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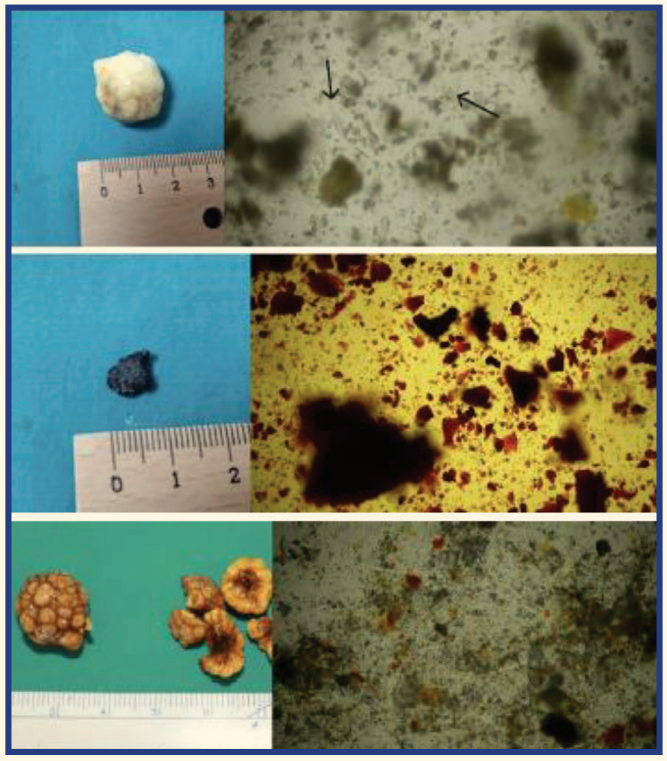

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EDITORIAL

Dear JPR Readers,

We are pleased to present the second issue of 2025. I would like to thank all the editors, reviewers, authors, and the publishing house for their valuable contributions to this issue. Our goal is to contribute to the literature with each new issue and to advance JPR further.

In this issue, we present studies on new biomarkers in non-alcoholic fatty liver disease, analysis of gallbladder stones, evaluating the outcomes of late preterm births, and the effects of aminoglycoside use on hearing in cystic fibrosis. Additionally, this issue includes studies evaluating changes in air pollution and respiratory problems, autoimmune thyroiditis, and epilepsy with occipital discharges. We also share a case series evaluating the control of coagulation problems with sodium benzoate in argininemia. A case presentation on tocilizumab treatment for rare acute necrotizing encephalopathy associated with the dengue/flavi virus, as well as a letter to the editor about clinical and peripheral blood smear findings for diagnosing Chanarin-Dorfman syndrome, also contribute valuable insights to this issue.

We hope that this issue, with its research articles and case presentations, will be of scientific interest to you. We look forward to connecting with you again as readers and authors in the upcoming issues of JPR.

Best wishes,

Dr. Yeliz Çağan Appak

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Original Article

Fibroblast Growth Factor-2 and Tumor Necrosis Factor-Stimulated Gene-6: New Biomarkers for Non-Alcoholic Fatty Liver Disease in Obese or Overweight Children?

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ABSTRACT

Aim: Pediatric non-alcoholic fatty liver disease (NAFLD) is the leading chronic liver disease in children, closely linked to obesity. While liver biopsy remains the gold standard for diagnosis, there is an urgent need for non-invasive biomarkers. This study evaluated the potential diagnostic value of fibroblast growth factor-2 (FGF-2) and tumor necrosis factor-stimulated gene-6 (TSG-6) levels in pediatric NAFLD.

Materials and Methods: This cross-sectional study included 38 children diagnosed with NAFLD via ultrasonography and 26 healthy controls. The patient group consisted of obese or overweight children with NAFLD attending a pediatric gastroenterology clinic. Healthy controls were age-matched, non-obese children without chronic diseases or active infections. Serum FGF-2 and TSG-6 levels were measured in both groups.

