Term	40 (90)
Preterm	2 (5)
No data (gestational age)	2 (5)
Family history of FS	13 (30)
Family history of epilepsy	7 (16)
Consanguineous marriage	
Yes	3 (7)
No	16 (36)
Unknown	25 (57)
Simple FS	32 (73)
Complicated FS	8 (18)
Unknown FS type	4 (9)
One-time FS	10 (23)
Recurrent FS	32 (73)
Unknown recurrence	2 (4)
Neurodevelopmental delay	4 (8)

FS: Febrile seizures

Table II. The comparison of the groups with epilepsy versus no-epilepsy in follow-up with respect to IL-10 (-1082) and IL-1β (-511) genetic polymorphisms

Polymorphism (Position)	Epilepsy status	Genotype	n (%)	p value
IL-1β (-511)	Epilepsy (+) n=19	G/A A/A G/G	15 (48) 1 (17) 3 (43)	p=0.407
	Epilepsy (−) n=25	G/A A/A G/G	16 (52) 5 (83) 4 (57)	
	Generalized Epilepsy n=8	G/A A/A G/G	7 (47) 1 (100) 0 (0)	p=0.228
	Focal Epilepsy n=11	G/A A/A G/G	8 (53) 0 (0) 3 (100)	
IL-10 (-1082)	Epilepsy (+) n=19	G/A A/A G/G	13[a] (59) 4[a] (67) 2[b] (13)	***p=0.006**
	Epilepsy (−) n=25	G/A A/A G/G	9 (41) 2 (33) 14 (87)	
	Generalized Epilepsy n=8	G/A A/A G/G	7 (54) 1 (25) 0 (0)	p=0.478
	Focal Epilepsy n=11	G/A A/A G/G	6 (46) 3 (75) 2 (100)	

*Chi-square test result with Bonferroni correction indicates significant differences, marked by different letters

No statistically significant association was found between carrying the A allele genotype in the IL-1β (-511) region and the development of epilepsy after FS (χ^2=0.62; p=1.00; Table III).

No statistically significant association was found between carrying the G allele genotype in the IL-10 (-1082) region and the development of epilepsy after FS (χ^2=2.16; p=0.378; Table III). Patients without the G allele genotype in this region showed a higher likelihood of epilepsy predisposition compared to those with the G allele genotype.

A statistically significant association was found between carrying the A allele genotype in the IL-10 (-1082) region and the development of epilepsy after FS (χ^2=2.84; p=0.002; Table III). Patients with the A allele genotype in the IL-10 (-1082) region were found to have a 10.8 times higher likelihood of epilepsy predisposition compared to those without the A allele genotype [Odds ratio (OR)=10.8; 95% confidence interval (CI): 2.04-57].

Table III. Relationship between the alleles identified for the IL-10 (-1082) and IL-1β (-511) regions and the development of epilepsy following FS

Region	Allele	Epilepsy (+) n (%)	Epilepsy (−) n (%)	χ^2; p value
IL-1β (-511)	G A	18 (47) 16 (43)	20 (53) 21 (57)	χ^2=0.012 p=0.213 χ^2=0.62 p=1.00
IL-10 (-1082)	G A	15 (40) 17 (61)	23 (60) 11 (39)	χ^2=2.16 p=0.378 χ^2=2.84 **p=0.002**

*Chi-square test result with Bonferroni correction indicates significant differences, marked by different letters
FS: Febrile seizures

Discussion

Analysis revealed a significant correlation between the IL-10 (-1082) polymorphism and the risk of developing epilepsy following FS (p=0.006). Polymorphism in the IL-10 (-1082) region manifested a statistically significant difference in epilepsy susceptibility among the G/A, A/A, and G/G genotypes.

Previous studies have examined cytokine levels and gene polymorphisms in FS (7,16). However, a research gap exists in investigating the prevalence and risk factors for long-term FS recurrence and epilepsy development in those patients with cytokine gene polymorphisms. Han et al. (14) argued against the routine application of genetic testing for all FS cases, instead emphasizing the need for close clinical monitoring. They suggested that genetic evaluations should be specifically reserved for those children who manifest complex FS, develop subsequent a FS, or suffer from accompanying neurodevelopmental disorders (14).

A study conducted by Haspolat et al. (17) using the enzyme linked immunosorbent assay (ELISA) method revealed a significant increase in cerebrospinal fluid IL-1β and nitrite levels in children with FS. In another study by Virta et al. (18) conducted in Finland using the RFLP-PCR method, FS patients exhibited an increased prevalence of the second allele of IL-1β (-511). Additionally, in a study conducted by Al Morshedy et al. (19) in Egypt using the RFLP-PCR and ELISA methods, the presence of the T allele or TT genotype in the IL-1β (-511) promoter region and the IL-1RA II/III genotype in FS patients were identified as risk factors. However, in a study conducted by Chou et al. (20) in Taiwan using the RFLP-PCR method, no significant difference was observed in IL-1β promoter, exon 5 regions, and *IL-10* gene polymorphism between an FS group and a control group.

For the IL-10 cytokine, in a study conducted by Virta et al. (18) using the ELISA method, while there was no significant increase in plasma IL-10 levels in those patients with FS compared to the control group, a noteworthy increase in the plasma IL-1RA/IL-1β ratio was observed (20). Research by Nur et al. (21), using the RFLP-PCR and ELISA methods, demonstrated an increased prevalence of the IL-10 (-1082) G allele genotype in FS patients. Children with previous FS manifested a significantly enhanced peripheral blood IL-1β and IL-10 synthesis; however, no statistical relationship was observed between the increased cytokine synthesis and IL-1β (-511) and IL-10 (-1082) genotypes (21).

Although the association between the IL-10 (-1082) A allele and epilepsy risk was statistically significant (OR=10.8), its clinical application should be interpreted with caution due to the small sample size and retrospective design of this study. These findings suggest that genetic screening could potentially aid in identifying high-risk children for closer neurological monitoring; however, larger prospective multi-center trials are necessary in order to validate these markers before routine clinical implementation.

Study Limitations

The present study had several limitations. First, the sample size was relatively small (n=44), which constrained the feasibility of a robust formal power analysis and may have limited the statistical power to detect weaker associations, particularly regarding IL-1β polymorphisms. The wide confidence interval observed for the risk of epilepsy associated with the IL-10 allele (95% CI: 2.04-57) reflects an imprecision in the effect estimate, which is a direct consequence of the limited cohort size. Second, this study was conducted at a single tertiary center, which may restrict the generalizability of our findings to other populations with different genetic backgrounds. Third, the retrospective design relies on the accuracy of medical records, which inherently carries the risk of missing data or recall bias regarding specific seizure details or family histories. Additionally, while the long-term follow-up (average 13±5 years) is a significant strength of this study, the inclusion of cases with a minimum follow-up of only three years might be a relatively short window for observing all potential cases of late-onset epileptogenesis. Finally, our genetic evaluation focused specifically on IL-1β and IL-10 polymorphisms; however, the pathogenesis of FS and epilepsy involves a complex network of numerous other cytokines and ion channels which were not evaluated in this research.

Conclusion

This study highlights a significant association between the IL-10 (-1082) A allele and the risk of epilepsy following FS, suggesting a potential genetic marker for potential epilepsy development related to FS. In contrast, IL-1β (-511) polymorphisms showed no clear link to seizure recurrence or epilepsy development. These findings underscore the role of certain cytokines gene variations in epileptogenesis and warrant further investigation in larger cohorts.

Ethics

Ethics Committee Approval: Ethical approval for this research was granted by the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee (approval no.: 749, date: 31.10.2018).

Informed Consent: Written informed consent was obtained from the parents or legal guardians of all of the pediatric participants included in this study.

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Footnotes

Authorship Contributions

Concept: A.A., S.A., B.N., Ş.H., Design: A.A., S.A., B.N., Ş.H., Data Collection or Processing: A.A., S.A., Ş.H., Analysis or Interpretation: B.N., Ş.H., Literature Search: A.A., S.A., B.N., Ş.H., Writing: A.A., S.A., Ş.H.

Conflict of Interest: The authors declare no conflict of interest.

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Original Article

The Impact of Remote Diabetes Education on Parental Training

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ABSTRACT

Aim: This study aimed to investigate the impact of remote education provided to parents of children newly diagnosed with type 1 diabetes on parental knowledge of diabetes care and the children's metabolic control.

Materials and Methods: This research was conducted with 32 children (aged 2-15 years) and their parents (remote education: n=16; face-to-face education: n=16). Structured diabetes education consisting of eight modules was conducted over an average of 12±2.5 days. At the end of the education and 3 months later, HbA1c values, parental knowledge levels, and 3-day food diaries were evaluated.

Results: At the 3-month follow-up, the median diabetes knowledge score was significantly higher in the remote education group [32 (interquartile range (IQR): 4.5)] compared to the face-to-face group [30.5 (IQR: 3.75)] (p=0.020). Baseline HbA1c levels were 11.4% (IQR: 1.7) for G1 (the remote education group) and 12.4% (IQR: 2.3) for G2 (The face-to-face education group) (p=0.262). By the 3rd month, these levels decreased significantly to 7% (IQR: 0.8) and 6.9% (IQR: 1.3), respectively, with no significant difference between the groups (p=0.862). Energy and macronutrient intakes were similar in both groups at baseline and at the 3rd month, meeting national and international recommendations. Paternal participation was markedly higher in the remote group compared to the face-to-face group (50% vs. 6.25%).

Conclusion: The remote education model is an effective method which can be integrated into diabetes management.

Keywords: Type 1 diabetes, diabetes education, remote education, parental training

Introduction

Type 1 diabetes (T1D) is the most common chronic disease in childhood. Improving self-care practices is fundamental for optimal diabetes management. The vast majority of day-to-day diabetes care is handled by the parents of those children with T1D (1). Educational interventions designed to facilitate the development of diabetes self-management skills can improve the quality of life for individuals with diabetes, as well as enhance their knowledge, self-care practices, coping skills, and the attitudes necessary for effective self-management (2).

Children with T1D and their parents should have access to comprehensive and structured education in order to empower them in the effective management of diabetes

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(3). In order to maximize the effectiveness of diabetes treatment, it is essential to ensure high-quality structured education. This education should also be repeated regularly in order to maintain its effectiveness (3,4). However, diabetes education provided in hospital settings presents certain disadvantages. During these sessions, parents are often required to take time away from their work, their other children, and their daily responsibilities. Additionally, other family members, caregivers, and particularly fathers often report limited access to diabetes education (5).

Remote education technologies offer a valuable opportunity for those parents of children with T1D, other caregivers, and anyone seeking access to information (4). Previous studies have supported the promising role of web-based interventions in improving diabetes management (6,7). However, few studies have evaluated online educational interventions for the parents of children with T1D in our country. This study examined the impact of online education provided to the parents of children with T1D on the parents' knowledge levels and the metabolic control of their children. The primary objectives of this research were to evaluate whether distance education significantly increases the average knowledge test scores of the parents and whether it leads to improved HbA1c levels in those children with T1D when compared to conventional face-to-face education.

Materials and Methods

Study Design and Participants

This study utilized an experimental design and was conducted from February to June 2023, following the CONSORT 2010 Statement (updated guidelines for reporting parallel group randomized trials). This study began with a cohort of 32 parents of children and adolescents newly diagnosed with T1D. The participants were assigned into 2 groups using systematic randomization based on their order of diagnosis. To prevent selection bias, allocation was determined by diagnosis sequence (odd numbers for G1, even numbers for G2), an external factor unpredictable by the researchers. A comparison of baseline clinical data, specifically HbA1c levels (p=0.262) and demographic characteristics, confirmed that this systematic allocation successfully produced balanced and homogeneous groups.

Inclusion and Exclusion Criteria

The eligible participants were the parents of children aged 0 to 18 years diagnosed with T1D within the prior 30 days, who were proficient in using digital devices (computers or smartphones), and were able to communicate in Turkish. The exclusion criteria included having vision or hearing impairments, a diagnosis period exceeding 30 days, or a refusal to participate.

The Intervention

Prior to the randomized phase, all participants received comprehensive training on insulin administration, blood glucose monitoring, and hypoglycemia management. The core intervention consisted of:

- **G1 (Remote education):** Individual, family-centered sessions conducted within the participants' home environment using remote education technologies.
- **G2 (Face-to-face education):** Individual, family-centered sessions conducted in hospital settings.

Both groups received a concentrated dose of one 60-minute session per day, totalling approximately 7 hours of contact time. The education modules were developed based on the Turkish Childhood Educator's Guide and ISPAD Clinical Practice Consensus Guidelines (2018, 2022). Following the training, a WhatsApp support group (including a diabetes nurse, dietitian, and pediatric endocrinologist) provided guidance for 30 days.

Outcome Measures

Data were collected at baseline (t-0) and 12 weeks after the training program (t-1):

- **Diabetes knowledge score:** This was assessed using a 34-item questionnaire (0-34 points). Content validity was confirmed by 13 experts using the Davis method, yielding a content validity ratio of 0.98 (α=0.05).
- **Metabolic control:** HbA1c values were retrieved from the patients' medical records.
- **Dietary intake:** This was evaluated using 3-day food diaries (two weekdays, one weekend). Dietitians provided oral and written instructions for weighing food. Total energy and nutrient intake were calculated using BeBiS 8.2 (Stuttgart, Germany).
- **Satisfaction:** This was measured using a 5-point rating scale ranging from "did not like it" to "very good".

Ethical Considerations

This study was approved by the Ege University Medical Clinical Research Ethics Committee (approval no.: 23-3.1T/33, date: 23.03.2023). The purpose of this study was explained to each participant, and written informed consent was obtained. All procedures adhered to the principles of the Declaration of Helsinki.

Statistical Analysis

Statistical analysis was performed using SPSS 25.0. Descriptive statistics are presented as median [interquartile range (IQR) for numerical variables as the data did not meet normality assumptions due to the sample size (n=32). The groups were compared using the Mann-Whitney U test. A p-value of less than 0.05 was considered statistically significant.

Results

During the study period, 32 parents of children newly diagnosed with T1D participated in the diabetes education program. The first follow-up assessment included all 32 parents, with 16 in the remote education group (G1) and 16 in the face-to-face group (G2). Three months later, during the second follow-up assessment, 28 parents participated, 12 from G1 and 16 from G2. Four parents were excluded from this study because they did not continue the education program. Comparing the initial assessment (t-0) to the second follow-up (t-1), the dropout rate was 25% for the remote education group and 0% for the face-to-face group.

The median age of the children was 8.62 years (IQR: 3.08) in the remote education group and 8.97 years (IQR: 5.88) in the face-to-face group. No significant differences were observed in HbA1c levels (%), basal and bolus insulin ratios, or total insulin dose (U/kg/day) between the two groups at baseline or at the three-month follow-up. At baseline, the median (IQR) HbA1c values were above the target for both groups: 11.4% (IQR: 1.7) for G1 and 12.4% (IQR: 2.3) for G2 (p=0.262). At the three-month follow-up, there was no significant difference in HbA1c levels between the groups: the median (IQR) for G1 was 7% (IQR: 0.8) and for G2, it was 6.9% (IQR: 1.3) (Table I).

The intervention effects on HbA1c were independent of socio-economic factors, including the child's gender, age, school type, family structure, mother's educational and employment status, or place of residence. Additionally, neither group experienced hypoglycemia, diabetic ketoacidosis, or hospitalization during the study period.

Table II displays the energy and nutrient intake of the participants at baseline and during the follow-up period. Carbohydrate, fat, and protein intakes met the recommended levels outlined in national and international guidelines at both time points. However, saturated fat intake exceeded recommendations, while fiber intake fell below recommendations at baseline and during the three-month follow-up.

The total education knowledge scores for the parents in the remote education group before and after online education were median (IQR) 32.5 (2.75) and 32 (4.5), respectively (p=0.063). In contrast, the scores for those parents in the face-to-face education group decreased from a median (IQR) of 33 (1.75) to 30.5 (3.75) (p=0.001). At the three-month follow-up, the total education score was higher in the remote education group (32, IQR: 4.5) compared to the face-to-face group (30.5, IQR: 3.75) (p=0.020). The scores obtained by the groups following the training are presented in Table III.

Satisfaction with the Intervention

The overall satisfaction with the education program was exceptionally high. All 12 parents who participated in the remote education group assessment rated the program as "very good", indicating a high level of satisfaction with the intervention.

Table I. Children's clinical characteristics (n=28)

Clinical and anthropometric parameters	Newly diagnosed Median (IQR)		p[1]	3 months after training Median (IQR)		p[2]
	G1	G2		G1	G2	
Weight SD score	0.16 (1.30)	-0.39 (1.30)	0.150	0.54 (1.85)	0.42 (1.35)	0.693
Height SD score	0.04 (1.33)	1.23 (1.26)	0.039	0.42 (1.84)	0.81 (2.27)	0.546
Body mass index SD score	0.66 (1.96)	-0.85 (1.64)	0.004	0.38 (1.36)	0.42 (1.25)	0.403
Total insulin (U/kg/day)	0.65	0.52	0,307	0.55	0.46	0.521
Basal insulin (%)	36	35	0.429	32	33	0.570
Bolus insulin (%)	64	65	0.429	68	67	0.570
HbA1c (%)	11.4 (1.7)	12.4 (2.3)	0.257	7 (0.8)	6.9 (1.3)	0.862

G1: The remote education group, G2: The face-to-face education group
p[1]: New diagnosis period, p[2]: Significance of difference between groups at 3 months
*Alpha at the 0.05 significance level
IQR: Interquartile range

Table II. Energy and nutrient intake of participants during the follow-up period

Clinical and anthropometric parameters	ISPAD recommendations	New diagnosis Median (IQR)		p¹	3 months after training Median (IQR)		p²
		G1	G2		G1	G2	
Protein intake (% energy)	15-25	19.67 (2.67)	18.58 (1.67)	0,640	17.66 (4.33)	19.00 (2.17)	0.111
Carbohydrate intake (% energy)	40-50	43.67 (4.33)	47.66 (6.33)	0.166	49.33 (4.67)	46.16 (6.17)	0.162
Fat intake (% energy)	30-40	38.00 (6.0)	33.66 (6.09)	0.244	33.66 (4.33)	34.33 (7.50)	0.467
Fiber intake (g/1.000 kcal)	14	13.00 (3.92)	12.81 (2.62)	1.00	13.08 (3.54)	11.68 (2.90)	0.412
Saturated fatty acid (% energy)	<10	16.15 (4.39)	15.79 (2.67)	0.584	14.86 (2.15)	15.43 (4.67)	0.572
Energy (kcal/day)	Varies according to age, gender and physical activity level	1.493 (240)	1.632 (557)	0.250	1.537 (564)	1.584 (523)	0.661

G1: The remote education group, G2: The face-to-face education group
p¹: New diagnosis period, p²: Significance of difference between groups at 3 months
*Alpha at the 0.05 significance level
IQR: Interquartile range

Table III. The diabetes knowledge scores of the groups

Diabetes education topics	New diagnosis Median (IQR)		p¹	3 months after training Median (IQR)		p²
	G1	G2		G1	G2	
What is diabetes	5 (1)	5 (0)	0.095	4 (1.75)	4 (1.5)	0.504
Hypoglycemia management	8 (0)	8 (0)	0.819	8 (0)	8 (1)	0.124
Insulin management	5 (0.75)	5 (0)	0.365	5 (1)	5 (1)	0.574
Hyperglycemia management	4 (0)	4 (0)	0.248	4 (1)	3 (1)	0.001*
Disease management	4 (0)	4 (1)	0.386	4 (0.75)	3,5 (1)	0.192
Exercise management	4 (1)	4 (0)	0.408	4 (0)	4 (1)	0.356
Healthy nutrition principles	4 (0)	4 (1)	0.036	4 (0)	4 (1)	0.356
All topics	32.5 (2.75)	33 (1.75)	0.469	32 (4.5)	30.5 (3.75)	0.020*

G1: The remote education group, G2: The face-to-face education group
p¹: New diagnosis period, p²: Significance of difference between groups at 3 months
*Alpha at the 0.05 significance level
IQR: Interquartile range

Discussion

Self-care skills and education are critical for managing T1D, a condition which requires significant responsibility and poses numerous challenges (11). This study evaluated the effectiveness of two diabetes education models for the parents of children with T1D, namely remote education or face-to-face education.

Diabetes education, delivered at diagnosis and during ongoing management, is essential for effective self-management. However, face-to-face education has limitations, particularly in engaging fathers. In clinic-based settings, mothers are often the primary accompanying parents, while fathers are frequently absent due to work or other commitments. This absence reduces paternal involvement in daily diabetes management, limiting their ability to support their children (12). Fathers are often perceived as less communicative and less likely to take action (13), a trend influenced by cultural norms which view childcare as primarily the mother's responsibility. Studies have shown that the fathers of children with T1D express a need for training to effectively manage their children's care (5,14,15). In our study, 50% of the fathers participated in the remote education group, compared to only one father in the face-to-face group. The flexibility of remote education, particularly in scheduling, accommodates the fathers' availability, giving it a significant advantage.

Family members of children with T1D often have unmet educational needs due to low attendance in clinic-based face-to-face education (12). Remote education can address this gap by increasing participation. In our study, 50% of families (mother, father, and child) participated in remote education, while participation in the face-to-face group was limited to mother-child or father-child pairs.

Access to education from a specialized diabetes healthcare team is crucial (11). Research by Zamanzadeh et al. (16) demonstrated that telephone and SMS-based education can empower patients with Type 2 diabetes. Similarly, online education for parents and family members outside clinical settings can improve self-efficacy in managing T1D. In our study, remote education increased the parents' diabetes knowledge, with the remote group achieving higher scores than the face-to-face group at the three-month follow-up [32 (IQR: 4.5) vs. 30.5 (IQR: 3.75), p=0.020].

Online support systems can be as effective as face-to-face guidance for children with diabetes and their families (17-19). However, some results from other studies have been mixed. For example, Pinsker et al. (20) found that remote education improved HbA1c values, while other studies showed no significant metabolic control improvements despite increased patient contact (21,22). In our study, HbA1c values for both groups aligned with international guidelines at the three-month follow-up, indicating that both methods were effective in achieving metabolic control (z: -0.174, p=0.862). Remote education is particularly beneficial for families with limited access to health services.

In cases of financial constraints, lack of social support, or time limitations, online support systems may be more convenient and efficient than clinic visits (17-19). Integrating messaging systems with online education can further enhance its effectiveness (23). The parents of children with T1D often need assistance with diabetes-related challenges, such as adjusting insulin doses based on dietary plans. Rapid telehealth responses are crucial, especially during the early diagnosis period. In our study, both groups received uniform telehealth support via WhatsApp for 30 days, ensuring timely assistance and guidance. This additional support likely contributed to the positive metabolic outcomes observed in both groups.

Study Limitations

This study had several limitations which should be considered when interpreting the results. First, the sample size was relatively small, and this research was conducted as a single-center study, which may limit the generalizability of the findings to a broader population. Second, the follow-up period was limited to three months; a longer observation period is necessary in order to assess the long-term sustainability of the educational outcomes and their lasting impact on metabolic control. Another significant limitation was the absence of continuous glucose monitoring or sensor-derived glycemic data (such as time-in-range or glycemic variability). While HbA1c is a standard measure of average glycemia, it does not fully reflect daily glycemic fluctuations or the risk of hypoglycemia. Therefore, the lack of sensor data prevented a more nuanced analysis of glycemic variability between the remote and face-to-face education groups. Lastly, as is common in educational interventions, the potential for social desirability bias in self-reported data (such as food diaries and satisfaction scales) cannot be entirely ruled out.

Conclusion

This study demonstrated that remote education is a highly effective and feasible alternative to traditional face-to-face education for those parents of children who have been newly diagnosed with T1D. While both educational models successfully achieved the target metabolic control (HbA1c ~7%) at the three-month follow-up, remote education led to significantly higher parental knowledge scores and substantially increased paternal involvement in the care process. From a clinical perspective, the flexibility and accessibility of remote education address common barriers such as work commitments and geographical limitations, and it particularly encourages fathers to take an active role in diabetes management. These findings suggest that integrating remote education technologies into standard pediatric diabetes care can empower families, maintain high-quality self-management skills, and provide a cost-effective, family-centered approach to long-term diabetes education.