Results: Among the 38 NAFLD patients (16 girls, 22 boys) and 26 controls (10 girls, 16 boys), the median FGF-2 level was significantly lower in the patient group (107.50 pg/mL, range: 25.90-533.80) compared to the controls (183.05 pg/mL, range: 50.90-709.80) (p=0.033). The median TSG-6 level was 3,564.60 pg/mL (range: 2,497.50-4,366) in the patient group and 3,504.15 pg/mL (range: 2,370.70-4,366) in the control group, with no statistically significant difference (p=0.199).

Conclusion: Lower FGF-2 levels may play a crucial role in NAFLD pathophysiology and serve as a potential biomarker for diagnosis. Further research is needed in order to validate these findings and to explore their clinical implications.

Keywords: Children, FGF-2, non-alcoholic fatty liver disease, TSG-6, obese, overweight

Introduction

Pediatric non-alcoholic fatty liver disease (NAFLD) stands as the most prevalent chronic liver condition in children, with its incidence steadily increasing alongside rising rates of overweight and obesity (1,2). The World Health Organization identifies being overweight or obese as the fifth most significant risk factor for global mortality (3). This escalating public health crisis is largely attributable to sedentary lifestyles. NAFLD is not merely a liver disorder; it is a multisystem disease which can impact various organs, leading to substantial morbidity and mortality (1,2). The term NAFLD encompasses

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a wide spectrum of conditions, ranging from isolated hepatic steatosis-characterized by fat accumulation without inflammation-to non-alcoholic steatohepatitis, which has the potential to progress to end-stage liver disease (1). Alarmingly, the prevalence of NAFLD is rising exponentially, paralleling the increasing rates of obesity and type 2 diabetes mellitus in both children and adults (4,5). Although the precise prevalence of NAFLD remains unclear, it is estimated to affect approximately 34% of obese children and around 10% of the general pediatric population (5). The pathophysiology of NAFLD stems from intricate hepatocellular metabolic dysfunctions which disrupt insulin action, impair fat metabolism, and free fatty acid processing, and subsequently lead to oxidant-mediated hepatocyte damage (6).

Fibroblast growth factor-2 (FGF-2) has demonstrated notable antifibrotic effects and the ability to promote tissue regeneration, particularly in the context of fibrotic diseases (7,8). As a potent hepatotropic mitogen, FGF-2 plays a crucial role in hepatocyte function. Research indicates that FGF-2 stimulates the regeneration of the extracellular matrix following liver injury and regulates hepatocyte proliferation and migration in vitro (9,10). Additionally, FGF-2 has been shown to exert anti-inflammatory effects by modulating cluster of differentiation (CD) 40 expression and the CD40-CD40L signaling pathway (11).

Furthermore, previous studies have highlighted the interaction between tumor necrosis factor-stimulated gene-6 (TSG-6) and the CD44 receptor on hepatic stellate cells (HSC), positioning TSG-6-based therapy as a promising target for treating liver fibrosis. TSG-6 is also recognized for its anti-inflammatory and tissue-protective properties (12,13).

While liver biopsy remains the gold standard for diagnosing NAFLD, its poor acceptance among patients underscores the urgent need for reliable, accurate, and non-invasive or minimally invasive biomarkers. In this study, we explored the hypothesis that levels of FGF-2 and TSG-6 could effectively differentiate between obese or overweight children with NAFLD and healthy controls.

Materials and Methods

This study included both a patient group and an age- and sex-matched healthy control group. The patient group comprised obese or overweight children under the age of 18 diagnosed with NAFLD through ultrasonographic examination at a pediatric gastroenterology, hepatology, and nutrition outpatient clinic between 2020 and 2022.

Anthropometric measurements were taken with children wearing light clothing and without shoes. At the time of admission, height, weight, and waist circumference measurements were recorded for the patient group. Body mass index (BMI) was calculated by dividing the patient's weight in kilograms by the square of their height in meters. A BMI of 25 to 29.9 is classified as overweight, while a BMI over 30 is categorized as obese. Patients with a history of medication use due to any chronic disease were excluded from this study. The control group consisted of children under age 18 with normal BMI according to their age and sex who presented to the pediatric outpatient clinic and who did not have any chronic diseases, active infections, or histories of chronic medication use. Liver steatosis is categorized into three grades based on ultrasonographic findings: Grade 1 (mild hepatic steatosis), Grade 2 (moderate hepatic steatosis), and Grade 3 (severe hepatic steatosis). Written informed consent was obtained from the parents of all participants in both groups, and ethical approval was obtained from the Cumhuriyet University Clinical Research Ethics Committee decision no.: 2022-05/03, dated: 31.05.2022).

Sample Collection

Fasting blood samples were collected at 9:00 a.m. into serum tubes and K3- ethylenediaminetetraacetic acid (K3-EDTA) tubes (Becton Dickinson, UK) from all patients and healthy controls. Patient samples were obtained upon admission. Serum tube samples were allowed to clot before centrifugation. After centrifugation at 4 °C for 15 minutes at 3,500 rpm, the serum was aliquoted and immediately frozen at -80 °C. K3-EDTA tubes were analyzed promptly.

Biochemical Analyses

The quantitative sandwich enzyme-linked immunosorbent assay technique was used for the determination of serum FGF-2 (Wuhan USCN Business Co., Ltd, China) and TSG-6 (Cloud Clone Corp.). Complete blood count, glucose, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, total bilirubin, direct bilirubin, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, triglyceride, albumin, ions, C-reactive protein (CRP) and erythrocyte sedimentation rate values were evaluated.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences 22.0 computer software. The normality of distribution of numerical variables was evaluated. Numerical

data were compared between the groups using the Mann-Whitney U test (non-normally distributed subjects) and the sample t-test (normally distributed subjects). Descriptive statistics were used to report on the demographical and clinical data from the NAFLD patients and the healthy controls. He data are expressed as medians, ranges, means and standard deviations (SD). Differences in continuous variables between the patients from each subgroup, and between the patients and the healthy controls were analyzed using the Mann-Whitney U test. The Kruskal-Wallis test was used for non-parametric numerical variables of multiple groups. We used Spearman's rank difference correlation to examine the correlation between TSG-6 and FGF-2 and acute phase reactants, and complete blood count parameters. A p-value less than or equal to 0.05 was considered statistically significant.

Results

A total of 38 children [16 girls (42%) and 22 boys (58%)] diagnosed with NAFLD and 26 healthy controls (10 girls and 16 boys) were included in this study. The mean age of the patient group was 12.55±3.04 years, while the mean age of the control group was 10.73±4.27 years.

In the patient group, the mean weight was 76.72±19.79 kg, the mean height was 157.75±15.67 cm, the mean BMI was 30.27±3.71, and the mean waist circumference was 99.17±10.05 cm. Additionally, the mean weight SD was 2.97±0.98, the height SD was 1.03±1.20, and the BMI SD was 2.62±0.65.

Laboratory data for both the patient and control groups are summarized in Table I. Although the absolute absolute neutrophil count/absolute lymphocyte count ratio (1.63±1.04 vs. 1.28±0.80, respectively) and white blood cell count (7,989.7± 2,277.66 vs. 7,180.38±1,499.10, respectively) were higher in the patient group, no statistically significant differences were observed between the two groups.

When comparing the two groups in terms of TSG-6 levels, the median TSG-6 level in the patient group was 3,564.60 pg/mL (range: 2,497.50-4,366), while the median TSG-6 level in the control group was 3,504.15 pg/mL (range: 2,370.70-4,366). This difference between the two groups was not statistically significant (p=0.199).