Ethics

Ethics Committee Approval: This study was approved by the Ege University Medical Clinical Research Ethics Committee (approval no.: 23-3.1T/33, date: 23.03.2023).

Informed Consent: The purpose of this study was explained to each participant, and written informed consent was obtained.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: D.G., Ş.D., S.Ö., E.A., Concept: G.D., Design: G.D., Y.A.A., Y.M., Data Collection or Processing: G.D., Y.A.A., Y.M., Analysis or Interpretation: G.D., Literature Search: D.G., G.D., Y.A.A., Y.M., Ş.D., S.Ö., E.A., Writing: D.G., G.D., Y.A.A., Y.M., Ş.D., S.Ö., E.A.

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Original Article

Kidney Outcome Predictors in Congenital Anomalies of the Kidney and Urinary Tract

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ABSTRACT

Aim: Congenital anomalies of the kidney and urinary tract (CAKUT) are a leading cause of chronic kidney disease in children. This study aimed to evaluate the frequency of adverse renal outcomes and also to identify early risk factors for guiding long-term follow-up strategies.

Materials and Methods: We conducted a retrospective cohort study of children born between 2010 and 2023 with diagnoses of unilateral kidney agenesis, multicystic dysplastic kidney, or posterior urethral valves (PUV) followed up at a tertiary pediatric nephrology center. Clinical and demographic variables were extracted from the electronic health records. Adverse renal outcomes included proteinuria, hypertension and an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73m^2 or age-equivalent thresholds. Univariate logistic regression analyses were performed in order to assess associations between potential predictors and adverse outcomes.

Results: Among the 104 patients [60% male; median age at last follow-up 7.2 years (interquartile range 6.9)], 13% developed adverse renal outcomes, most commonly proteinuria (7%). The median age at onset of these outcomes was 3.7 years. PUV, prematurity and a history of urinary tract infection (UTI) were significantly associated with adverse outcomes. Other factors, including low birth weight, additional CAKUT, reduced baseline eGFR, and kidney length to body length ratio at diagnosis, were not significantly associated with negative outcomes.

Conclusion: Adverse renal outcomes can occur early in children with CAKUT. Prematurity, UTI and PUV emerged as key determinants of adverse renal prognosis and may serve as valuable markers for identifying patients at higher risk who may require closer and more individualized follow-up.

Keywords: Congenital anomalies of kidney and urinary tract, pediatric, risk factors, chronic kidney disease

Introduction

Congenital anomalies of the kidney and urinary tract (CAKUT) represent a heterogeneous group of structural malformations resulting from disrupted urinary tract development during intrauterine life (1,2). They are among the most common congenital anomalies (3) and constitute the leading cause of chronic kidney disease (CKD) in children and young adults (4,5).

Clinically relevant forms of CAKUT include unilateral kidney agenesis (UKA), multicystic dysplastic kidney (MCDK), and posterior urethral valves (PUV). These conditions frequently result in a reduced nephron number, predisposing the remaining renal tissue to hyperfiltration injury, progressive fibrosis, and a subsequent loss of kidney function (6).

Long-term renal outcomes in children with CAKUT are highly variable. A considerable proportion of

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affected patients develop complications such as arterial hypertension, proteinuria, CKD, or kidney failure during childhood or adolescence. Although several studies have explored prognostic determinants, the available evidence remains incomplete, and early predictors of adverse renal outcomes have not been fully established (2,3).

The present study aimed to describe the frequency of adverse renal outcomes in a cohort of children with CAKUT followed at a tertiary pediatric nephrology center and to identify clinical and demographic factors associated with the increased risk of these outcomes.

Materials and Methods

We conducted a retrospective cohort study including pediatric patients diagnosed with UKA, MCDK, or PUV who were born between 2010 and 2023. Patients were excluded if the diagnosis could not be confirmed, if they were lost to follow-up, or if their demographic data were incomplete. This study was in accordance with the ethical standards of the institutional research committee and the principles of the Helsinki Declaration.

Data Collection

The data were extracted from the electronic medical records and included demographic variables (birth weight, gestational age, and antenatal diagnosis) and clinical parameters, including the presence of additional CAKUT (aCAKUT), a history of urinary tract infection (UTI), baseline estimated glomerular filtration rate (eGFR) and kidney length to body length (KL:BL) ratio. The clinical outcomes assessed included proteinuria, arterial hypertension, clinically significant CKD and kidney failure.

In those patients with multiple primary CAKUT diagnoses, PUV was prioritized over MCDK or UKA as the primary diagnosis. In those patients with PUV, hydroureter, hydronephrosis and vesicoureteral reflux were not classified as aCAKUT due to their pathophysiological relationship with bladder outlet obstruction.

Baseline eGFR was calculated using the Schwartz equation, using the first serum creatinine obtained after the seventh day of life to minimize maternal creatinine influence. In those patients with PUV, only eGFR values obtained after one year of age were considered. This approach was chosen because renal function measurements obtained earlier may reflect impairment related to obstructive uropathy before surgical decompression, potentially leading to inaccurate estimations of long-term renal function. Similarly, KL measurements used to calculate KL:BL were obtained from the first available ultrasound for UKA and MCDK and from the first measurement after one year of age for PUV.

Outcome Definitions

Proteinuria was defined as a urine protein-to-creatinine ratio >50 mg/mmoL in children aged 6 months to 2 years old or >20 mg/mmoL in children aged 2 years or above, confirmed in at least two samples collected three months apart.

Hypertension was defined as systolic and/or diastolic blood pressure >95th percentile for age, sex and height on at least two separate occasions (7).

Clinically significant CKD was defined as eGFR<60 mL/min/1.73 m^2 in children aged 2 years or above, or 2 or more standard deviation (SD) below the mean if younger, confirmed on two measurements at least three months apart (8).

Statistical Analysis

Statistical analysis was performed using SPSS version 29. Continuous variables are expressed as mean and SD for normally distributed variables and as median and interquartile range (IQR) for non-normally distributed variables. Categorical variables are summarized as absolute and relative frequencies. Univariate logistic regression was conducted in order to evaluate the association between each predictor and adverse renal outcomes. Odds ratios (OR) with 95% confidence intervals (95% CIs) were calculated. Continuous variables were entered as linear predictors, and their ORs reflect the change in odds of the outcome per one-unit increase in the variable.

Given the limited number of outcome events, multivariable regression was not performed to avoid model overfitting and instability. Statistical significance was defined as $p<0.05$.

Results

A total of 104 patients were included. UKA was the most frequent CAKUT subtype (n=47, 45%). Male patients predominated (62, 60%). The median age at last follow-up was 7.2 years (IQR 6.9) and the median follow-up duration was 7.0 years (IQR 6.4).

Prematurity was present in 13 patients (13%), and low birth weight was identified in 12 patients (12%). Most patients had an antenatal diagnosis (n=88, 85%). Non-renal congenital anomalies were identified in 15 patients (14%), and 21 patients (20%) presented aCAKUT (Table I).

Adverse renal outcomes were identified in 13 patients (13%), with proteinuria being the most frequent

Table I. Characteristics of the cohort

	Combined cohort (n=104)	UKA (n=47)	MCDK (n=45)	PUV (n=12)
Male sex (%)	62 (59.6)	27 (57.4)	23 (51.1)	12 (100)
Age at last follow-up (years)	7.7±3.9	6.5±3.8	8.7±3.7	8.6±3.5
Antenatal diagnosis (%)	88 (84.6)	37 (78.7)	41 (91.1)	10 (83.3)
Gestational age (weeks)	39 (IQR 2)	39 (IQR 2)	39 (IQR 2)	38 (IQR 2)
Preterm birth (%)	13 (12.5)	8 (17.0)	3 (6.7)	2 (16.7)
Birthweight (g)	3,216 (IQR 706)	3,195 (IQR 745)	3,180 (IQR 702)	3,295 (IQR 747)
Low birth weight (%)	12 (11.5)	7 (14.9)	4 (8.9)	1 (8.3)
Post-natal diagnosis (Months)	5 (IQR 83)	8.5 (IQR 80)	0; 4*	144*
UTI (%)	28 (26.9)	11 (23.4)	8 (17.8)	9 (75.0)
Additional CAKUT (%)	21 (20.2)	9 (19.1)	8 (17.8)	4 (33.3)
First eGFR<90/-1 SD (%)	48 (51.1)	22 (51.2)	21 (53.8)	5 (41.7)
KL:BL ratio	9.6 (IQR 2.3)	10.4 (IQR 1.7)	8.9 (IQR 3.0)	9.0 (IQR 1.5)

Values are presented as mean ± standard deviation for normally distributed variables and median (interquartile range) for non-normally distributed variables. *For variables with less than three data, individual values are shown
CAKUT: Congenital anomalies of the kidney and urinary tract, eGFR: Estimated glomerular filtration rate, KL:BL: Kidney length to body length, MCDK: Multicystic dysplastic kidney, PUV: Posterior urethral valves, UKA: Unilateral kidney agenesis, UTI: Urinary tract infection.

manifestation (7% of the total cohort, present in 54% of patients with adverse outcomes). The median age at onset of adverse renal outcome was 3.7 years old (IQR 2.6). Kidney failure occurred in one patient with PUV, who started dialysis at 13 months of age.

In univariate logistic regression analyses, prematurity (OR=6.48; 95% CI: 1.71-24.57, p=0.004) and a history of UTI (OR=13.52; 95% CI: 3.37-54.25; p<0.001) were the strongest predictors of adverse renal outcomes.

Regarding the CAKUT subtype, MCDK was associated with a lower likelihood of adverse outcomes (OR=0.20; 95% CI: 0.04-0.97; p=0.045), whereas PUV was associated with a significantly increased risk (OR=7.5; 95% CI: 1.93-29.15; p=0.004).

Other variables, including antenatal diagnosis, low birth weight, a CAKUT, reduced baseline eGFR, and the KL:BL ratio, were not significantly associated with adverse renal outcomes (p>0.05). Detailed results are presented in Table II.

Table II. Univariate analysis: odds ratios for the outcome by each factor

	Odds ratio	95% CI	p value
Malformation type			
UKA	1.05	0.33-3.35	0.941
MCDK	0.20	0.04-0.97	0.045
PUV	7.50	1.93-29.15	0.004
Antenatal diagnosis	0.42	0.05-3.50	0.424
Prematurity	6.48	1.71-24.57	0.006
Low birth weight	0.37	0.09-1.60	0.183
Urinary tract infections	13.52	3.37-54.25	<0.001
Additional CAKUT	0.52	0.12-1.88	0.316
Diminished baseline eGFR	0.71	0.21-2.44	0.591
KL:BL	0.94	0.70-1.26	0.295

Continuous variables were analyzed using univariate logistic regression; odds ratios represent the change in odds per one-unit increase in the variable
CAKUT: Congenital anomalies of the kidney and urinary tract, CI: Confidence intervals, eGFR: Estimated glomerular filtration rate, KL:BL Ratio of kidney length to body length, MCDK: Multicystic dysplastic kidney, PUV: Posterior urethral valves, UKA: Unilateral kidney agenesis.

Discussion

In this cohort of pediatric patients with CAKUT, 13% developed adverse renal outcomes, with proteinuria being the most frequent manifestation. Notably, these complications occurred at a median age of 3.7 years, suggesting that clinically significant renal impairment may develop early in life.

Children with CAKUT are known to be at increased risk of progressive kidney injury. Therefore, close clinical surveillance during early childhood is warranted, regardless of the initial presentation. The early identification of high-risk patients may allow for the timely implementation of nephroprotective strategies aimed at delaying or preventing CKD progression (3).

Among the variables analyzed, PUV, prematurity and a history of UTI were significantly associated with adverse renal outcomes. These findings are consistent with the current knowledge regarding nephron endowment and secondary renal injury mechanisms (2,5). PUV causes persistent bladder outlet obstruction, leading to increased intravesical and intrarenal pressures which often begin during fetal life. This process may result in renal dysplasia and progressive kidney injury. Furthermore, abnormal bladder function may persist even after surgical valve ablation, contributing to ongoing renal damage (9).

Prematurity is associated with reduced nephron number due to incomplete nephrogenesis. This reduced nephron endowment predisposes affected individuals to hyperfiltration injury and long-term renal dysfunction (10). Similarly, UTI may act as additional injurious events in structurally abnormal kidneys and so accelerate CKD progression.

Interestingly, and in contrast to some previous studies, the presence of aCAKUT, reduced baseline eGFR and reduced KL:BL ratios were not significantly associated with adverse outcomes in our cohort. This finding may be explained by the limited statistical power due to the relatively small number of outcome events (3,5).

Our results also suggest a protective association between MCDK and adverse renal outcomes. However, this finding should be interpreted with caution, as it may reflect the limited number of adverse events and the univariate nature of the analysis rather than a true protective biological effect. Larger studies are needed in order to further clarify this association.

Overall, our findings support the clinical relevance of easily identifiable early-life risk factors, such as prematurity and a history of UTI, in guiding risk-adapted follow-up strategies for those patients with CAKUT. Risk stratification based on these characteristics may facilitate targeted surveillance and timely interventions, potentially mitigating long-term kidney damage.

Study Limitations

The strengths of this study include the use of real-world data from a tertiary pediatric nephrology center and the inclusion of more than a decade of clinical experience.

However, several limitations must be acknowledged. First, the absence of a standardized follow-up protocol regarding the timing of laboratory and imaging evaluations may have introduced variability in data availability. Secondly, the relatively small number of outcome events limited statistical power and contributed to wide CIs for some predictors.

Despite these limitations, the identification of significant associations between adverse renal outcomes and prematurity, UTI, and PUV suggests that these factors represent clinically relevant predictors. Future multicenter studies with standardized follow-up protocols and larger cohorts are needed in order to validate these findings and refine risk stratification tools.

Conclusion

In this cohort of 104 children with CAKUT, 13% developed adverse renal outcomes, frequently occurring at an early age (median 3.7 years). PUV, prematurity, and a history of UTI were significantly associated with an increased risk of poor renal prognosis. These findings highlight the importance of incorporating early clinical risk factors into individualized follow-up strategies for those children with CAKUT.

Ethics

Ethics Committee Approval: According to the principles of the local ethics committee, observational retrospective studies with guaranteed anonymity are exempt from formal review.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: M.M.C., M.M., C.N., C.C., Carm. C., C.G., Design: M.M.C., M.G.L., Data Collection or Processing: M.M.C., M.G.L., M.M., C.N., Analysis or Interpretation: M.M.C., M.G.L., C.C., Carm. C., C.G., Literature Search: M.M.C., M.G.L., C.N., C.C., Carm. C., Writing: M.M.C., M.G.L.

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Original Article

Evaluation of Kidney Transplantation Outcomes of Pediatric Patients with Ciliopathy: A Single Center Experience

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ABSTRACT

Aim: Ciliopathies are rare genetic diseases referring to a group of syndromic diseases characterized by the deterioration of the structure of the cilia, which may cause kidney failure in childhood. Follow-up of the patients with ciliopathy after kidney transplantation is important for graft survival.

Materials and Methods: This study was designed as a retrospective cohort trial. One hundred and fifty-one renal transplanted children (111 were non-ciliopathy and 31 were ciliopathy) were evaluated. Sociodemographic characteristics and clinical information regarding transplantation stage were recorded.

Results: The mean age of the 31 patients (16 female/15 male) with the diagnosis of ciliopathy was 11.1±3.5 years and their mean follow-up duration was 7.7±4.8 years. Four of the patients (12.9%) experienced acute rejection and two patients had graft loss. Eleven patients had polycystic kidney disease, ten patients had cystic dysplasia and ten patients had nephronophthisis as their primary diagnosis. Graft survival rates were similar for transplants from living and cadaveric donors in those patients with ciliopathy. The data of the 31 patients who underwent kidney transplantation with the diagnosis of ciliopathy were compared with the 111 patients with the diagnosis of non-ciliopathy. The rates of hypertension, acute rejection and graft loss were similar in both groups. According to a Kaplan-Meier analysis, the graft and patient survival rates for those patients with ciliopathy and for those with non-ciliopathy were similar (p=0.123, p=0.370).

Conclusion: Kidney transplant outcomes of patients with ciliopathy from well-selected living donors in terms of graft and patient survival are favorable.

Keywords: Ciliopathies, pediatric kidney transplantation, polycystic kidney disease, nephronophthisis

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Introduction

Ciliopathy is a term which covers a wide group of diseases which occur as a result of many different genetic mutations. It may affect many organ systems which have ciliary cells, making it one of the most common causes of end stage kidney disease (ESKD), especially in childhood. In this group of diseases, known as hepatorenal fibrocystic diseases, fibrocystic diseases of the liver, diabetes and skeletal dysplasia can be observed, as well as kidney, eye, and central nervous system findings (1). The three leading causes of ESKD in children during 2012-2016 were reported to be primary glomerular diseases (22.3%), congenital anomalies of the kidney and urinary tract (CAKUT; 21.9%), and cystic/hereditary/congenital disorders (11.7%), respectively (2). This ranking was the same as that in the annual report published in 2023 (3). In those patients with ciliopathy, the risk of complications after kidney transplantation may increase due to extrarenal involvement due to cilia disorder. Therefore, a careful selection of suitable candidates for kidney transplantation and a careful follow-up after transplantation are required. Common post-transplant complications may include infections, transplant rejection, and problems with cilia. Therefore, the early recognition and management of post-transplant complications and a multidisciplinary team approach with the involvement of all stakeholders are critical. Ciliopathies are rare genetic diseases characterized by a deterioration of the cilia structure, leading to kidney failure in childhood. While their multisystemic nature is well-known, pediatric data regarding post-transplant outcomes remain limited. The aim of this study was to evaluate the clinical outcomes, graft survival, and patient survival of pediatric kidney transplant recipients with ciliopathy and to compare these results with a non-ciliopathy control group in order to provide insights into the management of these complex patients.

Materials and Methods

Design and Setting

This study was designed as a retrospective cohort trial. The study protocol was approved by Ege University's Medical Research Ethics Committee (approval number: 22-12.1T/4, date: 15.12.2022). This study was conducted at our University's Renal Transplantation Center. Following the early postoperative period, all pediatric patients are monitored in the Pediatric Nephrology ward and followed up in the outpatient clinic. Kidney biopsies were performed in those patients showing clinical signs of rejection. The diagnosis of rejection was made via the examination of the kidney biopsies by two experienced pathologists.

Study Population and Sampling

We retrospectively evaluated 151 children who underwent renal transplantation in our Renal Transplantation Center. The vast majority of kidney-transplanted patients (111 patients) were diagnosed with non-ciliopathic disorders. Thirty-one children were diagnosed with ciliopathy and 9 children had unknown etiology. Those with unknown etiologies were excluded from this study. Thirty-one of ciliopathy patients who met the requirement of at least six months of follow-up agreed to participate in this study. Although complete molecular genetic data were not available for all patients included in this study, the diagnoses of those patients in the polycystic kidney disease (PKD) subgroup were genetically confirmed. The follow-up results of those patients with ciliopathy were compared with the non-ciliopathy group.

Data Collection

The date of birth of the patients, their gender, the cause of ESRD, dialysis information, donor information, mismatch numbers, warm and cold ischemia times, post-transplant treatment protocols, rejection status, graft loss, and survival data were recorded. At their last visit, the urea and creatinine levels of the patients were recorded. The updated Schwartz formula was used to calculate estimated glomerular filtration rate (eGFR) levels (4).

Statistical Analysis

We used the IBM SPSS statistical software package version 20.0. Continuous data are presented as mean±standard deviation under parametric conditions and median (minimum-maximum) under non-parametric conditions. Categorical variables are presented as numbers and percentages. Chi-square analysis was used for categorical variables. When analyzing independent continuous variables, the Mann-Whitney U test was used under nonparametric conditions. The One-Way Analysis of Variance test was used for parametric conditions and the Kruskal-Wallis test was used for non-parametric conditions in order to compare the three groups of ciliopathies. Bonferroni correction was used to distinguish any differences between groups. Survival analysis was performed with the Kaplan-Meier method using the log-rank test. The results obtained were evaluated and interpreted by all of the researchers. Statistical significance was accepted as $p<0.05$.

Results

Of the 31 patients (16 female/15 male) with the diagnosis of ciliopathy, the mean age at the time of transplantation was 11.1±3.5 years and the mean follow-up duration was

7.7±4.8 years. Two patients who were siblings, diagnosed with PKD, had graft loss. The causes of the graft loss were chronic rejection. Two patients, one with a functioning graft, died. The causes of death of the patients were due to central nervous system malignancy and fungal pneumonia. The mean creatinine and estimated GFR levels of the patients at their last visit were 1.5±1.4 mg/dL and 60±26 mL/min/1.73 m^2, respectively.

As the primary diagnosis of the patients with ciliopathy, eleven patients had PKD, ten patients had cystic dysplasia and ten patients had nephronophthisis (NPHP). Of those patients diagnosed with PKD, 8 were autosomal recessive PKD (ARPKD), and 3 were autosomal dominant PKD (ADPKD). The patients with ciliopathy were similar in terms of age, gender, follow-up time, rejection, graft loss, creatinine and eGFR at their last visit when they were grouped according to their primary diagnosis. The only statistically significant difference between the 3 groups was that all of the patients with a primary diagnosis of polycystic kidney used Anti-thymocyte globulin (ATG) in their induction regimen. The demographic and clinical characteristics of the patients in terms of their primary diagnosis of ciliopathy are shown in Table I.

Regarding the comparison with the control group, Table II shows the comparative demographic, clinical, and laboratory data between the 31 ciliopathy patients and the 111 non-ciliopathy patients. Regarding the treatment protocols, the induction regimen and the preferred calcineurin inhibitor were similar in both groups. However, azathioprine was not used as a nucleoside agent in those patients with ciliopathy. The rates of hypertension, acute rejection and graft loss were similar in both groups, and there was no significant difference between creatinine and eGFR levels measured at the last visit. The use of induction regimens and calcineurin inhibitors were similar in both groups. The graft survival rate was 93.5% in those patients with ciliopathy and 81.1% in those with non-ciliopathy. Patient survival rates were 93.5% in those patients with ciliopathy and 97.3% in those with non-ciliopathy. According to Kaplan-Meier analysis evaluating the difference in graft survival of those patients with ciliopathy and those with non-ciliopathy using a log-rank test, graft survivals of both groups were similar (p=0.123) (Figure 1). Kaplan-Meier analysis also revealed that there was no statistically significant difference in terms of patient survival between those patients with a diagnosis of ciliopathy and those with non-ciliopathy (p=0.370).

Table I. Demographic and clinical characteristics of patients in terms of primary diagnosis of ciliopathy

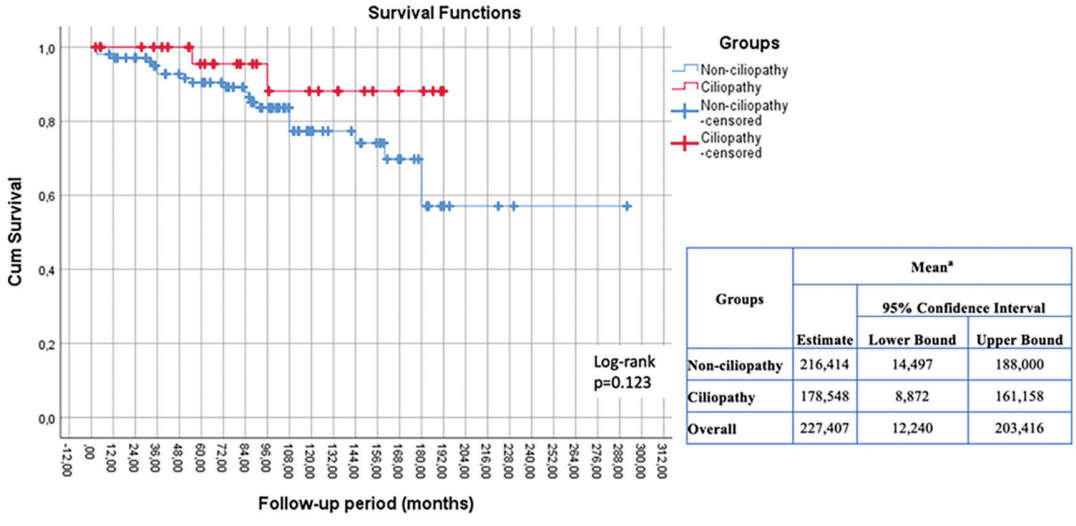
	Polycystic kidney n=11	**Cystic dysplasia n=10**	**Nephronophthisis n=10**	**Total n=31**	**p value**
Gender (male/female)	6/5	5/5	4/6	15/16	0.794
RRT (PD/HD/preemptive)	7/1/3	7/2/1	6/3/1	20/6/5	0.633
Donor type (living/cadaveric)	5/6	5/5	8/2	18/13	0.208
Induction (ATG/basiliximab)	11/0	7/3	7/3	25/6	0.049*
Calcineurin inhibitor (CsA/Tac)	5/6	5/5	5/5	15/16	0.971
Acute rejection, n (%)	3 (27%)	1 (10%)	0 (0%)	4 (12.9%)	0.108
Hypertension, n (%)	8 (72.7%)	7 (70%)	4 (40%)	19 (61.3%)	0.140
Graft loss, n (%)	2 (18.2%)	0 (0%)	0 (0%)	2 (6.5%)	0.111
Status (living/dead)	10/1	9/1	10/0	29/2	0.424
Age at transplant (years)¶	11.7±3.2	8.8±3.5	11.6±2.7	11.1±3.5	0.558
Time on RRT (months)Ω	31 (24-102)	43 (4-96)	16 (2-48)	30 (2-102)	0.191
Donor age (years)¶	21.4±21.3	27.0±16.8	34.7±10.4	29.8±17.7	0.841
Follow-up time (years)¶	7.8±2.6	11.7±2.8	6.8+5.7	7.7±4.8	0.489
Warm ischemia time (min)Ω	36 (4-90)	2.5 (1-10)	3 (1-32)	5 (1-90)	0.136
Cold ischemia time (min)Ω	450 (36-1,320)	208 (27-2,000)	55 (30-565)	121 (27-2,000)	0.259
Creatinine at last visit (mg/dL)¶	2.4±2.1	0.9±0.3	1.0±0.2	1.5±1.4	0.126
eGFR at last visit (ml/min/1.73 m^2)¶	48±33	72±22	58±12	60±26	0.107

¶Mean±SD, ΩMedian (min-max)
RRT: Renal replacement therapy, PD: Peritoneal dialysis, HD: Hemodialysis, ATG: Anti-Thymocyte Globulin, CsA: Cyclosporine, Tac: Tacrolimus

Table II. Comparison of the demographic, clinical and laboratory data of renal transplanted patients with a diagnoses of either ciliopathy or non-ciliopathy

Categorical variables	**Ciliopathy n=31**	**Non-ciliopathy n=111**	**p value¶**
Gender (male/female)	15/16	54/57	0.979
Donor type (living/cadaveric)	18/13	55/56	0.402a
Induction (ATG/basiliximab)	25/6	89/22	0.954
Calcineurin inhibitor (CsA/Tac)	15/16	50/61	0.991
Nucleoside inhibitor (MMF/AZA)	31/0	83/28	0.002*
Delayed graft function (yes), n (%)	4 (12.9 %)	9 (8.1%)	0.477
Hypertension after transplantation, n (%)	19 (61.2%)	65 (58.5%)	0.664
Acute rejection, n (%)	4 (12.9%)	20 (18%)	0.453
Graft loss, n (%)	2 (6.5%)	21 (18.9%)	0.096
Status (dead), n (%)	2 (6.5)	3 (2.7%)	0.090
Continuous variables			**p valueΩ**
Age at Tx (years)	10.9 (3.8-17.6)	12.9 (1.7-17.9)	0.183
Follow-up time (years)	7.4 (2.8-15.9)	8.5 (0.8-16.1)	0.449
Warm ischemia time (min)	5 (1-90)	5 (1-60)	0.850
Cold ischemia time (min)	121 (27-2,000)	67 (15-2,800)	0.683
Creatinine at 1st year of Tx	0.7 (0.4-1.7)	0.8 (0.3-1.8)	0.146
Creatinine at 5th year of Tx	0.9 (0.5-9.9)	1.0 (0.4-9.6)	0.282
Urea at last visit (mg/dL)	40 (17-207)	37 (14-155)	0.669
Creatinine at last visit (mg/dL)	1.24 (0.57-6.0)	1.33 (0.49-10.2)	0.099
eGFR at last visit (mL/min/1.73 m^2)	56 (9-123)	54 (5-125)	0.444

¶Chi-square test, ΩMann-Whitney U
RRT: Renal replacement therapy, PD: Peritoneal dialysis, HD: Hemodialysis, ATG: Anti-thymocyte globulin, CsA: Cyclosporine, Tac: Tacrolimus, AZA: Azathioprine, MMF: Mycophenolic acid, NTx: Transplantation



Groups	Mean[a]		
		95% Confidence Interval	
	Estimate	Lower Bound	Upper Bound
Non-ciliopathy	216,414	14,497	188,000
Ciliopathy	178,548	8,872	161,158
Overall	227,407	12,240	203,416

Figure 1. Graft survival of those patients with ciliopathy or non-ciliopathy

Discussion

Ciliopathic dysfunctions occur in any organ and the ones most predominately affected include the kidney, eye, liver and brain, with the kidneys being the most commonly affected (1). Kidney manifestations display pathologies ranging from a urinary concentration defect in normal appearing kidneys to cystic dysplastic kidneys. ADPKD and ARPKD represent the most common ones, followed by NPHP, cystic dysplastic kidneys, medullary sponge kidney, and several overlapping phenotypes. PKD is a group of monogenic disorders characterized by the presence of multiple cysts, primarily in the kidney and liver (5,6).

ADPKD is one of the most commonly encountered genetic origins of chronic kidney disease (CKD). Its incidence is estimated to be between 1 in 400 to 1 in 1,000 individuals. Conversely, ARPKD is a rare condition, with an estimated incidence of 1 in 20,000 individuals (1).

NPHP stands out as the most prevalent genetic cause of CKD disease occurring within the first three decades of life. Its prevalence among the population experiencing end-stage renal failure in childhood is estimated to be approximately 5%. Patients typically present with symptoms which include polyuria, polydipsia, enuresis, and anemia (1,7,8).

Renal dysplasia occurs as a result of defective differentiation of the renal parenchyma during kidney development (9). Histologically, dysplastic features may include incompletely branched collecting ducts surrounded by undifferentiated mesenchymal stroma. It is important to note that renal dysplasia has been observed in several ciliopathic disorders, such as Bardet-Biedl syndrome and Meckel-Gruber syndrome (1,9,10). Given that renal dysplasia is fundamentally a developmental phenotype, its presence within the context of a ciliopathy likely indicates a more severe genetic makeup.

Almost 3% of the population reach ESRD in the United States and as one of the leading causes of CKD, PKDs are common indications for dialysis or kidney transplant. While many studies have evaluated the results of kidney transplant in patients with PKD, most of these have only published the results after kidney transplant in patients with ADPKD (11-16).

In our study, we wanted to present the kidney transplantation results of all ciliopathies, including both PKDs (ADPKD and ARPKD), NPHP and cystic dysplasia. Our single center study comprises our 31-year experience and it is one of the largest single center studies covering children with different types of PKD who underwent kidney transplant. As expected, most of our study patients had PKD, similar to recent studies (17). In children, ADPKD is typically characterized by preserved renal function despite progressive structural changes (18). Reaching end-stage kidney disease (ESKD) is uncommon during childhood, with approximately 50% of patients reaching this stage by age 60. However, research has identified specific high-risk subgroups and systemic causes which can accelerate this progression. The progression to ESKD in the pediatric population varies greatly and depends largely on the age of onset and genetic factors (19). Cadnapaphornchai (20) reported a subset of ADPKD diagnosed before 18 months of age (very early-onset ADPKD) which is at the highest risk for early loss of kidney function and progression to ESKD during childhood or adolescence. While ADPKD typically progresses to ESKD in adulthood, the presence of three ADPKD patients in our pediatric cohort suggests a more aggressive clinical phenotype. In our study, the mean age at diagnosis for the three patients with ADPKD was 26 months. Although this exceeds the 18-month threshold established in the literature for very early-onset ADPKD, we believe this discrepancy is due to the small sample size (n=3), which prevents alignment with the standard definition. Despite the small cohort, these cases demonstrate clinical and structural characteristics consistent with early-stage disease progression. Therefore, we argue that this patient group should be considered within the very early-onset ADPKD spectrum for early loss of kidney function and progression toward ESKD as described in the literature.

In our study, two siblings diagnosed with PKD experienced graft loss due to chronic rejection. This finding is noteworthy and unlikely to be coincidental; it raises the possibility of shared genetic factors or familial disease-related triggers which may influence the immune response post-transplantation. The lack of molecular genetic data for all of the study group was a limitation in our retrospective study; however, the clinical presentation of the two siblings was consistent with severe polycystic disease.

Hypertension is an early and common symptom throughout the progression of both ADPKD and ARPKD and it also contributes to increased cardiovascular morbidity and mortality. Hypertension often develops without a decrease in kidney function. This indicates the existence of extrarenal causes in addition to renal causes in the etiology of hypertension. In some publications, the prevalence of hypertension in this patient group has been reported as being 50-70% (17,21-24). Conversely, in NPHP, blood pressure usually remains within the normal range without

progression to ESRD (25). In our study, we observed a high rate of hypertension in those patients diagnosed with ciliopathy, however, the frequency of hypertension was not different from the transplant recipients in the non-ciliopathy group. Regarding the frequency of HT in patients with PKD, NPHP and dysplasia, although post-transplant HT was more common in PKD and dysplasia, this difference was not statistically significant.

The necessity of native kidney nephrectomy before, after, or during kidney transplantation remains a matter of debate (26). None of the patients in this study required nephrectomy.

Most studies have reported more satisfactory results of kidney transplants from living donors than from cadavers (27). It has also been emphasized that living kidney donation deserves special attention and that genetic testing should be performed in transplants from living kidney candidates under the age of 30 (28). Due to the genetically inherited nature of the disease, adult studies have reported higher rates of cadaveric transplantation in those patients with ciliopathy (17). In our study, there was no difference in the frequency of cadaveric and living donors between the patient groups with and without ciliopathy. This can be explained by the fact that the median donor age (parents) in our patients was 40 years and above. The older average parental age can be considered as a reason for the increased frequency of transplants with living-related donors.

In the past years, it has been reported that the frequency of rejection in those patients who underwent kidney transplantation with a diagnosis of PKD was higher than in those with a diagnosis of non-ciliopathy (29). In our study, although the rejection rate was higher in patients with ciliopathy, it was not statistically significant.

Kanaan et al. (28) published a study showing excellent patient and graft survival rates after kidney transplantation in ADPKD patients. Barbouch et al. (29), in their study comparing kidney transplant patients due to ADPKD and other nephropathies in terms of graft and patient survival, reported that they did not observe any significant difference between the two groups. In our study, patient and graft survival were found to be similar in the ciliopathy and non-ciliopathy groups. This result shows that promising results can be obtained with close monitoring, even in genetic diseases with multisystem involvement, such as ciliopathy.

Mehrabi et al. (17) reported that the 1-year, 3-year, 5-year, and 10-year graft survival rates for cadaveric donor transplant recipients in 250 cases of PKD were 97%, 96%, 95%, and 85%. In the same study, cumulative 1-year, 3-year, 5-year and 10-year graft survival rates for living donor transplant recipients were reported as being 100%, 100%, 100% and 75%. Graft survival rates were found to be similar for kidney transplants from living and cadaveric donors (17). In our study, eighteen of the patients received transplants from a living donor and 13 from a cadaveric donor. The 1-year, 5-year and 10-year graft survival rates were 92%, 92%, and 85% for the cadaver donors and 100%, 100%, and 100% for the living donors, respectively. Our study supports that the idea that transplantation from a carefully selected living donor may be a good option even in genetically inherited diseases such as ciliopathy.

Our study highlights the complexity of pediatric ciliopathies in the context of transplantation. However, it is essential to acknowledge that "ciliopathy" functions as an umbrella term for a highly heterogeneous group of diseases, including ADPKD, ARPKD, and NPHP, which differ significantly in their pathophysiology and systemic manifestations. While combining these into a single analytical category was necessary for statistical viability in this rare pediatric cohort, it inherently limits our ability to derive disease-specific conclusions. Specifically, the inclusion of ADPKD, a condition more frequently studied in adults, underscores the aggressive nature of early-onset phenotypes within the ciliopathy spectrum.

Regarding prognosis, our findings suggest that kidney transplants from well-selected living donors yield more favorable outcomes in terms of graft and patient survival for those patients with ciliopathy.

Study Limitations

Several limitations of this small, single-center retrospective cohort study warrant consideration. First, the retrospective design prevented us from obtaining complete molecular genetic data for all patients, a significant drawback when studying genetically determined disorders. Second, the comparative analysis between the ciliopathy and non-ciliopathy groups was not fully adjusted for potential confounders, such as the duration of ESKD or the specific severity of extrarenal involvements. Additionally, unadjusted factors such as varying immunosuppressive regimens, driven by the primary disease's systemic manifestations, may have influenced the interpretability of our results.

Conclusion

Finally, our study was constrained by its small sample size, particularly after subdividing into specific disease groups. This reduced the statistical power to detect minor differences; therefore, the lack of significant differences in survival rates might reflect a Type II error (lack of power) rather than true clinical equivalence. Consequently, these results should be interpreted with caution and they should be validated by larger, multicenter studies.

Ethics

Ethics Committee Approval: The study protocol was approved by Ege University's Medical Research Ethics Committee (approval number: 22-12.1T/4, date: 15.12.2022).

Informed Consent: This study was designed as a retrospective cohort trial.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.T., B.S.K., S.Ş., G.K., T.Ö.S., S.C.T., A.K., İ.K.B., Concept: S.T., N.B.Ö., İ.K.B., Design: S.T., N.B.Ö., İ.K.B., Data Collection or Processing: S.T., N.B.Ö., S.Ö., Analysis or Interpretation: S.T., N.B.Ö., S.Ö., Literature Search: S.T., N.B.Ö., B.S.K., S.Ş., İ.K.B., Writing: S.T., N.B.Ö., G.K., İ.K.B.

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Original Article

Blood Glucose ≤30 mg/dL as a Predictor of Symptomatic Hypoglycemia among Hypoglycemic Neonates in the First Four Hours of Life

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ABSTRACT

Aim: To determine predictors of symptomatic presentation among neonates diagnosed with hypoglycemia within the first four hours of life.

Materials and Methods: A retrospective cohort study was conducted using the medical records of hypoglycemic neonates evaluated within four hours postpartum at neonatology unit of the Hospital Nacional Docente Madre Niño San Bartolomé in Lima, Peru. Neonates with symptomatic hypoglycemia were compared to those with asymptomatic hypoglycemia. Multivariate logistic regression and receiver operating characteristic (ROC) analysis were performed.

Results: Among 95 hypoglycemic neonates, 48 (50.5%) exhibited symptoms. A blood glucose level ≤30 mg/dL was strongly associated with symptomatic presentation [adjusted odds ratio: 5.84; 95% confidence interval (CI): 1.58-21.5]. ROC analysis demonstrated fair discriminatory capacity (area under the curve: 0.671; 95% CI: 0.562-0.779). No significant associations were found for sex, birth weight, or gestational age.

Conclusion: Among hypoglycemic neonates, a glucose level ≤30 mg/dL is a predictor of symptomatic presentation within the first four hours. The model's modest discriminatory performance highlights the need for larger prospective studies to refine risk stratification.

Keywords: Newborn, neonatal disease, hypoglycemia, risk factors, neonatal screening

INTRODUCTION

Neonatal hypoglycemia is the most prevalent metabolic disorder in newborns, with reported incidence rates of 5-7% in at-term newborns and 3-14% in preterm populations (1-3). Its high frequency is largely attributable to risk factors such as prematurity (4), small-for-gestational-age (SGA) status (1,5), and maternal diabetes (6-13), collectively accounting for approximately 50% of neonatal hypoglycemia cases. In at-risk neonates, auxiliary evaluations, most notably capillary glucose measurements are recommended within the first four hours of life.

During the immediate postnatal period, neonates experience a physiological decrease in blood glucose levels, due primarily to the interruption of maternal

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glucose flow at the moment of umbilical cord clamping (14). To maintain euglycemia, neonates rapidly activate endogenous regulatory pathways, including hepatic glycogenolysis and gluconeogenesis (14,15). Insufficiencies in these mechanisms can lead to a precipitous drop in serum glucose concentrations. Without appropriate and timely intervention, untreated hypoglycemia significantly increases the likelihood of clinical manifestations ranging from tremors, irritability, and lethargy to apnea, seizures, and coma and also heightens the risk of persistent neurological sequelae, such as psychomotor delays, cognitive impairments, or even epileptic syndromes (16-18).

The precise timing of symptomatic onset is critical for diagnosing and managing hypoglycemia. Existing guidelines suggest a broad temporal window, and studies of symptom sensitivity for hypoglycemia remain inconclusive (6,19). Some investigations have indicated that symptoms appear within the first 24 to 48 hours of life, whereas others have proposed that reduced serum glucose may persist until 72 hours before overt clinical signs manifest (2,20). Physiologically, however, glucose levels reach their nadir between 2 and 4 hours of life, following which homeostatic mechanisms become fully activated (21,22). As the current consensus on normal glycemia values for term, preterm, or high-risk neonates is lacking (4), the Spanish Society of Pediatric Endocrinology defines neonatal hypoglycemia as blood glucose <45 mg/dL while proposing additional thresholds based on postnatal age (23-25). This can be problematic, particularly since the lowest glucose concentrations occur during the initial hours of life, when diagnostic screenings are not typically administered unless symptoms are evident, and because screening devices show decreased accuracy at lower glucose levels (14,26).

Among neonates with established hypoglycemia (<45 mg/dL), the degree of glucose reduction is a key determinant of whether clinical symptoms develop. This relationship reflects the severity of metabolic disruption and the neonate's compensatory capacity. Thus, identifying a specific glucose threshold which predicts symptom onset within the hypoglycemic population is clinically relevant for guiding interventions.

Understanding the timing and predictors of symptomatic hypoglycemia may optimize the scheduling of glucose monitoring, reduce unnecessary interventions, and improve outcomes. This study aimed to identify predictors of symptomatic presentation among neonates diagnosed with hypoglycemia within the first four hours of life, to guide timely interventions and to minimize neurological complications.

Materials and Methods

This was a retrospective cohort study of neonates diagnosed with hypoglycemia (<45 mg/dL) within the first four hours of life. The study population was divided into two groups based on the presence or absence of clinical symptoms: symptomatic hypoglycemia (cases) and asymptomatic hypoglycemia (controls). The study design was therefore a comparative cohort analysis of hypoglycemic neonates, rather than a traditional case-control study of risk factors for developing hypoglycemia. This study was conducted at the neonatology unit of the Hospital Nacional Docente Madre Niño San Bartolomé, a national teaching and referral maternal-child hospital in Lima, Peru, from January 2022 to December 2023. The exposed group (symptomatic hypoglycemia) was defined as neonates with a capillary blood glucose level <45 mg/dL accompanied by at least one clinical sign such as tremors, jitteriness, lethargy, hypotonia, weak sucking, apnea, or seizures. The unexposed group (asymptomatic hypoglycemia) consisted of neonates with a capillary blood glucose level <45 mg/dL within the same timeframe but without any accompanying clinical signs.

The threshold of <45 mg/dL was selected based on guidelines from the Spanish Society of Pediatric Endocrinology and it aligns with operational thresholds recommended by the American Academy of Pediatrics for the first 4 hours of life. While other organizations such as the Canadian Paediatric Society use <47 mg/dL, our choice reflects a conservative approach commonly employed in our clinical setting.

Blood glucose measurement was performed within the first four hours of life as part of standard clinical protocol. Inclusion criteria for both groups were neonates of either sex within the first 4 hours of life with a diagnosis of hypoglycemia (capillary glucose <45 mg/dL) and complete medical record data for predefined risk factors. Exclusion criteria included neonates with congenital metabolic or genetic disorders such as congenital hypothyroidism, adrenal hyperplasia, phenylketonuria, galactosemia, or cystic fibrosis, as well as those from twin or multiple pregnancies.

Capillary blood glucose was measured using Accu-Chek® point-of-care glucometers calibrated according to the manufacturer's specifications. Quality control was performed daily per hospital protocol using standard control solutions. Confirmatory laboratory venous glucose testing was not routinely performed, as point-of-care measurements are standard practice for screening in the immediate care unit.

Data were retrospectively abstracted from medical records using a standardized data collection form. Capillary blood glucose was measured via a standardized heel prick procedure performed by trained nursing staff and recorded in mg/dL. The neonatal information and measurements collected included sex, birth weight, birth length, head circumference, and the precise time of glucose measurement. Gestational age was determined clinically using the Capurro B scale. Birth weight was categorized as low birth weight (<2,500 g), normal (2,500-4,000 g), or macrosomic. Weight for gestational age was classified as (SGA, <10th percentile), [appropriate for gestational age (AGA), 10th-90th percentile], or large for gestational age (LGA, >90th percentile) using established percentile charts. Maternal and pregnancy variables included advanced maternal age (>35 years), inadequate prenatal care (<6 visits), gestational diabetes, gestational hypertension (blood pressure ≥140/90 mmHg on two occasions 4 hours apart after 20 weeks), pregestational body mass index (BMI), maternal obesity (BMI≥30 kg/m^2), total gestational weight gain, excessive gestational weight gain according to Institute of Medicine guidelines, and mode of delivery.

The sample size was calculated *a priori* using G*Power software. Based on previous studies, we estimated a 30% prevalence of symptomatic hypoglycemia among neonates with hypoglycemia and expected to detect an odds ratio of 3.5 for the primary predictor. With a two-sided alpha of 0.05, 80% power, and 1:1 ratio of symptomatic to asymptomatic neonates, a minimum of 46 participants per group was required. A non-probabilistic convenience sampling method was employed, reviewing all eligible medical records until the target sample size was met, resulting in 95 neonates (48 symptomatic, 47 asymptomatic) for the final analysis (Figure 1).

The study protocol was approved by the Institutional Ethics Committees of Investigación de la Universidad Científica del Sur (CIEI-CIENTÍFICA) (approval no.: 537-CIEI-CIENTÍFICA-2024, date: 25.06.2024). The requirement for informed consent was waived due to the retrospective nature of this study using anonymized data. Data confidentiality was maintained through password-protected electronic files and the removal of identifying details prior to analysis, following the principles of the Declaration of Helsinki.