In contrast, when evaluating FGF-2 levels, the median FGF-2 level in the patient group was 107.50 pg/mL (range: 25.90-533.80), compared to a median of 183.05 pg/mL (range: 50.90-709.80) in the control group. This difference was statistically significant (p=0.033).

Radiologically, twenty-four patients exhibited Grade 1 hepatic steatosis, twelve had Grade 2, and two presented with Grade 3. Upon evaluating TSG-6 and FGF-2 levels across these hepatic steatosis grades, no statistically significant differences were found (p=0.777 for TSG-6 and p=0.624 for FGF-2).

Discussion

The prevalence of NAFLD among children is increasing alarmingly, presenting a significant health concern associated

Table I. Laboratory findings of the patient group and the heathy control group

	NAFLD n=38	**Heathy control n=26**	**p-value**
White blood cell (103/uL), mean ± SD	7,989.47±2,277.66	7,180.38±1,499.10	NS
Absolute neutrophil count/ Absolute lymphocyte count, mean ± SD	1.63±1.04	1.28±0.80	NS
TSG-6 (pg/mL), median (minimum-maximum)	3,564.60 (2,497.50-4,366)	3,504.15 (2,370.70-4,366)	NS
FGF-2 (pg/mL), median (minimum-maximum)	107.50 (25.90-533.80)	183.05 (50.90-709.80)	**0.033**
AST (U/L), median (minimum-maximum)	29 (16-105)	27 (9-35)	NS
ALT (U/L), median (minimum-maximum)	24 (8-244)	22 (11-33)	NS
Triglyceride, mean ± SD	110.52±44.03	105.33±24.30	NS
Total cholesterol, mean ± SD	161.45±39.12	124.15±22.34	NS
LDL-cholesterol, mean ± SD	110.70±30.17	105.51±33.21	NS
HDL-cholesterol, mean ± SD	43.16±8.26	48.45±19.28	NS
ESR (mm/h), mean ± SD	10.54±6.99	12.43±3.12	NS
CRP (mg/L), median (minimum-maximum)	0.37 (0.10-13.40)	0.32 (0.14-4.40)	NS

NAFLD: Non-alcoholic fatty liver disease, FGF-2: Fibroblast growth factor-2, TSG-6: Tumor necrosis factor-stimulated gene-6, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, NS: Not significant

with high morbidity and mortality rates. Despite this, there is a relative scarcity of studies focusing on NAFLD in pediatric populations when compared to adults. Our study is pioneering in evaluating FGF-2 and TSG-6 levels in overweight or obese children diagnosed with NAFLD. A thorough literature review revealed no existing studies investigating TSG-6 and FGF-2 levels specifically in this demographic.

FGFs play a crucial role in regulating HSC differentiation and liver fibrosis, along with exhibiting anti-inflammatory effects. FGF-2, a significant member of the FGF family, is pivotal in modulating HSC function, injury repair, and tissue regeneration. Active HSCs are primary drivers of extracellular matrix deposition in liver fibrosis. FGF-2 has demonstrated anti-fibrotic properties and the ability to promote tissue regeneration in fibrotic diseases, including liver fibrosis (7,14,15). It primarily interacts with FGF receptor-1, which is significantly overexpressed in activated HSCs, thereby inhibiting their activation. Kurniawan et al. (7) proposed a promising therapeutic approach utilizing FGF-2 for the treatment of liver fibrosis.

In obesity, adipocytes secrete pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin (IL)-6, which stimulate hepatic production of acute phase proteins, including CRP, and alter the immune response (16). Additionally, serum adiponectin levels, which are known for their anti-inflammatory effects, are diminished. The increase in reactive oxygen species and reduction in antioxidant substances further exacerbate this negative shift in the immune response, tipping the balance toward inflammation and subsequently decreasing growth factor production (17).