Statistical Analysis

Statistical analysis was performed using Stata Version 18. Normality of continuous variables was assessed with the Shapiro-Wilk test. Descriptive statistics included means with standard deviations for normally distributed variables, medians with interquartile ranges for non-normal variables, and frequencies with percentages for categorical variables. Bivariate analyses used Pearson's chi-square test (or Fisher's exact test) for categorical variables and Student's t-test (or the Mann-Whitney U test) for continuous variables. Variables for the multivariate logistic regression model were selected *a priori* based on clinical relevance and the

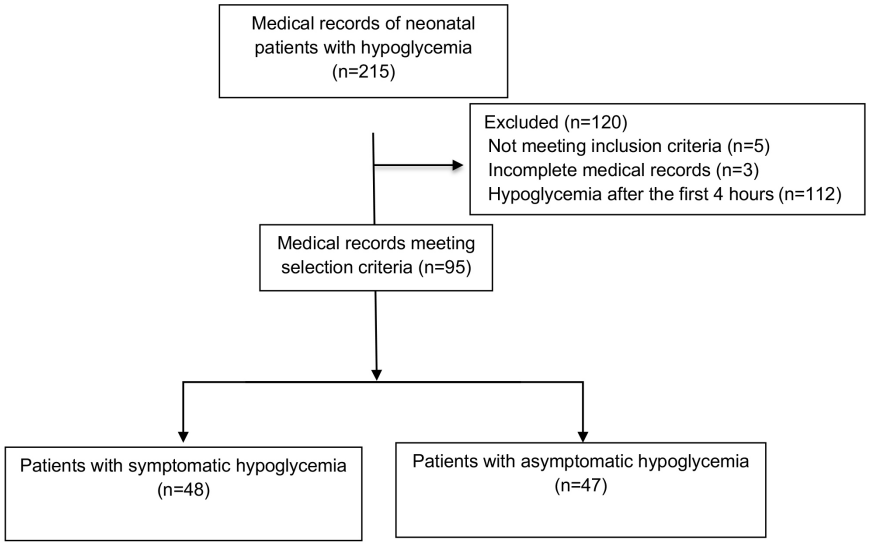

Figure 1. Study population (STROBE flow diagram)

established literature, including blood glucose level, sex, birth weight, birth length, gestational age, delivery type, maternal obesity, and time of glucose measurement. To minimize the risk of overfitting given the sample size (n=95), the model was limited to these 8 prespecified variables without automated stepwise selection. The results are presented as adjusted odds ratios with 95% confidence intervals. The model's discriminatory performance was assessed using receiver operating characteristic (ROC) curve analysis, with the area under the curve (AUC) calculated to quantify predictive accuracy. The optimal probability cut-point was determined based on the maximum sum of sensitivity and specificity.

Results

A total of 95 neonates were analyzed: 48 (50.5%) with symptomatic hypoglycemia and 47 (49.5%) asymptomatic. No statistically significant differences were found between the groups regarding sex, birth weight, length, head circumference, or gestational age. The mean time of measurement was 2.2±0.7 hours in both groups (p=0.793), with no significant difference in sampling timing between the symptomatic and asymptomatic neonates.

Most neonates were classified as AGA (54.7%), with no significant group differences in weight categories. Maternal characteristics such as advanced maternal age (>35 years), inadequate prenatal care (<6 visits), gestational diabetes,

Table I. Baseline neonatal and maternal characteristics stratified by symptomatic hypoglycemia status

Neonatal characteristics	**Total (n=95)**	**Symptomatic hypoglycemia (n=48)**	**Asymptomatic hypoglycemia (n=47)**	**p value**
Male sex, n (%)	62 (65.3)	30 (62.5)	32 (68.1)	0.568
Birth weight, g, mean±SD	3,173±789	3,236±807	3,108±773	0.430
Birth length, cm, mean±SD	48.4±2.8	48.4±2.8	48.3±2.8	0.797
Head circumference, cm, mean±SD	33.6±2.0	33.8±1.9	33.4±2.2	0.344
Blood glucose (first 4h), mg/dL, mean±SD	36.8±7.0	35.2±8.3	38.5±5.1	0.022†
Time of glucose measurement, hours, mean±SD	2.2±0.7	2.2±0.7	2.2±0.7	0.793
Birth weight category, n (%)				
Normal	53 (55.8)	25 (52.1)	28 (59.6)	1.00 (Reference)
Low	23 (24.2)	12 (25.0)	11 (23.4)	0.688
Macrosomic	19 (20.0)	11 (22.9)	8 (17.0)	0.422
Weight for gestational age, n (%)				
Appropriate	52 (54.7)	23 (47.9)	29 (61.7)	1.00 (Reference)
Small	24 (25.3)	15 (31.3)	9 (19.1)	0.138
Large	19 (20.0)	10 (20.8)	9 (19.1)	0.529
Maternal & pregnancy characteristics				
Gestational age, weeks, mean±SD	38.3±1.7	38.4±1.7	38.2±1.6	0.553
Advanced maternal age (>35 years), n (%)	25 (26.3)	15 (31.3)	10 (21.3)	0.270
Inadequate prenatal care (<6 visits), n (%)	34 (35.8)	17 (35.4)	17 (36.2)	0.939
Gestational hypertension, n (%)	3 (3.2)	0 (0.0)	3 (6.4)	--
Gestational diabetes, n (%)	10 (10.5)	6 (12.5)	4 (8.5)	0.526
Pregestational BMI, kg/m^2, mean±SD	27.8±5.8	27.7±4.9	27.9±6.5	0.858
Maternal obesity (BMI≥30), n (%)	18 (19)	7 (14.6)	11 (23.4)	0.273
Total gestational weight gain, kg, mean±SD	10.6±6.5	11.4±6.9	9.8±6.2	0.407
Excessive gestational weight gain, n (%)	17 (17.9)	11 (22.9)	6 (12.8)	0.197
Cesarean delivery, n (%)	34 (35.8)	19 (39.6)	15 (31.9)	0.436

†Variable with statistically significant in the univariate and multivariate analysis. Bold indicates statistical significance (p<0.05)
SD: Standard deviation, BMI: Body mass index

and pregestational BMI were similarly distributed between the groups and they were without statistical significance. Gestational hypertension was observed in three cases, all in the asymptomatic group (Table I).

Upon analyzing specific neonatal factors, symptomatic newborns had a significantly lower mean blood glucose when compared to the asymptomatic ones (35.2±8.3 mg/dL vs. 38.5±5.1 mg/dL; p=0.022). Notably, nearly one-third (29.2%) of the symptomatic neonates had blood glucose levels ≤30 mg/dL, compared to only 8.5% in the asymptomatic group. Although it did not reach statistical significance, a trend towards a higher frequency of SGA infants was observed in the symptomatic group (31.3% vs. 19.1%; p=0.138).

Regarding maternal factors, excessive gestational weight gain was more than twice as frequent in the mothers of symptomatic neonates (22.9% vs. 12.8%), although this difference was not statistically significant (p=0.197). Maternal obesity, by contrast, showed an inverse trend, being less frequent in the symptomatic case group (14.6% vs. 23.4%).

Box plot analysis showed a lower and more variable glucose distribution in the symptomatic group, while the asymptomatic group had a narrower, more centralized distribution (Figure 2).

In the multivariate logistic regression analysis, only blood glucose level emerged as a statistically significant independent predictor of symptomatic hypoglycemia (coefficient: -0.079; p=0.021). Sex, birth weight, birth length, gestational age, delivery type, maternal obesity, and time of glucose measurement showed no significant associations (all p>0.05) (Table II). The overall model demonstrated poor fit (LR $\chi2$=8.26, p=0.220; pseudo R^2=0.063).

ROC curve analysis of the logistic regression model yielded an AUC of 0.671 [95% confidence interval (CI): 0.562-0.779], indicating fair discriminatory capacity for predicting symptomatic presentation among hypoglycemic neonates. The optimal probability threshold was 0.30, corresponding to a glucose value of approximately 32 mg/dL, with 62.5% sensitivity and 65.9% specificity. This threshold, while statistically derived, should be interpreted cautiously given the modest model performance. No cut-point achieved both high sensitivity (>80%) and high specificity (>80%) simultaneously (Figure 3).

The multivariate logistic regression analysis confirmed that a blood glucose level ≤30 mg/dL was the only independent and statistically significant predictor of symptomatic hypoglycemia (adjusted Odds ratio: 5.84; 95% CI: 1.58-21.50), even after adjusting for birth weight, gestational age, gestational diabetes, and other relevant maternal factors.

Among symptomatic neonates, the most common clinical sign was tremor (64.5%), followed by hypoactivity (39.6%) and weak sucking (16.7%). Less frequent symptoms included respiratory distress (4.1%) and distal coldness (2.1%) (Figure 4).

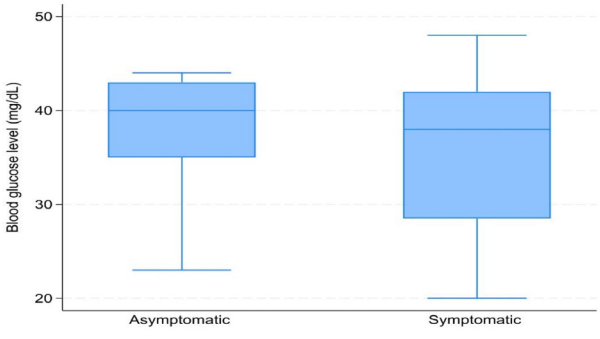

Figure 2. Distribution of blood glucose levels in symptomatic vs. asymptomatic neonates. *The box plot illustrates the lower and more variable blood glucose levels in the symptomatic group (n=48) compared to the asymptomatic group (n=47) within the first four hours of life. The central line within each box represents the median, the box encompasses the interquartile range (25th-75th percentiles), and the whiskers show the variability outside the upper and lower quartiles*

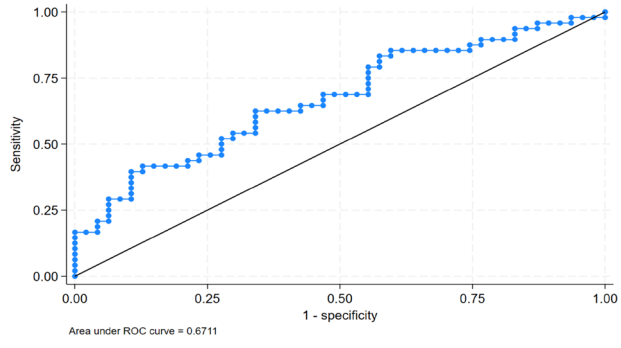

Figure 3. Receiver operating characteristic (ROC) curve for the prediction of symptomatic hypoglycemia. The area under the curve (AUC) is 0.671 (95% CI: 0.562-0.779), indicating fair discriminatory ability. The diagonal reference line represents no discriminatory power (AUC=0.5)
CI: Confidence interval

Table II. Crude and adjusted associations between neonatal/maternal factors and symptomatic hypoglycemia

Factor	Symptomatic n=48 n (%)	Asymptomatic n=47 n (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)
Neonatal factors				
Male sex	30 (62.5)	32 (68.1)	0.78 (0.33-1.82)	0.85 (0.32-2.31)
Blood glucose ≤30 mg/dL	14 (29.7)	4 (8.51)	**4.42 (1.33-14.67)**	**5.84 (1.58-21.5)**
Birth weight category				
Normal	25 (52.1)	28 (59.6)	Reference	Reference
Low	12 (25.0)	11 (23.4)	1.22 (0.45-3.25)	1.04 (0.27-3.94)
Macrosomic	11 (22.9)	8 (17.0)	1.54 (0.53-4.43)	2.61 (0.21-31.1)
Weight for gestational age				
Appropriate	23 (47.9)	29 (61.7)	1.00 (Reference)	1.00 (Reference)
Small	15 (31.3)	9 (19.1)	2.10 (0.77-5.66)	2.12 (0.59-7.67)
Large	10 (20.8)	9 (19.1)	1.40 (0.48-4.01)	0.57 (0.05-6.02)
Maternal & pregnancy factors				
Advanced maternal age (>35 years)	15 (31.3)	10 (21.3)	1.68 (0.66-4.25)	1.96 (0.65-5.90)
Inadequate prenatal care (<6 visits)	17 (35.4)	17 (36.2)	0.96 (0.41-2.23)	1.05 (0.38-2.85)
Gestational diabetes	6 (12.5)	4 (8.5)	1.53 (0.40-5.83)	1.27 (0.27-5.95)
Maternal obesity (BMI≥30)	7 (14.6)	11 (23.4)	0.55 (0.19-1.59)	0.44 (0.13-1.48)
Excessive gestational weight gain	11 (22.9)	6 (12.8)	2.03 (0.68-6.03)	3.32 (0.92-11.96)
Cesarean delivery	19 (39.6)	15 (31.9)	1.39 (0.60-3.24)	0.87 (0.24-3.05)

*Adjusted for all other variables listed in the table. Bold indicates statistical significance (p<0.05).
OR: Odds ratio, CI: Confidence interval, BMI: Body mass index

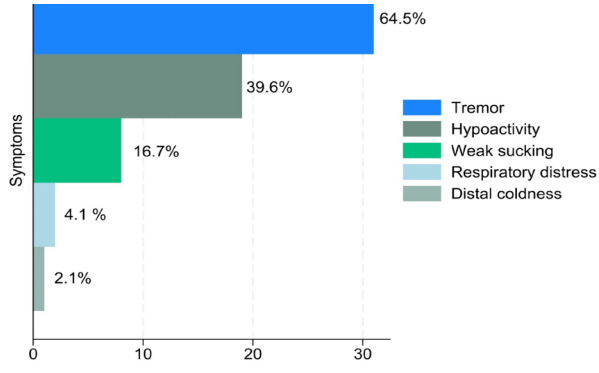

Figure 4. Prevalence of clinical manifestations among neonates with symptomatic hypoglycemia (n=48). The bar chart displays the frequency of clinical signs observed in the study cohort. Tremor was the most common symptom, present in 64.5% of symptomatic neonates, followed by hypoactivity (39.6%) and weak sucking (16.7%)

Discussion

Neonatal hypoglycemia represents a prevalent metabolic disorder in newborns, necessitating early recognition and intervention in order to mitigate associated complications. Identifying factors which predict symptomatic presentation among hypoglycemic neonates is essential in order to improve clinical outcomes and reduce long-term sequelae.

Our findings demonstrate that a blood glucose concentration of ≤30 mg/dL significantly increases the risk of symptomatic hypoglycemia. These results align with previous studies, such as those conducted in New Zealand and India, which showed that severe hypoglycemia (defined as glucose levels below 2 mmol/L or 35 mg/dL) correlates strongly with the onset of symptoms (27,28). One study demonstrated that lower glucose levels were significantly associated with the presence of hypoglycemia symptoms (29). Additional studies have reported mean glucose levels of 20±10 mg/dL in symptomatic neonates compared to 27.3±7 mg/dL in their asymptomatic counterparts, further corroborating our observations (30).

Severe hypoglycemia (≤30 mg/dL) has been implicated in neurodevelopmental impairments (31), particularly in cases of prolonged or recurrent episodes (32). Recurrent hypoglycemia in preterm neonates has been associated with lower scores on the Bailey scale, cognitive delays, and developmental deficits, reinforcing the necessity of prompt and aggressive management (31). The current clinical guidelines advocate for intravenous glucose administration in cases of symptomatic or severe hypoglycemia in order to prevent irreversible neuronal damage (33,34).

By contrast, our study did not find significant associations between low birth weight and symptomatic hypoglycemia. This contrasts with previous research from Japan (35), where low birth weight neonates frequently exhibited asymptomatic hypoglycemia within the first hour of life, without clear symptom development. Similarly, the classification as SGA did not emerge as a significant predictor of symptomatic hypoglycemia in our cohort. However, prior studies in India have reported symptomatic hypoglycemia rates of 10.3% and 31% in SGA neonates, a discrepancy which is potentially attributable to differences in study design and population characteristics (29,36).

The observed trend towards a higher frequency of SGA infants in the symptomatic group, while not statistically significant, warrants consideration. It is plausible that our study did not have the power to detect a moderate association. SGA neonates have limited hepatic glycogen stores and an impaired capacity for gluconeogenesis, theoretically rendering them more susceptible to symptomatic hypoglycemia. The discrepancy with those previous studies which reported a strong association could be attributed to differences in the definition of SGA, the timing of the glucose measurement, or the characteristics of the reference population (29,36). Future studies with a larger sample size are needed in order to clarify this relationship within the critical first four-hour window.

Our multivariate analysis established blood glucose level as the predominant predictor of symptomatic hypoglycemia in the immediate postnatal period, with a negative coefficient confirming the expected inverse relationship: decreasing glucose concentrations significantly increase the probability of symptomatic presentation. Notably, traditional risk factors such as birth weight and gestational age demonstrated limited predictive utility within this specific physiological window.

The model's discriminatory capacity, while statistically significant, was modest (AUC: 0.671), underscoring the complexity of symptomatic presentation and suggesting contributions from unmeasured variables. The inability to identify a probability cut-point with both high sensitivity and specificity further highlights the challenges in applying probabilistic models to individual clinical decision-making in this context.

The primary strength of this study lies in its focused investigation of the physiologically crucial first four hours of life, a period characterized by dynamic metabolic transitions but frequently understudied in the existing literature. Our identification of glucose ≤30 mg/dL as a strong, independent predictor provides clinicians with a clear, quantifiable threshold for targeted interventions during this vulnerable period.

Study Limitations

This study had several limitations. The retrospective design inherently limited data collection to previously documented medical records, potentially introducing information bias. The sample size, while adequate for detecting the primary association with glucose levels, may have constrained the statistical power in identifying more modest effects of other risk factors. Furthermore, being conducted at a single institution may affect generalizability to populations with differing demographic and clinical characteristics.

Additionally, point-of-care glucometers are known to have decreased accuracy at glucose levels <40 mg/dL, and confirmatory laboratory testing was not routinely performed. This may have introduced measurement bias, particularly in the severe hypoglycemia range, and should be considered when interpreting the threshold of ≤30 mg/dL.

Finally, the observed association between glucose ≤30 mg/dL and symptomatic presentation is physiologically expected; glucose level in this context functions more as a severity marker than as an independent risk factor. Our study quantifies this association but does not establish causality.

Conclusion

In this context, glucose ≤30 mg/dL should be viewed as a predictor of symptomatic presentation among hypoglycemic neonates within the first four hours of life. However, the modest discriminatory performance of our model (AUC: 0.671) and the limited sample size underscore the need for caution in clinical application. Larger prospective studies with standardized symptom assessment and confirmatory laboratory glucose measurement are needed in order to validate these findings and refine intervention thresholds.

Ethics

Ethics Committee Approval: The study protocol was approved by the Institutional Ethics Committees of Investigación de la Universidad Científica del Sur (CIEI-CIENTÍFICA) (approval no.: 537-CIEI-CIENTÍFICA-2024, date: 25.06.2024).

Informed Consent: The requirement for informed consent was waived due to the retrospective nature of this study using anonymized data.

Footnotes

Authorship Contributions

Surgical and Medical Practices: C.J.B.M., R.W.O.G., A.C.L., W.A.-Q., Concept: C.J.B.M., R.W.O.G., W.A.-Q., Design: C.J.B.M., R.W.O.G., W.A.-Q., Data Collection or Processing: C.J.B.M., R.W.O.G., A.C.L., Analysis or Interpretation: W.A.-Q., Literature Search: C.J.B.M., R.W.O.G., A.C.L., Writing: C.J.B.M., R.W.O.G., A.C.L., W.A.-Q.

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Original Article

Minimal Wheal Reactions on Skin Prick Testing Predict Future Aeroallergen Sensitization in Children: A Longitudinal Study

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ABSTRACT

Aim: Skin prick testing (SPT) provides a rapid, inexpensive, and reliable means of confirming IgE-mediated sensitization in the context of clinical history. This study aimed to evaluate whether baseline SPT reactivity, particularly minimal reactions, predicts the development of new aeroallergen sensitizations during long-term follow-up.

Materials and Methods: In this longitudinal observational study, 121 children who underwent repeat SPT after an interval of at least three years were included. The patients were stratified into four groups based on their baseline maximum wheal diameter and subcutaneous immunotherapy (SCIT) status: Group 1 (0 mm), Group 2 (1-2 mm), Group 3 (≥3 mm), and Group 4 (≥3 mm with SCIT). The primary outcome was new sensitization, defined as a wheal diameter ≥3 mm to an allergen which was previously negative.

Results: A total of 121 patients were included in this study. The rates of new sensitization were significantly higher in Groups 2, 3, and 4 compared with Group 1 ($p<0.001$). New house dust mite sensitization was strikingly more frequent in Group 2 (53.3%) than in all other groups ($p<0.001$). An increase in wheal diameter to the same allergen was most prominent in Group 2 (66.7%). Sensitization to pollens and cat epithelium increased significantly after 10 years of age ($p<0.05$). A history of coronavirus disease-2019 was associated with new sensitizations (odds ratio: 2.97, $p=0.034$).

Conclusion: Minimal SPT reactions (1-2 mm) in symptomatic children are clinically relevant and predict a high risk of developing frank aeroallergen sensitization during follow-up. Repeat SPT should be considered in this population in order to guide timely interventions.

Keywords: Aeroallergen sensitization, skin prick test, minimal wheal reaction, house dust mite, children

Introduction

Allergic rhinitis and asthma are among the most common chronic allergic diseases in childhood, and aeroallergen sensitization plays a key role in their pathogenesis (1,2). Identifying sensitization patterns is essential for diagnosis, environmental control, follow-up, and the selection of candidates for allergen immunotherapy. Skin prick testing (SPT) is widely used as a rapid, inexpensive, and reliable method for detecting IgE-mediated sensitizations (1,3).

However, aeroallergen sensitization in childhood is dynamic. Sensitization profiles evolve under the influence of age, genetics, environmental exposures, and immune maturation (4,5). Longitudinal studies have shown that new sensitizations frequently develop during follow-up,

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with a broadening allergen spectrum and a shift toward outdoor pollens and pet allergens in later childhood (4-8). Environmental factors, including passive smoke, indoor dampness/mold, pet ownership, and cockroach exposure, are linked to allergic sensitization and respiratory morbidity (9-11), yet their role in driving new sensitizations among children with minimal baseline reactivity remains unclear (12).

Although SPT is essential in pediatric allergy practice, indications and optimal timing for repeat testing are poorly defined. The conventional ≥3 mm positivity threshold may miss early or evolving sensitizations in children (13). Repeat testing is often considered for persistent symptoms, changing clinical findings, or borderline initial results (6). The clinical significance of minimal wheal reactions (1-2 mm) which fall below the standard cutoff is particularly uncertain.

Therefore, this study aimed to evaluate the prognostic significance of baseline SPT reactivity, especially minimal (1-2 mm) reactions, on subsequent sensitization patterns in children undergoing repeat SPT after ≥3 years. We also sought to identify any clinical or environmental factors associated with new sensitization developments.

Materials and Methods

Study Design and Patients

This longitudinal observational study included children with a history of allergic disease who were followed up at the pediatric allergy outpatient clinic of a university hospital. Eligible participants had undergone aeroallergen SPT at baseline and were reevaluated with a repeat SPT after an interval of at least 3 years. Exclusion criteria were as follows: (1) the use of antihistamines or systemic corticosteroids within 7 days prior to the SPT; (2) the presence of dermatographism or extensive eczema precluding skin testing; (3) incomplete clinical or laboratory data.

A total of 121 patients were included in this study. According to their baseline skin test reactivity and immunotherapy status, the patients were classified into four groups:

Group 1: Children without sensitization (all allergens with wheal diameter=0 mm; n=30).

Group 2: Children with minimal wheal reactions (wheal diameter of 1-2 mm to at least one allergen, but none ≥3 mm); n=30.

Group 3: Children with established sensitization (wheal diameter of ≥3 mm to at least one allergen); n=30.

Group 4: Children with established sensitization (≥3 mm) who were receiving subcutaneous immunotherapy (SCIT) during follow-up (Note: baseline SPT was performed prior to SCIT initiation); n=31.

Data Collection

Demographic, clinical, environmental, and laboratory data were recorded via a structured case report form. The variables which were collected included age, sex, birth characteristics, family history of atopy (≥1 first-degree relative with physician-diagnosed allergic rhinitis, asthma, or atopic dermatitis), sibling status, diagnoses, body mass index (BMI) z-scores, total and specific IgE, and absolute eosinophil count. The environmental/lifestyle variables included household smoking, open kitchen, residence location (urban/rural), pet exposure, cockroach exposure, indoor dampness/mold, indoor plants, vegetable intake, a history of the coronavirus disease-2019 (COVID-19), and junk food consumption frequency. A history of COVID-19 was recorded based on a parental report and referred to those infections which had occurred between the first and second SPT assessments. Laboratory confirmation was not consistently available. The presence of new sensitizations during follow-up was also recorded.