Our findings indicate that FGF-2 levels in the patient group were statistically significantly lower than those in the control group. This suggests a potential dysregulation of FGF-2 synthesis in obese or overweight pediatric patients with NAFLD. Insufficient FGF-2 expression may contribute to the development of NAFLD, positioning FGF-2 injection as a potential therapeutic intervention. The observed low FGF-2 levels in obese patients may reflect a shift toward pro-inflammatory processes.

TSG-6, a cytokine released by human mesenchymal stem/stromal cells (MSC), possesses anti-inflammatory and hepatoprotective effects (12,13). TNF-α and IL-1 activate the transcription of the TSG-6 gene in human fibroblasts (18). TSG-6 is produced in response to various inflammatory stimuli and exhibits anti-inflammatory effects through multiple mechanisms (19,20). Recent studies have identified TSG-6 as a crucial factor in inducing the immunoregulatory effects of MSC and as a promising biomarker for their therapeutic effects (21). Wang et al. (13) demonstrated the therapeutic benefits of TSG-6 injections in mice with liver fibrosis, while Miyaji et al. (22) showcased similar effects in rats with liver damage.

In our study, we did not find a statistically significant difference in TSG-6 levels between obese or overweight children with NAFLD and the control group. Importantly, none of our patients presented with end-stage liver disease. The absence of significant differences in TSG-6 levels may be attributed to the fact that NAFLD had not progressed to an advanced stage in our patient cohort.

Study Limitations

Our study does have limitations, notably the small sample size and the absence of liver biopsy for definitive diagnosis. Liver biopsy is invasive and carries risks such as sampling errors and complications (e.g., pain, bleeding, pneumothorax). One of the limitations of our study is the low number of patients in the liver steatosis groups. Another limitation of this study was the significantly smaller number of participants in the healthy group compared to the patient group. This situation may have had a negative impact on statistical power and so may reduce the validity and reliability of the results. Smaller sample sizes can make the findings more susceptible to random fluctuations, leading to questions about how representative the results are for the general population. Therefore, the limited number of individuals in the control group may restrict the generalizability of this study's findings.

Conclusion

In conclusion, our results suggest that low FGF-2 levels may play a role in the pathophysiology of NAFLD and could be beneficial for diagnostic purposes. However, further multicenter studies with larger patient cohorts are warranted in order to support these findings.

Ethics

Ethics Committee Approval: This study was approved by the Cumhuriyet University Clinical Research Ethics Committee (decision no.: 2022-05/03, dated: 31.05.2022).

Informed Consent: Written informed consent was obtained from the parents of all participants in both groups.

Acknowledgements: We would like to thank the Radiology Department of Sivas Numune Hospital for their contribution.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.K.T., Concept: E.K.T., K.D., Design: E.K.T., K.D., Data Collection or Processing: E.K.T., K.D., Analysis or Interpretation: E.K.T., Literature Search: E.K.T., K.D., Writing: E.K.T., K.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

Gallstone Biochemical Analysis: A Key to Unlocking Disease Etiology?

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ABSTRACT

Aim: The widespread use of ultrasound imaging has increased detection rate of gallstones (GSs) in the pediatric age group. However, their etiology remains unclear in some patients. GS analysis of patients who had undergone cholecystectomy in our department were reviewed and the relationships of etiological factors were evaluated.

Materials and Methods: The records of those patients who had undergone cholecystectomy for GS disease in our clinic between November, 2006 and April, 2024 were reviewed retrospectively and demographic characteristics, comorbidities, and stone analysis results were obtained. Statistical analysis was performed using the chi-square test. A p-value <0.05 was considered significant.

Results: Cholecystectomy was performed on a total of 335 patients during the given period. Data for stone analysis were available for 184 patients (105 females, 79 males). The mean age of the patients at the time of surgery was 10.89 (±5.1) years. Stone analysis revealed calcium bilirubinate stones in 104 (56.5%), cholesterol and calcium bilirubinate (mixed) stones in 67 (36.4%), and cholesterol stones in 15 patients (8.1%). A statistically significant difference was found when stone types were analysed by gender (female/male: 105/79; p<0.015). The etiologic factor for GS formation was identified in 56 patients (30.43%); 31 had haemolytic disease and calcium bilirubinate stones were significantly more common in those patients (p=0.006). Additionally, when the weight percentiles for age were evaluated for the 125 patients (67.9%) with available weight data, it was found that cases with cholesterol stones had significantly higher weight percentiles (>90th percentile, p<0.0001).