Skin Prick Testing

Skin prick testing was performed using standardized extracts (ALLERGO®) per the European Academy of Allergy and Clinical Immunology (EAACI) recommendations (14). The volar forearm was cleaned with alcohol, and allergens were applied with negative (saline) and positive (10 mg/mL histamine) controls. A histamine wheal ≥3 mm was required for validity. Reactions were evaluated after 20 minutes, and wheal diameters were measured at their widest point and also perpendicular to it, with the mean of these two measurements recorded in millimeters. The aeroallergen panel included Dermatophagoides farinae, Dermatophagoides pteronyssinus, cat epithelium, weed mix, grass mix preparations, mugwort, ribwort plantain, nettle, meadow fescue/timothy-type grass components, olive tree, ash tree, poplar tree, tree mix, Alternaria, and Aspergillus. The same aeroallergen panel was used for each patient at both their baseline and follow-up SPT assessments.

Outcomes

The primary outcome was a new sensitization (wheal ≥3 mm to an allergen with a baseline <3 mm). Secondary outcomes included increase/decrease in wheal diameter (≥2 mm change) and the loss of prior sensitization (≥3

mm falling to <3 mm). Factors associated with new sensitizations were also evaluated.

Ethical Considerations

This study was approved by the Ege University Medical Research Ethics Committee (approval no.: 23-7.1T/42, date: 27.07.2023) and conducted per the Declaration of Helsinki. Written informed consent was obtained from the parents or legal guardians of the participants, and assent was obtained from the children when appropriate.

Statistical Analysis

Statistical analyses were conducted using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Normality was assessed using the Shapiro-Wilk test and histograms. Normally distributed variables are presented as mean±standard deviation and were compared using one-way analysis of variance (ANOVA), with Tukey honestly significant difference tests for post-hoc pairwise comparisons. Non-normally distributed variables are presented as median (minimum-maximum) and were compared using the Kruskal-Wallis test; when the overall comparison was statistically significant, exploratory pairwise comparisons were performed using the Mann-Whitney U test. Categorical variables are presented as numbers and percentages and were compared using the chi-square test or Fisher's exact test, as appropriate; when the overall comparison was statistically significant, exploratory pairwise comparisons of proportions were performed. Univariable logistic regression was used to explore predictors of new sensitization, with results expressed as odds ratios (ORs) and 95% confidence intervals (CIs). A limited multivariable logistic regression model was constructed in order to assess whether the association between COVID-19 history and new sensitizations remained independent after adjustments for age at first SPT, sex, and baseline aeroallergen-specific IgE. Subgroup analysis was conducted in order to examine predictors of wheal increase in Group 2. A p value of <0.05 was considered statistically significant.

Results

A total of 121 children were included in this study. Based on their baseline skin prick test reactivity and subcutaneous immunotherapy status, the patients were allocated into four groups: Group 1 (n=30), Group 2 (n=30), Group 3 (n=30), and Group 4 (n=31). The mean age at the first SPT was 99.4±33.6 months, the mean age at the second SPT was 144.8±34.0 months, and the mean interval between the two tests was 54.9±14.0 months. At baseline, 24 patients (19.8%)

Table I. Baseline demographic, clinical, and laboratory characteristics of the study groups

Variable	Group 1 n=30	Group 2 n=30	Group 3 n=30	Group 4 n=31	p value
Age at first SPT (months) mean±SD	89.6±36.0	104.0±46.0	101.2±33.8	106.6±32.1	0.423
Age at second SPT (months) mean±SD	136.6±33.3	157.6±51.3	160.8±33.2	159.7±31.3	0.058
Interval between tests (months) median (min-max)	43 (36-69)	54.5 (36-101)	57 (36-96)	54 (36-63)	0.057
Male sex, n (%)	17 (56.7)	18 (60)	23 (76.7)	25 (80.6)	0.110
Family history of atopy, n (%)	14 (46.6)	16 (53.3)	16 (53.3)	14 (48.3)	0.935
Cesarean delivery, n (%)	13 (43.3)	12 (40)	13 (43.3)	13 (41.9)	1.000
Presence of siblings, n (%)	15 (50.0)	23 (76.6)	18 (60)	22 (70.9)	0.221
Diagnosis n (%) **Asthma** **AR** **Asthma+AR**	 16 (53.3) 7 (23.3) 7 (23.3)	 9 (30) 14 (46.6) 7 (23.3)	 8 (26.7) 13 (43.3) 9 (30.0)	 11 (35.4) 13 (41.9) 7 (22.5)	0.830
Total IgE (kU/L) median (min-max)	134^{ab} (0-1186)	102^{a} (6.5-1009)	309^{b} (37.3-1222)	517^{c} (51-2940)	**<0.001**
Aeroallergen-specific IgE (kU/L) median (min-max)	0.07^{a} (0-2.23)	0.69^{b} (0-22.4)	12.4^{c} (0.04-88.79)	32.2^{d} (0-180)	**<0.001**
Eosinophil count, (/mm^3) median (min-max)	231^{ab} (11-1050)	200^{a} (10-967)	361^{b} (83-1450)	747^{c} (123-1514)	**<0.001**
Body mass index (kg/m^2) mean±SD	22.06±3.81	20.83±4.03	22.08±3.92	23.50±3.20	0.150

P values were calculated using one-way ANOVA, Kruskal-Wallis test, chi-square test, or Fisher's exact test, as appropriate. For laboratory variables with significant overall differences, superscript letters indicate exploratory post-hoc pairwise comparisons; values sharing at least one superscript letter are not significantly different. Those results shown in bold are statistically significant
Group 1: 0 mm; Group 2: 1-2 mm; Group 3: ≥3 mm; Group 4: ≥3 mm with SCIT
AR: Allergic rhinitis, IgE: Immunoglobulin E, SPT: Skin prick test

were younger than 5 years, 56 (46.3%) were between 5 and 10 years, and 41 (33.9%) were older than 10 years.

The baseline demographic and clinical characteristics were comparable across the four groups (Table I). No significant intergroup differences were observed in terms of age, interval between tests, sex, family history of atopy, cesarean delivery, sibling status, diagnosis, or body mass index between the first and second SPT (p>0.05). However, total IgE, inhalant allergen-specific IgE, and absolute eosinophil counts differed significantly among the groups (p<0.001), with the highest values observed in Group 4 and the lowest in Groups 1 and 2.

The changes in SPT reactivity during follow-up are presented in Table II. The rate of new sensitization was significantly lower in those children with completely negative baseline tests (Group 1, 26.7%) compared to the other three groups (Group 2: 80.0%, Group 3: 66.7%, Group 4: 61.3%; p<0.001). No significant differences were found between Groups 2, 3, and 4 (p>0.05).

An increase in wheal diameter to the same allergen was most prominent in Group 2 (66.7%), and post-hoc analyses confirmed significant differences between Group 2 and both Group 3 (20.0%, p<0.001) and Group 4 (29.0%, p=0.003). A decrease in wheal diameter or the loss of prior sensitization did not differ significantly between the groups (p>0.05).

Newly developed aeroallergen sensitivity patterns are presented in Table III. New house dust mite (HDM) sensitization was strikingly more frequent in Group 2 (53.3%) than in Group 1 (13.3%), Group 3 (20.0%), and Group 4 (6.5%) (p<0.001). Similarly, new cat sensitization was observed more often in Group 2 (36.7%), Group 3 (26.7%) and Group 4 (25.8%) than in Group 1 (3.3%) (p=0.018). New weed pollen sensitization also differed between the groups (p=0.047). In contrast, no significant between-group differences were found for newly developed grass pollen, tree pollen, or mold sensitization (p>0.05).

Potential factors associated with the development of new sensitizations were further examined using univariable logistic regression analyses (Table IV). Among the environmental and clinical variables, a history of COVID-19 was significantly associated with increased odds of new allergen sensitization (OR: 2.97, 95% CI: 1.08-8.15; p=0.034). No significant associations were observed for age at first SPT, the interval between tests, sex, family history of atopy, cesarean delivery, sibling status, baseline total or specific IgE, eosinophil count, residential area, household smoking exposure, open kitchen, pet exposure, mold/dampness, cockroach exposure, indoor live plants, junk food consumption, or vegetable consumption (p>0.05).

A limited multivariable logistic regression model was performed in order to assess whether the association between COVID-19 history and new sensitization remained independent after adjustments for age at first SPT, sex, and baseline aeroallergen-specific IgE. In this model, a history of COVID-19 remained independently associated with the development of new sensitization (adjusted OR: 3.06, 95% CI: 1.01-9.32; p=0.049). Age at first SPT, sex, and baseline aeroallergen-specific IgE were not independently associated with new sensitizations.

In an exploratory subgroup analysis restricted to those children with baseline wheal diameters of 1-2 mm (Group 2), univariable logistic regression did not identify any significant predictors of an increase in wheal diameter to the same allergen during the follow-up (p>0.05).

Age-stratified analyses showed no significant differences in histamine wheal diameters according to age groups or baseline sensitization status (p>0.05). Likewise, there were no significant differences among the age groups in

Table II. Changes in aeroallergen skin prick test reactivity at follow-up according to the study groups

Outcome	Group 1 n=30 (%)	Group 2 n=30 (%)	Group 3 n=30 (%)	Group 4 n=31 (%)	p value
Development of new sensitization to a previously negative allergen	8 (26.7)[a]	24 (80)	20 (66.7)	19 (61.3)	**<0.001**
Increase in wheal diameter to the same allergen	-	20 (66.7)[b]	6 (20.0)	9 (29.0)	**<0.001**
Decrease in wheal diameter to the same allergen	-	8 (26.6)	2 (6.7)	6 (19.4)	0.120
Loss of previous positive sensitization	-	-	9 (33.3)	3 (17.7)	0.059

Overall p values were calculated using the chi-square test or Fisher's exact test, as appropriate. Post-hoc pairwise comparisons were performed using pairwise comparisons of proportions. Group 1 had no baseline sensitization; therefore, changes in wheal diameter to the same allergen and loss of sensitization were not applicable. Group 2 had no baseline positive sensitization (≥3 mm); therefore, loss of sensitization was not applicable. Significant p values are shown in bold.
[a]Post-hoc pairwise comparisons showed significant differences between Group 1 and Group 2 (p<0.001), Group 1 and Group 3 (p=0.002), and Group 1 and Group 4 (p=0.006)
[b]Post-hoc pairwise comparisons showed significant differences between Group 2 and Group 3 (p<0.001) and Group 2 and Group 4 (p=0.003)

Table III. Newly developed aeroallergen sensitizations during follow-up according to the study groups

Allergen group	Group 1 n=30 (%)	Group 2 n=30 (%)	Group 3 n=30 (%)	Group 4 n=31 (%)	p value
House dust mite	4/30 (13.3)	16/30 (53.3)[a]	6/30 (20.0)	2/31 (6.5)	**<0.001**
Cat epithelium	1/30 (3.3)[b]	11/30 (36.7)	8/30 (26.7)	8/31 (25.8)	**0.018**
Grass pollen	5/30 (16.7)	9/30 (30.0)	7/30 (23.3)	3/31 (9.7)	0.232
Weed pollen	0/30 (0.0)[c]	6/30 (20.0)	7/30 (23.3)	4/31 (12.9)	**0.047**
Tree pollen	6/30 (20.0)	10/30 (33.3)	10/30 (33.3)	6/31 (19.4)	0.409
Mold	4/30 (13.3)	7/30 (23.3)	4/30 (13.3)	2/31 (6.5)	0.319

Values are n/N (%) of patients who developed a new sensitization (≥3 mm) to the specified allergen group among those who were negative (<3 mm) at baseline. Overall p values were calculated using Fisher's exact test or chi-square test, as appropriate. For allergen groups with significant overall differences, exploratory post-hoc pairwise comparisons were performed. Significant p values are shown in bold.
[a]Post-hoc pairwise comparisons showed significant differences between Group 2 and Group 1 (p=0.001), Group 2 and Group 3 (p=0.007), and Group 2 and Group 4 (p<0.001)
[b]Post-hoc pairwise comparisons showed significant differences between Group 1 and Group 2 (p=0.001), Group 1 and Group 3 (p=0.026), and Group 1 and Group 4 (p=0.013)
[c]Post-hoc pairwise comparisons showed significant differences between Group 1 and Group 2 (p=0.024) and Group 1 and Group 3 (p=0.011), whereas the difference between Group 1 and Group 4 was not statistically significant (p=0.113)

Table IV. Univariable logistic regression analyses of factors associated with the development of new allergen sensitizations

Variable	OR (95% CI)	p value
Age at first SPT, months	1.004 (0.995-1.013)	0.391
Interval between tests, months	1.020 (0.993-1.048)	0.143
Male sex	1.578 (0.728-3.423)	0.248
Family history of atopy	1.469 (0.655-3.293)	0.350
Cesarean delivery	1.552 (0.671-3.591)	0.304
Not having a sibling	1.326 (0.566-3.105)	0.516
Baseline specific IgE	1.010 (0.996-1.024)	0.161
Baseline total IgE	1.000 (0.999-1.001)	0.950
Baseline eosinophil count	1.001 (1.000-1.002)	0.216
Living in a city	1.492 (0.316-7.056)	0.614
Household smoking exposure	1.707 (0.720-4.048)	0.225
Open kitchen	2.432 (0.772-7.641)	0.128
Pet exposure at home	1.119 (0.453-2.761)	0.807
Mold/dampness at home	2.589 (0.834-8.038)	0.100
Cockroach exposure at home	1.385 (0.562-3.418)	0.479
Indoor live plants	1.655 (0.738-3.709)	0.221
History of COVID-19	2.972 (1.084-8.153)	**0.034**
Junk food consumption (overall)	—	0.291
Vegetable consumption (overall)	—	0.666

For junk food consumption and vegetable consumption, category-specific ORs are not presented because sparse cell counts in some categories resulted in unstable parameter estimates; therefore, only the overall p values for these categorical variables are shown
OR: Odds ratio, CI: Confidence interval, SPT: Skin prick test

Table V. Allergen sensitization profiles according to age groups at the first and second skin prick tests

Allergen group	SPT time	<5 years n=24 (%)	5-10 years n=56 (%)	>10 years n=41 (%)	p value
House dust mite	First	3 (12.5)	16 (28.6)	7 (27.1)	0.190
	Second	6 (25.0)	26 (46.4)	18 (43.9)	0.190
Cat epithelium	First	6 (25.0)	10 (17.9)	10 (24.4)	0.700
	Second	7 (29.2)	15 (27.3)	22 (53.7)	**0.020**
Grass pollen	First	4 (20.0)	5 (11.1)	10 (32.3)	0.070
	Second	7 (29.2)	24 (42.9)	30 (73.2)	**0.010**
Tree pollen	First	5 (20.8)	10 (17.9)	13 (31.7)	0.270
	Second	7 (29.2)	22 (39.3)	27 (65.9)	**0.006**
Weed pollen	First	1 (4.2)	7 (12.5)	8 (19.5)	0.220
	Second	3 (12.5)	11 (19.6)	16 (39.0)	**0.020**
Mold	First	1 (4.2)	4 (7.1)	3 (7.3)	0.900
	Second	7 (29.2)	8 (14.3)	10 (24.4)	0.280

Values are n (%) of patients with a positive SPT (≥3 mm) to the specified allergen group. P values were calculated using chi-square test or Fisher's exact test. Significant p values are shown in bold
SPT: Skin prick test

their baseline sensitization to individual allergen groups (Table V). However, at the second SPT, sensitization to cat epithelium, grass pollen, tree pollen, and weed pollen differed significantly across the age groups, with higher rates observed in those children older than 10 years (p=0.020, p=0.010, p=0.006, and p=0.020, respectively).

Discussion

In this longitudinal observational study, we aimed to evaluate the effects of baseline aeroallergen SPT reactivity on subsequent sensitization patterns in children who underwent repeat SPT after at least three years. Our findings demonstrated that baseline wheal diameter is a significant predictor of new allergen sensitization over time, and they underscore the clinical relevance of minimal wheal reactions (1-2 mm) which fall below the conventional 3-mm positivity threshold. Notably, those children with a baseline reactivity of 1-2 mm (Group 2) developed new sensitizations at a remarkably high rate, with house dust mite sensitization occurring in 53.3% of this group at follow-up.

The prognostic significance of small SPT reactions has been a subject of ongoing debate. Current guidelines from the EAACI and the American Academy of Allergy, Asthma & Immunology generally define a positive SPT as a wheal diameter of ≥3 mm, a threshold primarily validated in adult populations (14,15). However, emerging evidence suggests that lower cutoffs may be more appropriate in children, in whom the immune response is still maturing and evolving (13). Schoos et al. (13) recently demonstrated that the optimal specific IgE cut-off for predicting clinical allergy varies by allergen and is often lower in children, challenging the universal application of adult-derived thresholds. Similarly, Lockey et al. (16) reported that a wheal size as small as 1 mm at age one year was predictive of allergic sensitization by age two. Our findings suggest that minimal wheal reactions (1-2 mm) in symptomatic children should not be dismissed as clinically irrelevant, as they may represent early or incipient sensitizations which can progress to frank positivity over time.

Previous longitudinal studies have reported that sensitization status changes in a substantial proportion of children during follow-up (17,18). In agreement with these reports, our study found that new sensitizations developed in all groups, including those with completely negative baseline tests (Group 1).

The observation that new HDM sensitization was most frequent in Group 2 merits special attention. HDM is a ubiquitous perennial allergen with potent immunostimulatory properties. It is plausible that an initial low-level IgE response to HDM reflects an early phase of the "atopic march" which can rapidly progress to clinical sensitization under conditions of continuous high-dose exposure (19,20). In contrast to pollens, which typically require cumulative seasonal exposure over many years to induce sensitization, HDM sensitization can occur and amplify more quickly in predisposed children (21). This

finding aligns with the longitudinal data from Nokkaew et al. (22) who reported that HDM sensitization had the lowest rate of negative conversion over time, indicating its persistence once established.

Our age-stratified analyses revealed a clear temporal sequence in the acquisition of aeroallergen sensitizations. While HDM sensitization was already prevalent in the younger age groups, sensitizations to cat epithelium, grass pollen, tree pollen, and weed pollen were significantly more common in those children older than 10 years at the second SPT. This pattern is consistent with the natural history of allergic diseases, in which sensitization to indoor allergens often precedes sensitization to outdoor seasonal allergens (21,23). Recent large-scale studies have confirmed this age-dependent shift in sensitization profiles. Shin and Lee (7), in a cross-sectional analysis of over 14,000 individuals, demonstrated that the pattern of aeroallergen sensitization changes markedly across an individual's lifespan, with pollen sensitization peaking in adolescence and early adulthood. Similarly, the longitudinal study by Kölli et al. (8) showed that the prevalence of sensitization to outdoor allergens increases with age, while indoor allergen sensitization remains more stable. These findings reinforce the importance of considering a child's age when interpreting SPT results and when deciding on the timing of repeat testing.

Our exploratory analyses showed that a history of COVID-19 was associated with the development of new sensitizations in univariable analysis and remained independently associated after adjustments for age at first SPT, sex, and baseline aeroallergen-specific IgE. Several studies have reported changes in the aeroallergen sensitization profiles of children during the COVID-19 pandemic, including increased rates of sensitization to HDM and other indoor allergens, as well as higher rates of polysensitization when compared with the pre-pandemic period (24-27). These changes have generally been attributed to pandemic-driven lifestyle modifications, such as increased indoor time, altered ventilation, cleaning practices, and reduced outdoor exposure. However, these factors and a prior SARS-CoV-2 infection were rarely measured directly, limiting causal inference. In our cohort, the positive association with COVID-19 history may therefore serve as a proxy for the intensity of pandemic-related behavioral and environmental changes rather than indicating a direct biological effect of the virus. Furthermore, the absence of systematic laboratory confirmation may have resulted in exposure misclassification, potentially affecting the strength and interpretation of this association. Future studies incorporating detailed exposure assessments and objective biomarkers are needed in order to differentiate the potential effects of the viral infection itself from the broader environmental and behavioral changes which occurred during the pandemic period.

Study Limitations

This study had several limitations. First, its observational design precluded causal inference. Second, the interval between tests was variable, although the mean interval of approximately 4.5 years was consistent across the groups. Third, the relatively small sample sizes in the subgroup analyses may have limited statistical power to detect certain associations.

Despite these limitations, our findings have important clinical implications. For children with persistent allergic symptoms and baseline wheal diameters between 1 and 2 mm, a strategy of watchful waiting may be suboptimal. These children are at high risk of developing frank sensitization, particularly to HDM, within a 3- to 4-year window. Therefore, we suggest that clinicians consider repeat aeroallergen testing after 2-3 years in this specific subgroup, even if the initial test is reported as "negative" based on the conventional 3-mm threshold. Furthermore, given the age-dependent increase in pollen and cat sensitization, repeat testing should also be considered in older children (≥10 years) with new-onset or worsening seasonal/perennial symptoms, as their sensitization profile may have expanded since their initial evaluation.

Conclusion

Baseline aeroallergen SPT reactivity is a strong predictor of subsequent sensitization patterns in children. Minimal wheal reactions (1-2 mm) in symptomatic children are associated with a high risk of developing clinically significant sensitization, particularly to HDM, and should not be dismissed as irrelevant. Repeat SPT after an appropriate interval can provide valuable information in order to guide environmental control measures, pharmacotherapy, and the timely initiation of allergen immunotherapy in this evolving pediatric population.

Ethics

Ethics Committee Approval: This study was approved by the Ege University Medical Research Ethics Committee (approval no.: 23-7.1T/42, date: 27.07.2023).

Informed Consent: Written informed consent was obtained from the parents or legal guardians of the

participants, and assent was obtained from the children when appropriate.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: E.T., H.D.Ş., A.P., M.G., F.G., E.D., Concept: F.G., E.D., Design: H.D.Ş., E.D., Data Collection or Processing: E.T., A.P., M.G., Analysis or Interpretation: E.T., H.D.Ş., F.G., E.D., Literature Search: E.T., H.D.Ş., Writing: E.T., H.D.Ş.

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Original Article

Neutrophil-to-lymphocyte and Platelet-to-lymphocyte Ratios in Pediatric Sickle Cell Disease: Association with Vaso-occlusive Crises and Treatment Modalities

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ABSTRACT

Platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) are emerging markers for inflammation. In sickle cell disease (SCD), inflammation is a central feature of vaso-occlusive crises (VOC). This study evaluated NLR and PLR dynamics in pediatric SCD patients during VOC and it examined the impacts of treatments such as hydroxyurea and chronic transfusion therapy on these markers. This cross-sectional study included 100 SCD patients aged 2-27 years presenting for VOC. Paired t-tests and ANOVA were used to compare VOC and steady-state values with $p<0.05$ considered statistically significant. Total white blood cell count, absolute neutrophil count, and NLR were significantly elevated during VOC. Platelet counts were significantly higher during steady state in untreated patients, but no significant differences were observed in PLR. In treated patients, platelet counts remained elevated both at steady state and during VOC. No significant differences in NLR or PLR were found between the treatment groups. These findings support NLR as a sensitive marker of inflammation during VOC in pediatric SCD patients. However, treatment modalities such as hydroxyurea and chronic transfusions may not significantly impact NLR and PLR levels. Larger, prospective studies are needed to further define their roles in disease monitoring.

Keywords: Platelet-lymphocyte ratio, neutrophil-lymphocyte ratio, sickle cell disease, vaso-occlusive crisis

Introduction

Sickle cell disease (SCD) is an autosomal recessive disorder caused by a point mutation in the beta-globin gene (on chromosome 11) which substitutes glutamic acid for valine at position 6 of the β-globin chain. This mutation promotes hemoglobin polymerization, leading to red cell deformation, hemolysis and vaso-occlusion. Vaso-occlusion is a well-known sequalae of SCD often manifesting as painful episodes, particularly in the bones.

Hydroxyurea is a pharmacological agent which increases fetal hemoglobin in red blood cells (RBCs) by inhibiting ribonucleotide reductase. It has been shown to reduce the frequency of pain crises and hospitalizations in patients with SCD (1). While chronic transfusions therapy is primarily

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used for stroke prevention, it has also been suggested to prevent acute pain episodes (2).