Conclusion: In our series, cholesterol stones were more common in overweight children, while calcium bilirubinate stones were more common in those with haemolytic diseases. It appears that the composition of the stones can provide clues into understanding the etiology of cholelithiasis.

Keywords: Cholecystectomy, cholelithiasis, gallstone, gallstone analysis, pediatrics

Introduction

Cholelithiasis, once considered uncommon in pediatric populations, has become increasingly recognized due to improved access to imaging modalities such as ultrasonography and growing clinical awareness. Gallstones (GSs) are solid concretions which develop within the biliary system and are primarily composed of cholesterol or bilirubin. Their formation is thought to result from disturbances in the physicochemical balance of bile, often driven by altered cholesterol or bilirubin metabolism (1). The crystals which accumulate and precipitate in the bile as a result of this imbalance are induced by various etiological factors. Therefore, the chemical composition of the GS can indicate the factors involved in their development. In GS formation,

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***This study was presented as an abstract at National Pediatric Surgery Congress 2022 Aydın, Türkiye**

cholesterol primarily accumulates due to a supersaturation of cholesterol in the bile, while calcium bilirubinate precipitates due to defective bilirubin conjugation, leading to its accumulation (2-4). Additionally, calcium carbonate, calcium phosphate, and infection stones can also be minor components in GS formation. However, GSs are generally categorized into two main types based on their primary components: cholesterol and pigment stones. Although cholesterol is the main chemical compound identified in GS formation, calcium bilirubinate is the primary chemical compound in pigment stone formation (4).

The prevalence and chemical composition of GS vary among different populations, suggesting that multiple etiological factors contribute to their formation. The chemical structure of GS may provide valuable insights into the underlying mechanisms of cholelithiasis. In pediatric patients, the widespread use of imaging techniques such as ultrasonography has led to an increased detection of GS, particularly in those presenting with symptoms such as abdominal pain, postprandial discomfort, or unexplained irritability in infants. Although several risk factors, such as obesity, haemolytic diseases, parenteral nutrition, and certain medications have been associated with GS formation in children, a notable proportion of cases remain idiopathic.

The aim of this study was to investigate the chemical composition of GS in pediatric patients who were operated on at our centre through an in-house laboratory-based analysis, and to explore the possible associations between stone type and clinical variables such as age, sex, body weight, and comorbid conditions. We believe that understanding the detailed composition of GS can enhance our knowledge of pediatric cholelithiasis and contribute to better etiological classification and individualized management strategies.

Materials and Methods

Study Design

The records of those patients who had undergone cholecystectomy for GS in our clinic between 2006 and 2024 were retrospectively reviewed. All patients underwent laparoscopic cholecystectomy. Based on the operating surgeon's preference and patient-specific considerations, either a standard four-port or a three-port laparoscopic technique was utilized. All procedures were performed by experienced pediatric surgeons under general anaesthesia, following standard aseptic protocols.

The demographic characteristics, clinical history, comorbidities, medication use, anthropometric measurements, and stone analysis results of the patients were retrospectively and comprehensively evaluated using data obtained from archived patient files and the electronic medical record system. Those patients for whom stone analysis was performed and recorded were compiled. Patients with choledochal cysts and malignancies of the gallbladder (GB), as well as those whose body weight at the time of operation was not available making percentile calculations impossible were excluded from this study. Additionally, cases with GB polyps or those who underwent cholecystectomy in conjunction with other procedures were also not included. Weight data were obtained for all accessible patients and included in the analysis and all patients received preoperative ursodeoxycholic acid (UDCA) therapy initiated by the pediatric gastroenterology department. UDCA was administered at a standard dosage of 30 mg/kg/day, regardless of the patient's symptomatic status. While treatment dosage was uniform across the cohort, data on the exact duration of UDCA therapy varied between patients and were not consistently documented.