Vaso-occlusion triggers inflammation through various mechanisms including endothelial activation, tissue ischemia and re-perfusion injury. In response, various components of the immune system become activated promoting investigation into their role during vaso-occlusive crises (VOC) (3). Studies have demonstrated increased platelet activation and changes in platelet counts as well as higher absolute neutrophil count (ANC) and neutrophil activation during VOCs (4,5). In recent years, systemic inflammatory markers such as platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) have emerged as potential markers of inflammation during VOC. These ratios have demonstrated utility in a variety of inflammatory conditions, such as osteoarthritis, coronary microcirculatory disease, Chron's disease, and rheumatoid arthritis (6-9).

This study aimed to evaluate PLR and NLR as markers of inflammation in pediatric patients with SCD during VOC and to assess further their potential prognostic value in disease monitoring. In addition, we examined the effects of therapeutic interventions such as the use of hydroxyurea and chronic transfusions on these inflammatory biomarkers.

Materials and Methods

This retrospective cross-sectional study included 100 patients with SCD aged 2-27 who presented to the St. Christopher's Hospital Emergency Department for VOC. VOC was defined as acute pain in the extremities, back, or chest in known SCD patients without an alternative identifiable cause. Steady state was collected during outpatient follow-up. NLR, PLR were calculated using absolute values on CBC. Patients were grouped based on treatment status: untreated, hydroxyurea-treated, or on chronic transfusions. Statistical analysis included paired t-testing and ANOVA with a significance threshold of $p<0.05$.

Results

The demographic characteristics of the study participants are summarized in Table I. A total of one hundred patients with SCD who presented to the St. Christopher's Hospital Emergency Department for VOC over a 3.5-year period were included. The mean age of the cohort was 14.6 (range: 2-26) years. Of the participants, 52% were male and 48% were female. Genotypes included were hemoglobin SS, SC, Sb^+ thalassemia and Sb^0 thalassemia. Of the patients, 41 were not receiving disease modifying therapies, 48 had been on hydroxyurea for at least one year, and 11 were receiving chronic transfusions therapy.

There was a significantly elevated total white blood cell count (WBC), ANC and NLR in the SCD patients in the VOC state ($p<0.0001$). Platelet count was significantly higher during the steady state when compared to VOC ($p<0.05$). There was no significant difference in lymphocyte count or PLR (Table II).

The patients were grouped based on their treatment status into treated (hydroxyurea or chronic transfusions), not treated, and further subdivided by specific therapy. Across all groups, except for the transfusion only group, there was a significant increase in ANC and NLR ratio in the SCD patients in the VOC state ($p<0.001$) (Figures 1 and 2). Moreover, the relative increase in NLR during VOC was greater than ANC alone, suggesting that NLR may serve as a more sensitive indicator during acute episodes.

When comparing treated patients (hydroxyurea or chronic transfusions) to untreated patients, WBC, platelets and lymphocytes were significantly higher in the treated groups during both the steady state and VOC. However, no significant differences were observed between the treatment groups for ANC, NLR or PLR (Table III).

Table I. Demographic characteristics of the study participants

Variable	Average/ Number	Range/ Percentage
Age (years)	14.6	2-26
Gender		
Male	53	53%
Female	47	47%
Ethnicity		
Black or African American	78	78%
Hispanic or Latino	19	19%
Other	3	3%
Genotype		
SS	67	67%
SC	25	25%
Sb^+ thalassemia	4	4%
Sb^0 thalassemia	4	4%
Therapy		
None	41	41%
Hydroxyurea	48	48%
Chronic transfusions	11	11%

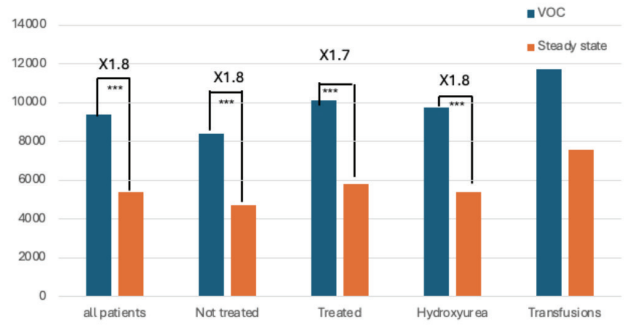

Figure 1. Neutrophil count during steady vs. VOC state grouped by treatment status. ***p<0.001 and X represents the VOC/steady state value

VOC: Vaso-occlusive crises

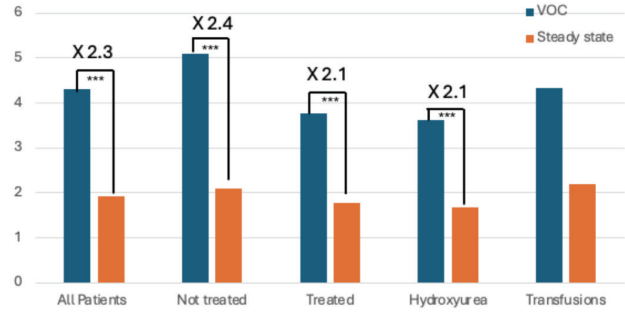

Figure 2. NLR during steady state vs. VOC state grouped by treatment status. ***p<0.001 and X represents the VOC/steady state value

NLR: Neutrophil-to-lymphocyte ratio, VOC: Vaso-occlusive crises

Table II. Cell line counts, NLR, and PLR in SCD patients during steady and VOC state

	Steady state	VOC	p value
WBC (x10³/mL)	10.32	14.38	<0.0001**
Neutrophils (x10³/mL)	5.367	9.372	<0.0001**
Lymphocytes (x10³/mL)	3.469	3.418	0.817
Platelets (x10³/mL)	391	356	<0.05*
Neutrophil-to-lymphocyte ratio	1.93	4.30	<0.0001**
Platelet-to-lymphocyte ratio	0.128	0.142	0.181

NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SCD: Sickle cell disease, VOC: Vaso-occlusive crises, WBC: White blood cell count

Table III. Cell line counts, NLR and PLR in SCD patients treated (with either chronic transfusions or hydroxyurea) compared to untreated patients in both steady state and VOC state

	Treated	Untreated	p value
WBC (x10³/mL)			
Steady	11.5	8.59	<0.01*
VOC	15.8	12.3	<0.01*
Neutrophils (x10³/mL)			
Steady	5,791	4,712	0.146
VOC	10,090	8,379	0.085
Platelets (x10³/mL)			
Steady	433.65	328.1	<0.01*
VOC	393.85	299.2	<0.01*
Lymphocytes (x10³/mL)			
Steady	3,984	2,747.8	<0.001**
VOC	3,950	2,674	<0.01*
NLR			
Steady	1.77	2.1	0.366
VOC	3.765	5.1	0.228
PLR			
Steady	0.127	0.128	0.922
VOC	0.132	0.156	0.324

*p<0.01, **p<0.001
NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SCD: Sickle cell disease, VOC: Vaso-occlusive crises, WBC: White blood cell count

Discussion

It is well known that VOC increases inflammation and is associated with leukocytosis. As the most predominant leukocytes in the blood stream, the elevation in neutrophil number during VOC state has been studied extensively. Elevated neutrophil counts have been associated with disease severity in SCD, including higher rates of VOC and complications (10). For instance, the use of GM-CSF or G-CSF increasing the number neutrophils leads to more severe VOC with worse outcomes and it is contraindicated in SCD (11). Conversely, one case study showed that congenital neutropenia was associated with better outcomes (12).

Numerous studies have investigated the role of neutrophil in the pathophysiology of VOC. Sickled RBCs lead to hemolysis and tissue ischemia, which in turn cause injury to the endothelium and trigger an inflammatory response which includes margination of neutrophils. Neutrophils are recruited to post-capillary venules by P- and E-selectins. In murine models, the absence of these selectins reduces neutrophil recruitment and protects against VOC (13). The binding of neutrophils to E-selectins then activates Mac-1 (CD11b/CD18). This enhances adhesion of neutrophil to endothelium and facilitates interaction with RBC. These adherent neutrophils, when bound to sickled RBC are believed to exacerbate VOC by slowing

blood flow and increasing the likelihood of polymerization in the microvasculature. The inactivation of Mac-1 or the use of antibodies against it have been shown to diminish neutrophil-RBC interactions and improve circulation in mice during VOC (14). Furthermore, Mac-1 expression is upregulated in SCD, and SS-RBC adhere to PMN more than normal erythrocytes (14,15). These findings underscore the complex and critical role of neutrophils in the development of VOC. As expected, neutrophil counts were significantly elevated during VOC when compared to the steady state for our cohort.

NLR has been found to be useful as a marker of inflammation in various other chronic diseases (16). In line with prior studies in adults, NLR was found to be higher in VOC groups when compared to steadystate groups. Prior adult studies have also found a higher NLR in SCA patients than HbA controls (5). NLR was significantly increased during the VOC state in this pediatric study and correlated positively with WBC and ANC. While the elevation of NLR could be partially attributed to elevated neutrophil counts, the magnitude of the change in NLR exceeded that of neutrophils alone suggesting that NLR may serve as a more stable marker of inflammation in the setting of VOC.

Hydroxyurea has been shown to reduce the frequency and severity of episodes in patients with SCD (13). While its primary mechanism is to increase levels of HbF, it also reduces neutrophil counts and suppresses inflammatory activation (14). Several studies have explored the effect of hydroxyurea on neutrophil function, including expression of integrins and adhesion markers which are known to be associated with increased neutrophil activation (13,14,17). However, in our study, we observed no significant difference in neutrophil count or NLR between those patients on hydroxyurea and those untreated. This may be explained by a lack of adherence to the medication or by worsened disease severity at baseline for those patients on medication.

While hydroxyurea therapy has been shown to decrease leukocytosis and supress increased neutrophil activation, the impact of transfusions on neutrophils is less clear. One pediatric study of patients with SCD aged 2-18 on an exchange transfusion (ET) program found no significant change in neutrophil, monocyte, or platelet counts between baseline (before the ET program was started) and during the ET program (18). Another study in SCD children observed persistent neutrophilic leukocytosis and unchanged expression of neutrophil activation markers in those patients receiving monthly exchange transfusions (17). In our study, no significant changes in neutrophil count or NLR were seen in the transfusion group, though the small sample size (n=11) limited our ability to detect meaningful differences. Larger studies are needed in order to better determine the immunologic impact of chronic transfusions in SCD.

In our cohort, the platelet counts were significantly higher during the steady state than the presentation with VOC, consistent with previous observations that platelet counts decline in the acute phases and rise during recovery. Following VOC, rebound thrombocytosis is believed to occur due to the structural similarity between erythropoietin and thrombopoietin which increases due to hemolysis. Prior studies in adults with SCD have demonstrated similar trends: elevated platelet counts during asymptomatic periods, a moderate decrease in platelet count during crises, followed by marked thrombocytosis in recovery (15). Furthermore, declining platelet counts during VOC have been associated with complications such as acute chest syndrome (19).

Interestingly, when stratified by treatment groups, a significant drop in the platelet count during VOC was only observed in the non-treated cohort. In contrast, patients receiving hydroxyurea or chronic transfusions maintained higher platelet counts at both steady state and during VOC. This may suggest that treatments such as hydroxyurea and chronic transfusions either attenuate the drop in platelets during the initial phase of VOC, accelerate recovery or help maintain platelet counts consistently. However, despite this difference in the platelet dynamic, no significant changes in PLR were observed, suggesting that PLR may be a less sensitive marker in this context.

Conclusion

In this study of pediatric patients with SCD, NLR significantly increased during VOC compared to the steady state, supporting its utility as sensitive inflammatory marker. While neutrophil counts contributed to this rise, the proportionally greater increase in NLR suggests that it may offer added value beyond absolute counts. PLR did not show significant changes across disease states or treatment groups. Additionally, neither hydroxyurea nor chronic packed RBC transfusions significantly affected NLR or PLR levels in this cohort. This study had several limitations which may impact the interpretation of its results. The cross-sectional design does not account for intra-patient variability over time. The sample size, particularly in the chronic transfusion group, was small and may limit its statistical power. Treatment adherence to hydroxyurea

was not objectively measured, potentially confounding comparisons between the treated and untreated groups. Additionally, only single timepoints were used for VOC and steady-state measurements, which may not fully capture the dynamic nature of inflammatory markers in SCD. Future prospective studies with longitudinal sampling and better adherence tracking are needed in order to validate these findings.

Ethics

Ethics Committee Approval: Ethical committee approval for this study was obtained from Drexel University Office of Research and Innovation (approval number: HRP-200, protocol number: 240901773, date: 02.01.2020).

Informed Consent: A waiver of consent and HIPAA authorization was granted due to the retrospective nature of the study (data collected during routine clinical care and poses minimal risk or affect).

Footnotes

Authorship Contributions

Concept: J.Z., N.A., Design: J.Z., N.A., Data Collection or Processing: J.Z., J.H., Analysis or Interpretation: M.Z., Literature Search: J.Z., Writing: J.Z., N.A.

Conflict of Interest: All authors declare that they have no conflict of interest.

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Original Article

Phase 1 Evaluation of a Novel Otoscope Tip Aimed at Improving Pediatric Otoscopy Visualization and Cerumen Management: The Otoshow

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ABSTRACT

Aim: Cerumen is a common barrier to accurate otoscopic examinations in children, yet pediatricians lack effective removal tools. The Otoshow is a novel otoscope speculum with a retractable curette attachment designed to address this gap. This study aimed to characterize cerumen impaction as a barrier to tympanic membrane (TM) visualization and to evaluate the safety, effectiveness, and clinician satisfaction of the Otoshow.

Materials and Methods: A prospective, non-randomized, survey-based, phase 1 study was conducted in two pediatric otolaryngology clinics from March to May 2025. Five Advanced Practice Providers (APPs) used the Otoshow tip during clinic encounters, replacing or supplementing standard specula and cerumen removal tools at their discretion. The data consisted of clinician surveys including pre-study, per-encounter, and post-study surveys.

Results: A total of 101 encounters were surveyed. The children ranged in age from 6 months to 17 years, with 80% aged 1-10 years. The pre-survey showed all clinicians encountered cerumen at least occasionally, and none were very satisfied with current removal methods. Per-encounter surveys showed cerumen obstructed the TM in 29% of the children and 33% with ear-related complaints. The Otoshow curette was used in 72% of obstruction cases, improving TM visualization in 43%. The APPs were satisfied with its use in 34% of encounters. In the post-study survey, the Otoshow was rated as equally safe or safer, more time-efficient, and more comfortable than the standard methods. No device-related adverse events occurred.

Conclusion: Cerumen is a significant barrier to TM visualization in children. The Otoshow otoscope tip demonstrated safety, feasibility, and the potential to improve visualization and child comfort without prolonging procedure times. While satisfaction with the device was modest, iterative design enhancements may increase clinical adoption. Future studies are warranted to assess the device's impact in primary care and emergency settings where cerumen impaction poses an equal or greater diagnostic challenge.

Keywords: Pediatrics, otoscopy, cerumen managment, otitis media

Introduction

Cerumen is a frequent and often overlooked impediment to an efficient otoscopic exam in children, particularly for acute otitis media (AOM). In the emergency department, AOM is the second most common pediatric diagnosis after upper respiratory infection, with 80% of children experiencing an episode of AOM by the age of three years (1,2). Additionally, there are approximately 30 million

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visits related to AOM in the United States each year (1,2). According to the American Academy of Pediatrics, pediatricians must clearly visualize the tympanic membrane (TM) to evaluate for bulging, otorrhea, or erythema in order to make a diagnosis of AOM (3). In routine clinical practice, pediatricians and urgent care practitioners encounter obstacles performing an adequate examination of the TM due to complete or partial obstruction by cerumen impaction, leading to diagnostic ambiguity and potentially unnecessary antibiotic prescription (3,4-10).

Studies have shown that physicians are uncertain of AOM diagnosis in up to 40% of cases, yet still prescribe antibiotics in 75% of instances when the perceived probability of an ear infection is 50% or lower (2). This practice of overdiagnosis can lead to increased adverse drug reactions, rising antibiotic resistance, and unnecessary surgical interventions such as tympanostomy tube placement (4). The non-specific symptoms of AOM in children, such as fever and irritability, occur in approximately 72% of children without AOM, which further complicates the diagnostic process and increases reliance on accurate physical exam findings (2). When cerumen obstructs visualization, clinical decision-making becomes compromised, increasing the likelihood of overtreatment (4,5,11).

Additionally, several studies have documented the high incidence of cerumen in children and its effect on the accuracy of diagnosis. In one study of 819 children aged 1 month to 12 years, cerumen was found in 70% of the ears examined, and in over 40%, the cerumen obstructed at least half of the canal (5). In another study, children with unilateral AOM required mechanical removal of cerumen in about 30% of cases in order to adequately visualize the TM, which rose to over 50% in infants (7). Both studies indicated that cerumen is more than a minor nuisance and a significant barrier to pediatric ear examinations. Adequate visualization of the TM is the only way to differentiate between AOM and otitis media with effusion (OME), which directly influences treatment decisions (3,8).

However, cerumen was removed in only 30% of children with a final diagnosis of AOM by general pediatricians compared to over 95% of the time by otolaryngologists which could be due to the specialized cerumen removal tools available in specialized clinics (5). Standard manual removal methods, such as using a curette, carry a notable risk of aural trauma. One study reported bleeding of the ear canal in up to 10% of children undergoing these procedures (7). Although irrigation is generally considered safer than curettage, it is often slower, more cumbersome, and uncomfortable (6). Furthermore, irrigation is contraindicated with a perforated TM, which is present in approximately 30% of children with AOM (9).

This suggests that improving diagnostic accuracy for AOM and ensuring high-quality routine ear examinations in pediatric care requires a renewed emphasis on effective cerumen management tools which can be utilized in general care settings (5,10). The Otoshow is a novel otoscope speculum designed to fill this gap. It consists of a retractable curette within the wall of the otoscope speculum, allowing for simultaneous cerumen removal and visualization. Its design also incorporates a guide rail and an elastic joint ensuring safety and the maneuverability of the curette while in use. Furthermore, the Otoshow incorporates an ergonomic handle which can be operated by one finger and a standardized base which can fit most standard otoscopes, enabling easy use and adoption by a large number of clinicians (Figure 1).

Although the Otoshow is primarily designed for general pediatric settings, the choice of a specialized pediatric ear, nose, and throat clinic for this phase 1 evaluation was intentional and strategic. It ensured that any safety concerns would be immediately addressed by experienced clinicians, while also facilitating high-quality feedback for iterative improvement. With safety data and user feedback from this phase 1 study, the Otoshow has the potential to become an effective tool in broader clinical settings, significantly improving otoscopic exams and thereby reducing the misdiagnosis of AOM and inappropriate antibiotic use.

Materials and Methods

Study Design

A prospective, non-randomized, survey-based, exploratory pilot study was carried out in two pediatric otolaryngology clinics between March and May 2025.

Participants

Five Advanced Practice Providers (APPs) in a pediatric otolaryngology clinic were recruited by convenience sampling without a separate comparator arm. Verbal consent was obtained from the clinicians, and they received no financial incentives for participation. Children were enrolled through convenience sampling as they presented during periods of APP availability. The inclusion criteria were: (i) children aged 0-18 years, (ii) scheduled clinic visit in which a routine otoscopic ear examination was to be performed, and (iii) willingness to use the Otoshow device during the visit. The exclusion criteria were children with any

major craniofacial abnormalities and non-English speaking parents. Written consent was obtained from the caregivers prior to the clinic visit. IRB approval was obtained.

Intervention

Each APP used either a small or large Otoshow otoscope tip according to their choice with the Welch Allyn MacroView otoscope during otoscopic examinations. The device replaced or augmented standard methods (curettes, suction, irrigation) at the APP's discretion. The APPs were trained on how to use the device via a 1-minute video which explained how to place the Otoshow on the otoscope, how to best hold the otoscope for Otoshow use, and how to maneuver the curette attachment. Any further questions regarding device functionality were answered in the clinic by the study team.

Instruments and Data Collection

Data was obtained electronically via three non-validated Redcap surveys made by the research team based on prior studies evaluating the use of novel otoscope examination tools (12,13). The pre-survey measured perceived cerumen prevalence in practice, prior cerumen-removal experience, and any limitations of the existing tools using a 5-point Likert scale and free text questions (Supplementary Figure 1). A per-encounter survey was completed immediately after each device use, documenting information pertaining to, but not limited to, the child's age, cerumen prevalence, percentage of TM visualization impairment by cerumen, complications, clinician satisfaction, perceived child comfort, and the efficiency and effectiveness of the Otoshow using a 5-point Likert scale and free text prompts. The post-survey included questions assessing overall satisfaction, intent to continue use, comparative effectiveness, and final recommendations about the Otoshow using a 5-point Likert scale and free-text questions. Descriptive statistics were used to summarize the findings. Given the pilot nature and small sample size (n=5 clinicians), inferential statistics were not performed. A full list of the questions and response options for the surveys can be found in Supplementary Figure 1. Semi-structured verbal interviews were conducted exploring ergonomics, workflow integration, and feature refinements.

Outcome Measures

The primary outcome measures were the safety of the Otoshow device, measured by complication rates and clinician perceived safety, the effectiveness and efficiency of the device, clinician satisfaction with Otoshow, and feedback regarding design changes. Secondary outcomes included the prevalence of cerumen partially or fully obstructing visualization of the TM, the frequency of Otoshow curette attachment use, and the prevalence of cerumen obstruction with suspicion of AOM.

Ethical Considerations

The University of Texas Southwestern Institutional Review Board Office of Clinical Research (approval no.: STU-2024-0470, date: 19.08.2024) evaluated and approved this study along with measures to mitigate any conflicts of interest of the researchers who invented the Otoshow. No patient-identifying data was stored. Verbal consent was obtained from the participating APPs, and written consent was obtained from the caregivers.

Results

On the pre-survey, four out of the five APPs reported that they frequently encounter cerumen obstructing their view of the TM with one answering very frequently (Figure 2a). All reported preferring the use of a curette to clear the obstruction compared to irrigation or cerumenolytics with three of five (60%) stating that they frequently used curettes to remove cerumen, one selecting very frequently, and one selecting occasional use of cerumen removal tools (Figure 2b). Four of the five (80%) were satisfied with the current cerumen removal tools, indicating that the tools were mostly effective but could be improved, and one APP was neutral. None were very satisfied with their current cerumen removal tools.

A total of 101 surveys were collected over the study period. Ages ranged from 0 to 17 years with the largest number of children being in the 1-5 year range (42%),

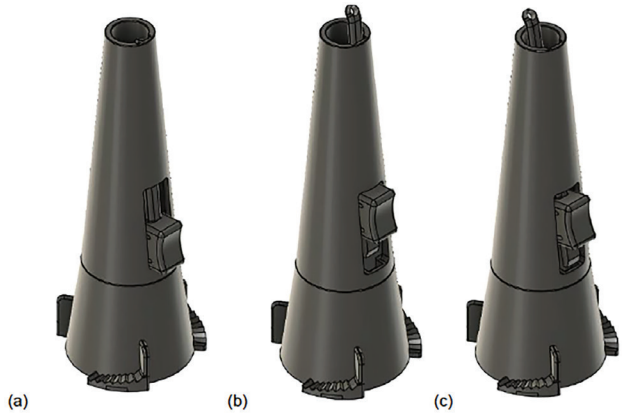

Figure 1. Otoshow otoscope speculum design in three different configurations. **(a)** Standard configuration with curette not engaged. **(b)** Curette engaged in the forward position. **(c)** Curette engaged forward and advanced along the depth axis, utilizing an elastic hinge mechanism for enhanced maneuverability

followed by 5-10 years (40%), over 10 years (13%), and 0 months to 1 year (6%). Further demographic information can be seen in Supplementary Figure 2. The small Otoshow tip was used in 55% and the large Otoshow tip was used in 45% of encounters. APPs reported that they suspected AOM in 34% of children, and of those, 28% had partial to complete obstruction of the TM by cerumen. A total of 29% of the children had cerumen which obstructed the view of the TM (Figure 3a). In those children with cerumen obstruction, APPs used the Otoshow curette attachment in 72% of encounters. Of the children with cerumen obstruction, visualization was improved by using the Otoshow tip's curette attachment in 43% of encounters (Figure 3b). Overall, APPs reported satisfaction with using the Otoshow tip in 34% and dissatisfaction in 7% of encounters. Of the encounters in which the Otoshow curette attachment was

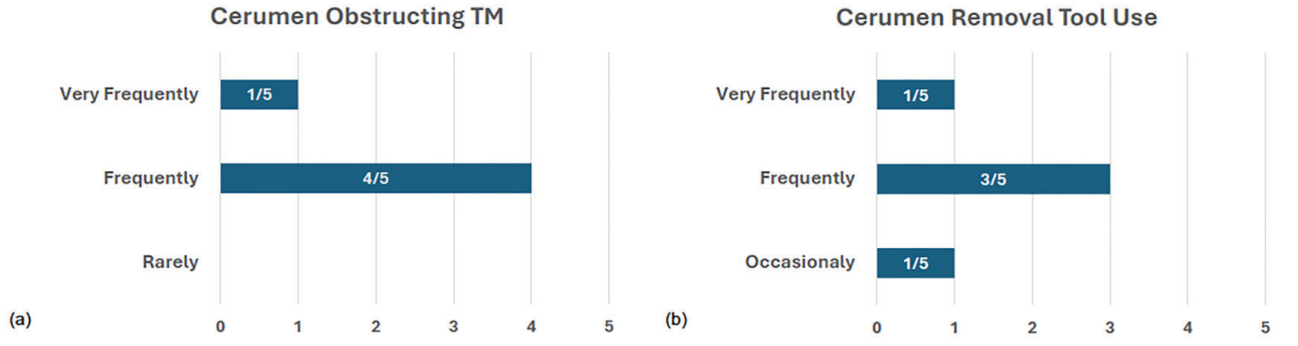

Figure 2. Pre-survey responses completed by 5 APPs. **(a)** Frequency of reported cerumen obstructing the view of the TM. **(b)** Frequency of use of cerumen removal tools
APPs: Advanced Practice Providers, TM: Tympanic membrane

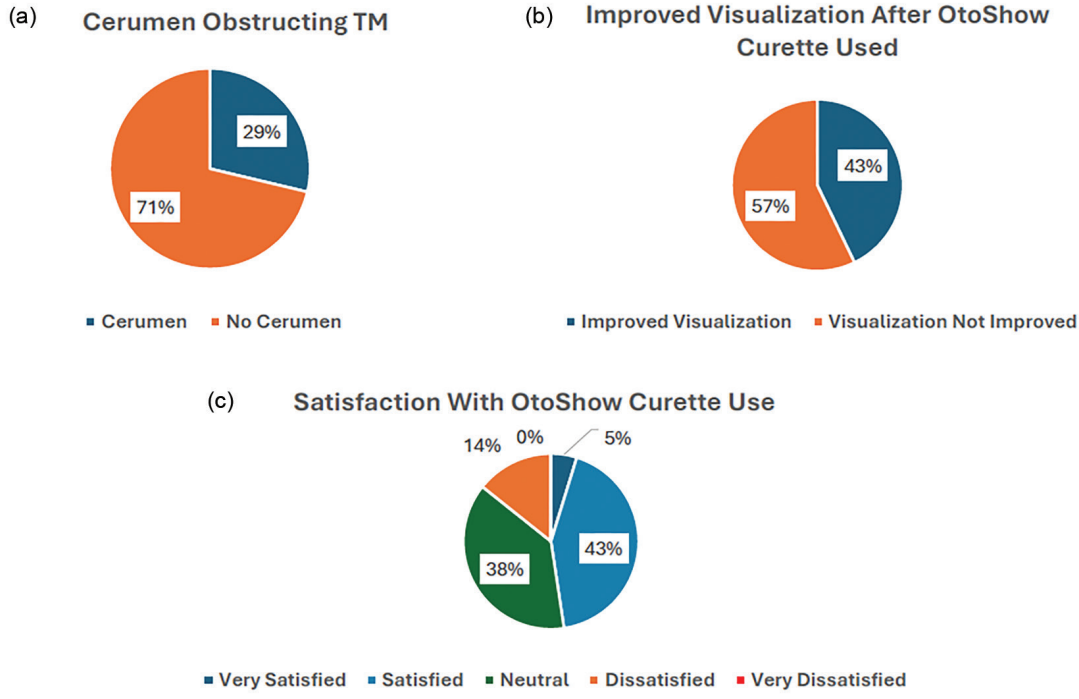

Figure 3. Per-encounter survey findings illustrated in pie chart format. **(a)** Frequency of patients with any amount of TM obstruction by cerumen in at least one ear. **(b)** Frequency of improved TM visualization after the Otoshow curette attachment was used. **(c)** APP satisfaction with Otoshow use on a 5-point Likert scale
APP: Advanced Practice Provider, TM: Tympanic membrane

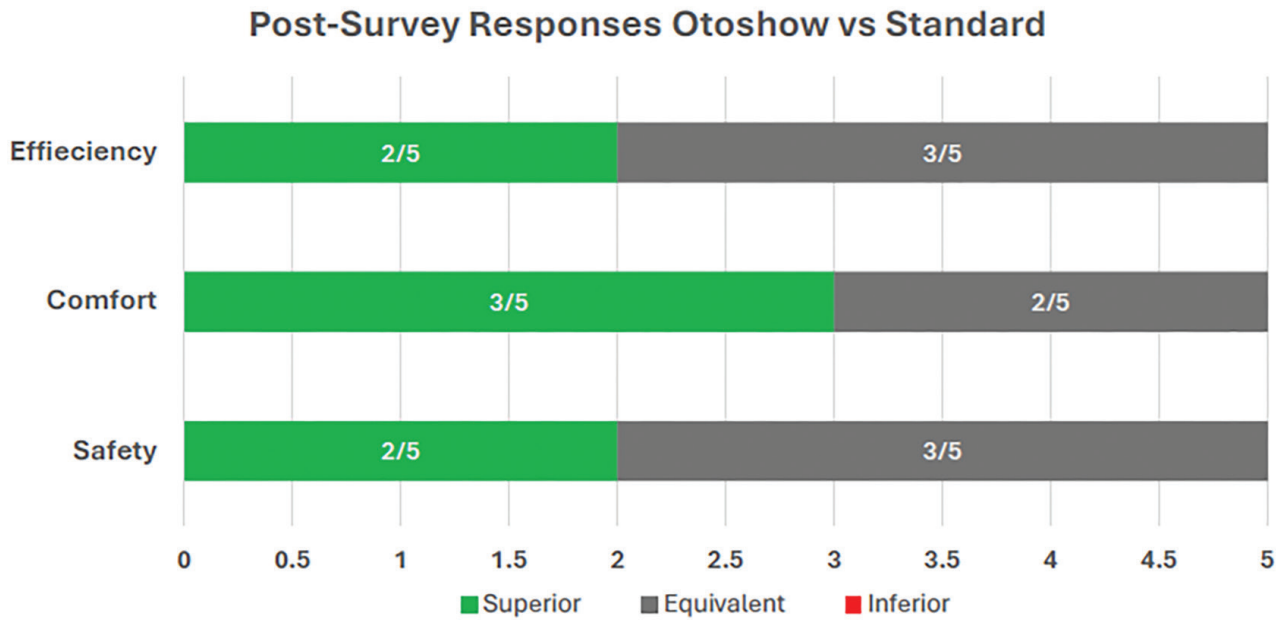

Figure 4. Post-survey responses completed by 5 APPs. Perceived efficiency, comfort, and safety of the Otoshow compared to standard otoscopy tools used in the ENT office
APPs: Advanced Practice Providers, ENT: Ear, Nose, and Throat

used, satisfaction increased to 48% (Figure 3c). Of the 101 patients, only 6 required the use of additional cerumen removal tools to be able to see the TM. None of the APPs reported any Otoshow related complications or adverse events during the study period.

Post-surveys showed that three of five (60%) APPs encountered cerumen obstructing the TM at least 50% of the time during the study period. All APPs found the Otoshow tip to be safe for children, with two of the five (40%) reporting that it was safer than their standard tools (Figure 4). Additionally, all perceived that the children felt comfortable with the Otoshow tip, and three out of five (60%) felt it was more comfortable for children than their traditional cerumen removal methods (Figure 4). Furthermore, they indicated that visualization with the Otoshow otoscope speculum took the same amount of time or was faster than using a standard otoscope speculum (Figure 4). Yet, four of the five (80%) were either unlikely or very unlikely to continue to use the current Otoshow in their practice. Although when asked if changes were made to improve the Otoshow, how likely it was that they would replace the standard otoscope tip with the Otoshow, only two selected unlikely with the others indicating either neutral or likely. The most common feedback on the design was that the curette attachment was too short and obstructed too much of the view.

Discussion

This study characterized the clinical barrier posed by cerumen impaction and evaluated the safety, feasibility, and clinician impressions of the Otoshow otoscope tip.

Safety and Feasibility Outcomes

Safety was a key outcome in this phase 1 study. No device-related complications or adverse events were reported, and all clinicians rated the Otoshow as either equally safe or safer than standard cerumen removal tools. This is notable given that manual curettage is known to cause trauma, with prior studies reporting canal bleeding in up to 10% of children (6). In contrast, no trauma or bleeding was reported in this study. Furthermore, three of the five (60%) APPs reported that children appeared more comfortable with the Otoshow than with traditional techniques, and the remaining two reported equal comfort.

Clinician satisfaction was modest: 34% of all encounters were satisfactory, and 7% were unsatisfactory. The satisfaction rate increased to 48% in encounters where the curette attachment was used, indicating that during encounters in which cerumen was present and needed to be removed, clinicians were more satisfied with the Otoshow. Notably, the clinicians were able to use the device after a single 1-minute instructional video, demonstrating that the

training burden is minimal and the device can be rapidly adopted.

This pilot study showed that the Otoshow was effective in improving perceived TM visualization for 43% of children. Multiple providers stated that this could be significantly improved by simply increasing the curette attachment length in order to be able to reach cerumen deeper in the ear canal. In terms of efficiency, all five APPs rated the time to TM visualization with the Otoshow as equivalent to or faster than standard techniques. This is clinically meaningful, particularly in settings where time constraints limit the thoroughness of otoscopic exams, such as emergency departments or urgent care clinics. The sub-analysis of the encounters in which the curette attachment was used showed that for the provider with the most frequent curette attachment use (n=7), visualization success rates improved from 33% to 75% from the first half to the second half of the study period. However, other providers with fewer encounters did not demonstrate a consistent trend, suggesting that while individual learning curves may exist, the small sample size limits the ability to characterize a broader learning effect.

With less than 6% of patients requiring the use of any additional tools other than the Otoshow for cerumen removal, the Otoshow alone was seen to be effective for standard otoscope exams in the majority of patients. Previous research has shown that cerumen impaction can lead to diagnostic ambiguity, unnecessary antibiotic prescriptions, and delayed treatment (5,7). A tool such as the Otoshow which allows for simultaneous removal and visualization has the potential to streamline effective care.

Clinical Implications

The study population was predominantly between the ages of 1 and 10, an age group which accounts for the majority of AOM diagnoses and where cerumen is frequently encountered (2,4). These demographics support the clinical relevance of targeting cerumen management in this group.

The prevalence of cerumen partially or fully obstructing the TM was common, with obstruction present in 29% of children and in 28% with suspected AOM. This supports prior studies demonstrating a high prevalence of cerumen in children. For example, one study found cerumen in 72% of ears examined and at least partial canal obstruction in 44% of children (5). Even in this specialized otolaryngology setting, where children are likely to receive more frequent ear exams and better cerumen hygiene, obstruction remained a consistent impediment to TM visualization.

In cases where cerumen was present, clinicians used the Otoshow curette attachment in 72% of encounters, and of those, 43% reported improved TM visualization. These preliminary observations suggest this device was selectively and meaningfully deployed. Importantly, clinicians suspected AOM in over one-third of those children, and when cerumen obstructed the TM, visualization was critical for diagnosis. Given that TM assessment is essential to differentiate AOM from OME (2,3), these findings reinforce the need for effective cerumen management tools in children. However, this study did not directly measure changes in diagnostic accuracy or antibiotic prescribing behavior.

While only one clinician indicated that they would replace their current tool with the Otoshow, most expressed an openness to continued use depending on further improvements. This indicates that this device is still in its early developmental stages and requires design improvements. The clinicians noted that small design changes including increasing the length of the curette attachment and moving it more out of view could enhance the device's usability and increase adoption.

Study Limitations

The study design demonstrated the Otoshow as a safe and feasible adjunct in pediatric otolaryngology settings, but further studies are needed in order to evaluate the use of the Otoshow as a standalone device in option-limited sections such as primary care or emergency departments. The sample size of the study only included a small number of participating clinicians. In addition, the clinician reported outcomes relied on subjective survey responses. The surveys used were developed for this initial pilot study and were not validated instruments. They were created in order to efficiently capture early safety, satisfaction, and usability data in this phase 1 evaluation.

Furthermore, this study has several potential biases which may have occurred due to the study design. Selection bias was a known risk as device use was at the clinician's discretion. The absence of blinding and a control group introduced potential observer and expectation bias. Improvement of visualization was a subjective measurement which could have increased reporter bias. The absence of validation possibly limited reproducibility and limits the interpretation of outcomes such as perceived diagnostic accuracy and satisfaction. The clinician assessments of child comfort were observational rather than self or caregiver reported which limits the interpretation of these findings.

Additionally, the exclusion of non-English-speaking parents, which was necessary for this initial pilot due to

resource constraints, may further limit the generalizability of this study's results. The device's impact on AOM diagnosis and management are also needed in order to assess its clinical impact. These factors underscore the need for broader trials with objective performance metrics such as validated usability, comfort, and satisfaction scales along with objective assessment of TM visualization using video otoscopy and a blinded image assessment.

Future Directions

Having demonstrated its safety and feasibility, the next step is to evaluate the Otoshow in general pediatric and urgent care settings, where cerumen impaction may be more frequent and challenging. Future studies should incorporate direct patient feedback, validated outcome measures, and video-based assessments of TM visualization. Given the impact of cerumen on diagnostic accuracy, efficiency, and antibiotic stewardship, broader adoption of improved tools such as the Otoshow could contribute to more accurate AOM diagnoses and reduced overtreatment in pediatric care (3,5,7,14).

Ethics

Ethics Committee Approval: The study was approved by the University of Texas Southwestern Institutional Review Board Office of Clinical Research on August 19th, 2024 with study number STU-2024-0470.

Informed Consent: Verbal consent was obtained from the participating APPs, and written consent was obtained from the caregivers.

Footnotes

Authorship Contributions

Concept: L.N., A.M., R.M., Design: L.N., A.M., R.M., Data Collection or Processing: L.N., A.M., N.B., R.M., Analysis or Interpretation: L.N., A.M., N.B., R.M., Literature Search: L.N., A.M., N.B., R.M., Writing: L.N., A.M., N.B., R.M.

Conflict of Interest: Lith Nasif and Ron Mitchell are the co-inventors of the Otoshow device described in this manuscript. Ron Mitchell's involvement in this study was limited to the study design and manuscript review. Lith Nasif was involved in the study design, patient consent, and manuscript review. The data analysis and writing of the manuscript were primarily completed by the other authors with feedback from Ron Mitchell and Lith Nasif when needed. While there are no current financial deals or gains, there is the potential for future financial gain. The institutional review board evaluated and approved this study along with measures to mitigate the conflict of interest of the researchers who invented the Otoshow.

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Supplementary Figure 1: https://d2v96fxpocvxx.cloudfront.net/1dda20c2-8b22-466b-a98e-85ecfb39ceaf/content-images/3af15e34-9a01-41dd-9f87-b1c358ecda29.pdf

Supplementary Figure 2: https://d2v96fxpocvxx.cloudfront.net/1dda20c2-8b22-466b-a98e-85ecfb39ceaf/content-images/d9c9f70d-7c36-4a15-aaf7-ee869ff6c6f3.pdf

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Case Report

Late-diagnosed Incomplete Kawasaki Disease Complicated by Giant Coronary Artery Aneurysms and Ischemic Heart Failure: A Pediatric Case Report

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ABSTRACT

Incomplete Kawasaki disease may present significant diagnostic challenges in young infants, frequently leading to delayed diagnosis and severe coronary complications. We report on a 3.5-month-old infant with a delayed diagnosis of incomplete Kawasaki disease who developed bilateral giant coronary artery aneurysms with progressive coronary obstruction. Despite appropriate medical management including immunoglobulin therapy and antithrombotic treatment, the patient developed ischemic heart failure and ultimately required coronary artery bypass grafting. This case highlights the diagnostic difficulty of incomplete Kawasaki disease in early infancy and emphasizes the importance of early echocardiographic evaluation in infants with prolonged unexplained fever.

Keywords: Kawasaki disease, incomplete Kawasaki disease, coronary artery aneurysm, ischemic cardiomyopathy, coronary artery bypass surgery

Introduction

Kawasaki disease is an acute, self-limited systemic vasculitis predominantly affecting infants and young children and represents the leading cause of acquired heart disease in developed countries (1). The disease is characterized by prolonged fever and mucocutaneous inflammatory findings. However, approximately 7-10% of patients, particularly infants younger than one year of age, present with incomplete Kawasaki disease, lacking the full set of classical diagnostic criteria (2,3).

In such cases, delayed diagnosis is common and it is associated with an increased risk of coronary artery abnormalities (1). Without treatment, coronary artery aneurysms develop in approximately 20-25% of patients (1). Early recognition and timely administration of intravenous immunoglobulin and acetylsalicylic acid (ASA) significantly reduce the risk of coronary complications (4). Delayed diagnosis is associated with severe outcomes, including giant coronary artery aneurysms, myocardial ischemia, and sudden death (5).

We report on a rare and severe case of delayed diagnosis of incomplete Kawasaki disease in a 3.5-month-old infant who developed bilateral giant coronary artery aneurysms, progressive coronary artery occlusion, and ischemic heart failure requiring coronary artery bypass grafting.

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Case Report

A previously healthy 3.5-month-old male infant presented with persistent fever (38 °C) and generalized rash. The chief complaint at admission was persistent fever accompanied by irritability and skin rash. Initial laboratory evaluation demonstrated marked leukocytosis (38,000/mm^3), elevated C-reactive protein (CRP) (94 mg/L), and thrombocytosis (720,000/mm^3). Empirical intravenous antibiotic therapy was initiated due to a suspicion of bacterial infection. Day 13 of illness: Fever persisted despite antibiotic therapy. Repeat laboratory tests revealed leukocytosis (31,000/mm^3), anemia (hemoglobin 8.1 g/dL), thrombocytosis (601,000/mm^3), elevated inflammatory markers (CRP 138 mg/L, erythrocyte sedimentation rate 78 mm/h), hypoalbuminemia (1.9 g/dL), and sterile pyuria. Due to meningismus, a lumbar puncture was performed. Cerebrospinal fluid analysis demonstrated pleocytosis with negative bacterial cultures, consistent with aseptic meningitis. Physical examination revealed persistent rash, hyperemic oropharynx and cracked lips, without conjunctivitis or cervical lymphadenopathy. Day 25 of illness: Due to persistent fever and elevated inflammatory markers, transthoracic echocardiography was performed. Echocardiography revealed giant coronary artery aneurysms, measuring 6 mm (Z-score 15.6) in the right coronary artery (RCA) and 10 mm (Z-score 23.0) in the left main coronary artery. Based on clinical findings, laboratory abnormalities, and coronary involvement, a diagnosis of incomplete Kawasaki disease according to the American Heart Association (AHA) diagnostic algorithm was established. Treatment with intravenous immunoglobulin (2 g/kg) and high-dose ASA (30-50 mg/kg/day) was initiated. Fever resolved rapidly and inflammatory markers normalized. Due to the presence of giant coronary artery aneurysms, antithrombotic therapy consisting of ASA and low-molecular-weight heparin was started in accordance with the current guidelines (4). At 16 months of age, systemic arterial involvement was detected, including bilateral axillary artery aneurysms and a focal aneurysm of the right internal iliac artery. The patient was followed with serial echocardiography and coronary computed tomography angiography. During long-term follow-up, electrocardiography demonstrated ischemic changes. Progressive left ventricular dilation and a decline in left ventricular ejection fraction from 65% to 55% were observed. Coronary angiography demonstrated complex coronary artery pathology. Aneurysmatic and calcified dilation was observed in the proximal and mid segments of the left anterior descending artery (LAD). Severe eccentric stenosis of approximately 80-90% was detected in the proximal circumflex artery. The distal circumflex artery was filled retrogradely through collateral circulation originating from the RCA posterior descending branch. The proximal RCA was found to be chronically totally occluded.