Stone Analysis

One of the most distinctive aspects of this study lies in the real-time biochemical analysis of the GS, performed intraoperatively at our institution. Unlike many previous reports where stone specimens were sent to external laboratories with delayed reporting, our clinical workflow enabled the immediate on-site analysis of the GS composition. Following completion of cholecystectomy, the excised GB was directly delivered to a laboratory located within our surgical unit.

Under the supervision of trained laboratory staff, the stones were promptly examined using the Olympus CX43 stereo microscope system, allowing high-resolution visualization of the surface morphology. As part of the preparation process, the stones were first crushed using a mortar and pestle to reduce their size. This powdered sample was then combined with ammonia, thus facilitating the identification of the calcium bilirubinate and cholesterol components through a chemical reaction. The entire analysis was typically completed within approximately 5 minutes, enabling rapid insight into the biochemical nature of the stones while the surgical team remained present. This integrated, near real-time diagnostic approach not only ensured the reliability of the data but also opened up the possibility of establishing early correlations between GS composition and the underlying disease etiology. The ability to perform stone analysis at the point of care, using both stereomicroscopic and chemical evaluation techniques,

represents a novel and practical model for future studies which aim to link biochemical stone profiles with patient-specific risk factors and metabolic conditions.

Ethical Approval and Helsinki Information

This study was approved by the study was obtained from the Ethical Review Committee of Ege University Faculty of Medicine (approval no.: 2024-2772 24-4.1T/49, date: 25.04.2024). All admissions and surgical procedures were performed after receiving informed consent from the family/parents/caregivers.

Statistical Analysis

All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 21.0 software for Windows (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp., USA). Statistical analysis was performed using the chi-square test, and a p-value <0.05 was considered statistically significant.

Results

Between November 2006 and April 2024, a total of 335 patients underwent cholecystectomy in our clinic. We confirm that the surgical method applied in all patients was laparoscopic cholecystectomy. Importantly, no intraoperative or postoperative complications were observed in any of the patients, and all surgeries were completed successfully without the need for conversion to open surgery. A total of 184 patients with stone analysis results and weight data available in medical records were included in this study. The demographic data of the patients are summarized in detail in Table I. All patients referred to us from pediatric gastroenterology were initially started on UDCA for litholysis, and this group included asymptomatic patients.

Of our patients, 104 (56.5%) had calcium bilirubinate stones, 67 (36.5%) had both cholesterol and calcium bilirubinate stones, and 13 (7%) had cholesterol stones (Figures 1-3). Four patients had infection stones in addition to calcium bilirubinate stones. A statistically significant difference was observed in the types of stones when analysed by gender (female/male: 105/79; p<0.015). The majority of stones in male patients were calcium bilirubinate stones, while cholesterol stones were significantly more common in female patients.

Among the 56 patients (30.43%) for whom an etiological factor could be identified, 31 had haemolytic disease. The most common haematologic condition was hereditary spherocytosis, followed by thalassemia major, acute myeloid leukaemia, acute lymphoblastic leukaemia, and glucose-6-phosphate dehydrogenase deficiency. All stones in this group were calcium bilirubinate stones. It was found that calcium bilirubinate stones were significantly more common in those patients with haemolytic disease (p=0.006). Additionally, when the weight percentiles for age were evaluated for the 125 patients (67.9%) with available weight data, it was found that cases with cholesterol stones had a statistically significant higher weight percentiles

Table I. Demographic and clinical findings of the patients (n=184)