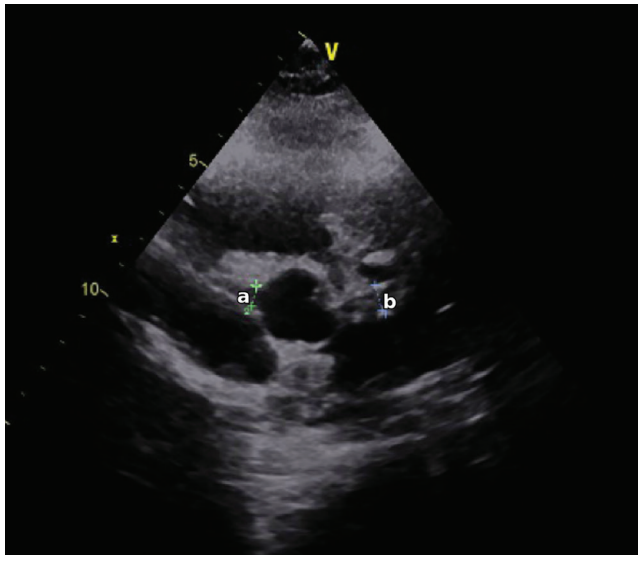

Figure 1. Image of aneurysms observed on transtrasic echocardiography at the time of diagnosis aneurysm (a) RCA aneurysm (b) LCA aneurysm
RCA: Right coronary artery, LCA: Left coronary artery

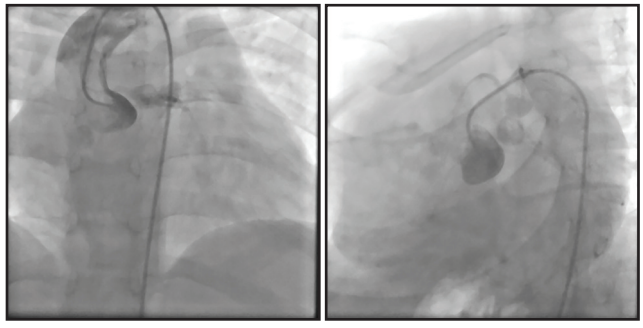

Figure 2. a) Angiographic imaging of coronary artery aneurysms, developing obstructions and collaterals: A distinct aneurysmatic calcified appearance is observed in the LAD proximal and mid segments. In the circumflex trunk/proximal segment, 80-90% eccentric stenosis is observed. It can be seen that the distal Cx is filled retrogradely from the RCA PD branch via collaterals. The RCA proximal is observed to have 100% chronic total occlusion. The collaterals originating from the sinus node branch are connected to the LAD proximal. b) Angiographic imaging of coronary artery aneurysms, developing obstructions and collaterals: A distinct aneurysmatic calcified appearance is observed in the LAD proximal and mid segments. In the circumflex trunk/proximal segment, 80-90% eccentric stenosis is observed. It can be seen that the distal Cx is filled retrogradely from the RCA PD branch via collaterals. The RCA proximal is observed to have 100% chronic total occlusion. The collaterals originating from the sinus node branch are connected to the LAD proximal
LAD: Left anterior descending artery, RCA: Right coronary artery, PD: Posterior descending artery

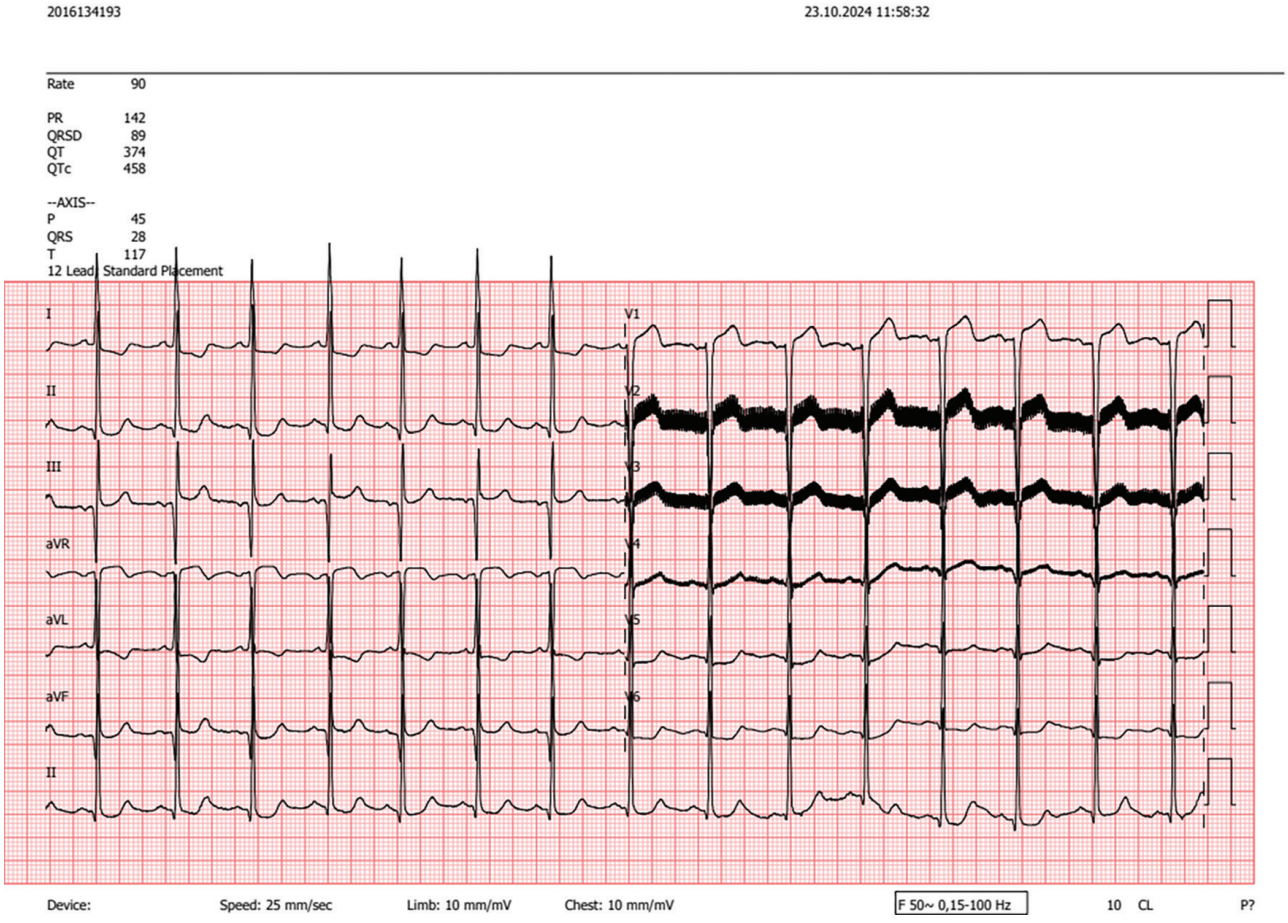

Figure 3. Ischemic ECG changes: The heart axis is slightly shifted to the left. 2 mm depletion is observed in the S-T segment in all versions
ECG: Electrocardiogram

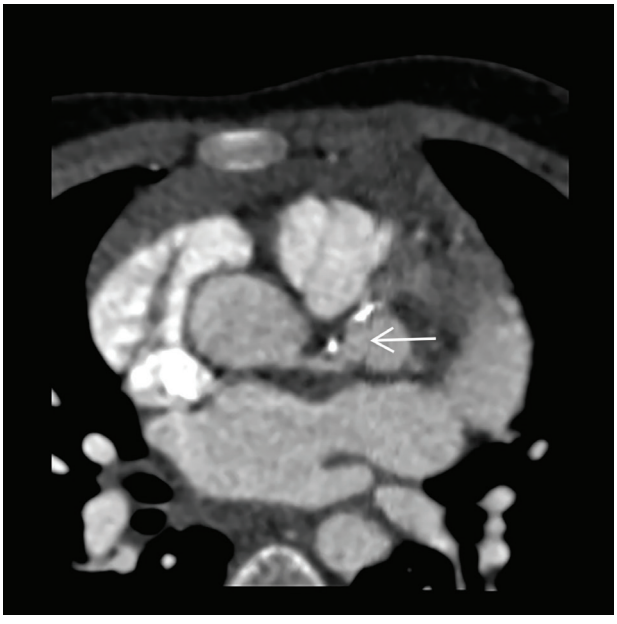

Figure 4. Left coronary aneurysm

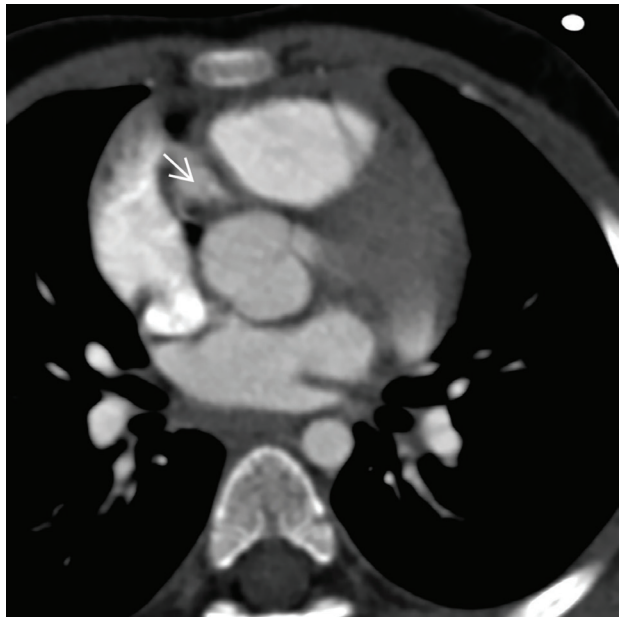

Figure 5. Right coronary aneurysm

In addition, collateral vessels arising from the sinus node branch were seen supplying the proximal LAD. These findings indicated severe multivessel coronary involvement with chronic occlusion and collateral circulation. Due to progressive coronary obstruction and objective evidence of myocardial ischemia, the patient underwent three-vessel coronary artery bypass grafting. Median sternotomy was performed and the left internal mammary artery (LIMA), right internal mammary artery (RIMA), and a saphenous vein graft were prepared. The LIMA was anastomosed to the LAD, the RIMA to the RCA, and a saphenous vein graft to the distal bifid LAD. The cardiopulmonary bypass time was 204 minutes and the aortic cross-clamp time was 104 minutes. The patient was successfully weaned from cardiopulmonary bypass and postoperative hemostasis was achieved without complications. Postoperative follow-up demonstrated improvement in left ventricular systolic function and clinical stabilization (Tables I-III).

Table I. Clinical timeline of illness, laboratory findings, imaging studies, and treatments in the reported patient

Illness Day	Clinical findings	Laboratory	Imaging	Treatment
Day 1	Fever, rash	↑WBC	-	Antibiotics
Day 13	Persistent fever	↑CRP, anemia	-	-
Day 25	KD suspected	Inflammatory markers	ECHO: giant CAA	IVIG + ASA
Follow-up	Ischemia	-	Angiography	CABG

WBC: White blood cell, CRP: C-reactive protein, KD: Kawasaki disease, ECHO: Echocardiography, CAA: Coronary artery aneurysm, IVIG: Intravenous immunoglobulin, ASA: Acetylsalicylic acid, CABG: Coronary artery bypass grafting

Table II. Application of the AHA incomplete Kawasaki disease diagnostic algorithm in the present case

AHA incomplete KD criteria	Findings in the patient
Fever ≥5 days	Fever for 12 days
Elevated CRP or ESR	CRP 138 mg/L, ESR 78 mm/h
Supplemental laboratory criteria	Anemia, thrombocytosis, hypoalbuminemia, sterile pyuria
Echocardiographic findings	Giant coronary aneurysms (RCA 6 mm, LMCA 10 mm)
Final diagnosis	Incomplete Kawasaki disease

AHA: American Heart Association, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, RCA: Right coronary artery, LMCA: Left main coronary artery

Table III. Serial coronary artery measurements and imaging findings during follow-up

Time point	Coronary segment	Diameter (mm)	Z-score	Thrombus	Stenosis	Imaging modality
Day 25 (Diagnosis)	RCA	6 mm	+15.6	No	-	Echocardiography
	LMCA	10 mm	+23.0	No	-	Echocardiography
Follow-up	LAD	Aneurysmatic dilation	-	No	-	CT angiography
	Circumflex	-	-	No	80-90%	Coronary angiography
	RCA	-	-	No	100% occlusion	Coronary angiography

RCA: Right coronary artery, LMCA: Left main coronary artery, LAD: Left anterior descending artery, CT: Computed tomography

Discussion

Incomplete Kawasaki disease represents a significant diagnostic challenge, particularly in infants younger than six months, who frequently present without the full spectrum of classical diagnostic criteria (2,3). As a result, delayed diagnosis is common in this age group and may lead to severe coronary artery complications (5,6).

Cerebrospinal fluid pleocytosis has been reported in Kawasaki disease and it is considered a manifestation of Kawasaki-related aseptic meningitis. This finding may lead to an initial misdiagnosis of infectious meningitis, particularly in young infants presenting with fever and meningeal irritation. In such cases, negative bacterial cultures and the presence of systemic inflammatory findings should prompt consideration of Kawasaki disease in the differential diagnosis (2-5).

According to the AHA guidelines, echocardiographic evaluation should be performed in children with five or more days of unexplained fever and suspected Kawasaki disease (4). In infants younger than six months, echocardiography should be considered even more promptly when fever persists for seven days or longer without a clear source, as incomplete presentations are particularly common in this age group (7-9).

Giant coronary artery aneurysms rarely regress and carry a substantial risk of thrombosis, progressive stenosis, and myocardial ischemia. Current recommendations support anticoagulation therapy in those patients with giant aneurysms, with escalation to triple antithrombotic therapy when significant stenosis or thrombosis develops (4,9).

Although systemic arterial aneurysms are recognized complications of Kawasaki disease, particularly in those patients with giant coronary artery aneurysms, alternative etiologies should also be considered in the differential diagnosis. These include systemic vasculitides, monogenic autoinflammatory syndromes, and connective tissue disorders. Careful clinical evaluation and appropriate laboratory investigations are therefore important in order to exclude other causes of systemic aneurysmal disease (8,9).

Progressive coronary artery stenosis, chronic total occlusion, and objective evidence of myocardial ischemia may necessitate surgical revascularization. Coronary artery bypass grafting remains an important treatment option in selected pediatric patients with Kawasaki disease complicated by severe multivessel coronary involvement (8-10).

This case highlights the serious cardiovascular consequences of delayed diagnosis in incomplete Kawasaki disease and underscores the importance of early recognition, prompt echocardiographic evaluation, and close long-term cardiovascular surveillance.

Ethics

Informed Consent: Written informed consent for publication was obtained from the patient's legal guardians.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ş.Ş.Ö., E.D., B.B.A.A., H.K., B.K.B., O.N.T., Y.A., R.E.L., Concept: Ş.Ş.Ö., E.D., Z.Ü., B.B.A.A., H.K., B.K.B., Y.A., R.E.L., Design: Ş.Ş.Ö., Z.Ü., H.K., O.N.T., Y.A., R.E.L., Data Collection or Processing: Ş.Ş.Ö., Z.Ü., M.Y., B.K.B., R.E.L., Analysis or Interpretation: Ş.Ş.Ö., Z.Ü., M.Y., B.B.A.A., B.K.B., O.N.T., R.E.L., Literature Search: Ş.Ş.Ö., E.D., M.Y., B.B.A.A., H.K., B.K.B., O.N.T., Y.A., R.E.L., Writing: Ş.Ş.Ö., E.D., M.Y., B.B.A., B.K.B., H.K., Y.A., R.E.L.

Conflict of Interest: The authors declare no conflict of interest.

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Case Report

Hemoptysis in Childhood: A Rare Cause and a Diagnostic Challenge

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ABSTRACT

Hemoptysis in children is uncommon and may represent a life-threatening condition. Its rarity and broad differential diagnosis often delay the recognition of potentially serious underlying causes. Awareness of neoplastic etiologies, even in healthy children, is essential in order to avoid diagnostic delay and ensure optimal outcomes.

Keywords: Hemoptysis, carcinoid tumor, bronchoscopy

Introduction

Hemoptysis is rare in the pediatric population and may represent a diagnostic and therapeutic challenge, particularly when it is massive (1). Furthermore, it is not always easy to recognize, as it is often misinterpreted as gastrointestinal, nasopharyngeal or oral bleeding (2).

In most cases, hemoptysis is mild and self-limited, typically associated with respiratory infections. However, the range of potential etiologies is broad, including bronchiectasis, trauma, foreign bodies, pulmonary malformations, vasculitis and tumors, among others (1).

Case Report

We report the case of a 12-year-old girl, with a past medical history of anxiety, attention-deficit hyperactivity disorder and functional dyspepsia, receiving treatment with sertraline and methylphenidate. Her immunizations were up to date according to the national immunization program, including the "Bacille Calmette-Guérin" vaccine.

She was brought to the emergency department after a sudden episode of coughing up a large amount of blood without symptoms suggestive of respiratory infection, weight loss, night sweats, fever or any other complaints. Over

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the preceding six months, she had experienced occasional episodes of small-volume blood-streaked sputum, always interpreted as vascular fragility in the context of upper respiratory tract infections. She described these episodes as a sensation of discomfort in the oropharynx, followed by coughing and bloody expectoration, occurring approximately once per month. There was no known epidemiological context, no history of contact with tuberculosis patients, and no identifiable triggers.

On examination, blood pressure was 117/70 mmHg (P50-90 for sex, age and height), heart rate was 63 beats per minute, oxygen saturation of 99% on room air, and tympanic temperature was 36.5 °C. She appeared visibly anxious and had frequent coughing episodes accompanied by moderate amounts of blood and clots. Her skin and mucous membranes were pink and well hydrated, without rash or signs of bleeding diathesis. Oropharyngeal examination and anterior rhinoscopy revealed no bleeding lesions and the remaining physical exam, including cardiopulmonary auscultation and abdominal palpation, were unremarkable.

Laboratory tests showed that hemoglobin was 12.6 g/dL, mean corpuscular volume was 84.1 fL, mean corpuscular hemoglobin concentration was 32.8 g/dL, red cell distribution width was 16.2%, leukocytes were 9,000/µL and platelets were 328,000/µL. Coagulation studies revealed that prothrombin time was 14.7 seconds, INR was 1.11 and activated partial thromboplastin time was 29.1 seconds. Lactate dehydrogenase was 196 U/L and renal function, electrolytes, and liver enzymes were within normal limits. Chest radiography was unremarkable.

She received tranexamic acid (10 mg/kg) and was transferred to a tertiary care hospital for otorhinolaryngology evaluation, which did not identify any bleeding source. She was admitted for observation and further investigation.

In the following hours, she continued to have episodes of coughing with blood-streaked sputum, followed by another episode of massive hemoptysis (Figure 1). A repeat complete blood count showed a hemoglobin level of 11.6 g/dL. Re-evaluation of the chest radiograph suggested a heterogeneous left retrocardiac opacity (Figure 2). Computed tomography angiography of the chest revealed a solid endobronchial lesion within the lumen of the left lower lobar bronchus, measuring approximately 26×18 mm, with contrast enhancement (Figure 3).

Given the suspicion of a neoplastic lesion, diagnostic flexible bronchoscopy was performed without complications. It revealed a rounded, regular, whitish-gray mass at the origin of the left lower lobar bronchus, almost completely obstructing the lumen, without active bleeding (Figure 4). Biopsy followed by histopathological and immunohistochemical analysis confirmed the diagnosis of a carcinoid tumor (strong immunoexpression of chromogranin, synaptophysin, CD56, and TTF1).

Figure 1. Massive hemoptysis

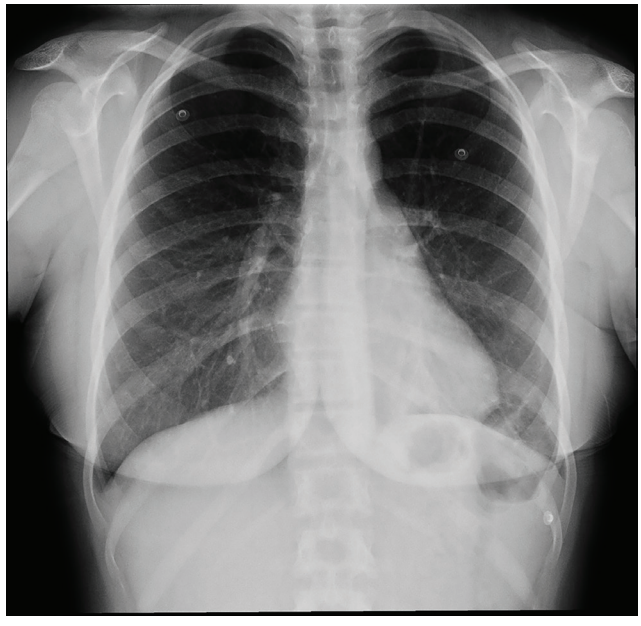

Figure 2. Chest radiograph with a heterogeneous left retrocardiac opacity

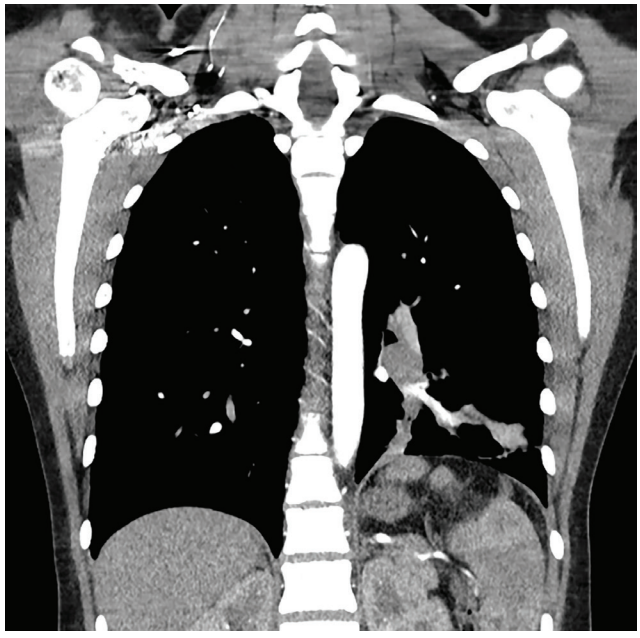

Figure 3. Computed tomography angiography of the chest with an endobronchial lesion on the left lower lobar bronchus

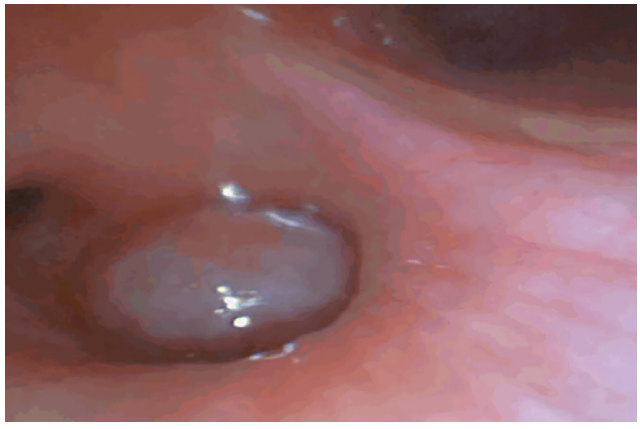

Figure 4. Bronchoscopy showing a whitish-gray mass at the origin of the left lower lobar bronchus

Neuron-specific enolase was 13 ng/mL (reference <15.0), and chromogranin A was 25.8 ng/mL (reference <85.0). Positron emission tomography with a somatostatin analogue (^{68}Ga-DOTANOC) showed an uptake consistent with a left endobronchial carcinoid tumor, without evidence of nodal or distant metastasis.

Video-assisted thoracoscopic surgery with left lower lobectomy and mediastinal lymphadenectomy was performed. Histological examination confirmed a typical carcinoid tumor (carcinoid morphology, <2 mitosis/mm^2, no necrosis and Ki-67 <5%). Lymph node examination revealed no tumor involvement.

Following the surgery, the patient was asymptomatic and without limitations in daily activities. Follow-up imaging at 6 months was scheduled, along with an evaluation by the genetics team.

Discussion

Although rare in the pediatric population, neoplasms can underlie cases of hemoptysis (1). Pulmonary neuroendocrine tumors include carcinoid tumors, large cell neuroendocrine carcinoma and small cell lung carcinoma, the last two being poorly differentiated and high-grade (3). Carcinoid tumors are generally well differentiated and associated with a favorable prognosis. Although most cases are diagnosed between the fourth and sixth decades of life, in children they represent the most common primary malignant lung tumor, accounting for 63-80% of all cases (3,4).

Bronchial carcinoid tumors bleed easily because they are highly vascular neoplasms with a rich submucosal capillary network and fragile tumor vasculature which is prone to disruption. In addition, these tumors typically arise in the central airways, where their endobronchial location exposes them to mechanical trauma from coughing, instrumentation or even spontaneous rupture, leading to bleeding into the bronchial lumen (5,6), as may have occurred in this case.

Given their rarity and frequent presentation with nonspecific respiratory symptoms such as cough, chest pain, or wheezing, alternative diagnoses are often initially assumed (4) leading to delays in tumor identification. In the present case, the patient had minor hemoptysis for 6 months before the diagnosis was established, culminating in an episode of massive hemoptysis (defined as >100 mL of expectorated blood within 24 hours) (7).

The differential diagnosis of pediatric hemoptysis may require computed tomography with angiography (8) which should not be delayed, particularly in cases of recurrent or massive hemoptysis. Nevertheless, a definitive diagnosis relies on histological analysis, for which bronchoscopy plays a key role in obtaining biopsy samples (4,9). Following histological confirmation, accurate staging is essential in order to define the therapeutic strategy, and ^{68}Ga-DOTA-Tyr^3-octreotate (DOTATATE) PET imaging is currently the modality of choice, given its strong uptake in typical carcinoid tumors (10). In this case, PET imaging confirmed findings consistent with an endobronchial carcinoid tumor.

When localized and of primary bronchial origin, these tumors are usually amenable to surgical resection, which remains the treatment of choice (4). As lymphatic spread occurs in up to 20% of pediatric patients, mediastinal

lymph node dissection is recommended for both staging and therapeutic purposes (4). Accordingly, lobectomy with mediastinal lymphadenectomy was performed, and although there was no evidence of nodal or distant disease, follow-up will be maintained.

As carcinoid tumors are rare in pediatric patients, most treatment recommendations are extrapolated from adult guidelines (4). The development of pediatric-specific management protocols is therefore essential in order to ensure optimal care in this population.

Ethics

Informed Consent: The teenager and her mother gave us consent for the publication of the images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: R.P., T.R.S., N.L., J.L., R.P., I.R.L., A.D., M.F., Concept: M.S.S., R.P., M.F., Design: M.S.S., R.P., M.F., Data Collection or Processing: M.S.S., Analysis or Interpretation: M.S.S., R.P., T.R.S., N.L., J.L., R.P., I.R.L., A.D., M.F., Literature Search: M.S.S., F.S., A.M.S., Writing: M.S.S., F.S., A.M.S.

Conflict of Interest: All authors declare that they have no conflict of interest.

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