Parameters	Value
Gender F/M (%)	105 (57.1)/79 (42.9)
Mean age ± SD, years (range)	10.89±5.1, (0.5-19)
Obesity (>90th percentile), n (%)	46 (40.7)
Identifiable etiology n (%) Haematologic n (%) Non-haematologic conditions n (%) (e.g., FMF, portal hypertension, PCOS, and multiple sclerosis...)	 56/184 (30.43) 31 (55.35) 25 (44.65)

F/M: Female/male, FMF: Familial mediterranean fever, PCOS: Polycystic ovary syndrome, SD: Standard deviation

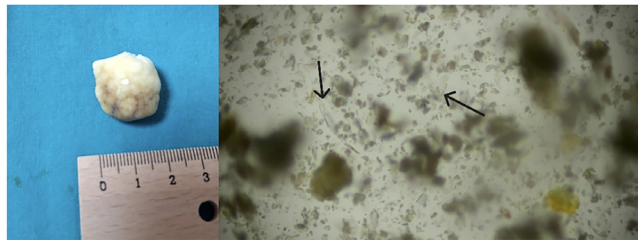

Figure 1. Cholesterol stone, macroscopic and microscopic view- arrows: cholesterol plaques

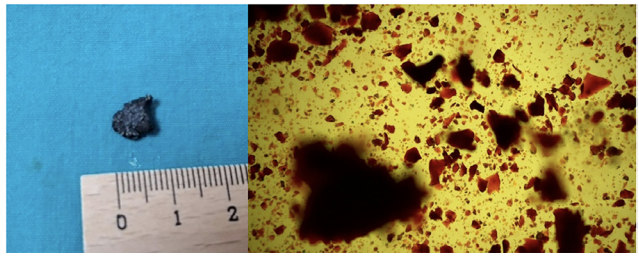

Figure 2. Calcium bilirubinate stone, macroscopic and microscopic view

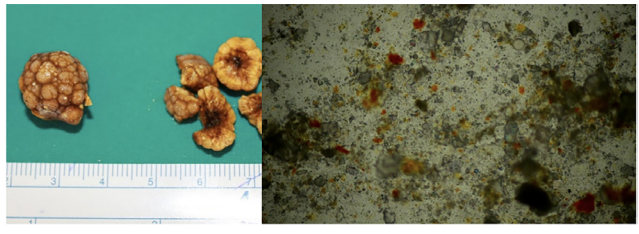

Figure 3. Mixed stones, cholesterol+calcium bilirubinate macroscopic and microscopic view

(>90th percentile, p<0.0001). Also, among the patients with available weight data (n=125), the age-appropriate weight percentile classification revealed that 46.0% (n=52) were above the 97th percentile, 9.7% (n=11) were below the 3rd percentile, and the remaining patients were distributed across intermediate percentile ranges. This distribution indicates a predominance of overweight and obese patients in the cohort. Although body mass index (BMI) could not be calculated due to the lack of height data, weight percentiles for age served as a useful surrogate indicator of nutritional status (Table II).

Discussion

The incidence of GSs detected in children has increased with the widespread use in non-invasive imaging techniques and a global increase in dietary disorders and obesity (5,6). Studies have shown that the etiology of GS formation varies between populations, although the primary factors contributing to these differences remain a subject of debate (7). There is also no clear consensus on whether cholecystectomy should be performed on asymptomatic patients (8).

In our study, the age group most frequently affected by cholelithiasis was 10-16 years, with a predominance of females in this age range. Calcium bilirubinate stones were the most common type of GS observed. Haematologic diseases have been identified as the most frequent risk factor for GS formation, with incidences reported to range from 9% to 50% (9). The higher incidence of cholesterol stones in females was statistically significant, possibly related to a decrease in bile acid reserve and an increased cholesterol saturation of bile in females during puberty when compared to males (10,11).

In pediatric patients, data regarding post-cholecystectomy outcomes remain extremely limited. These findings are primarily based on adult populations, and their applicability to the pediatric age group remains uncertain due to the lack of long-term, large-scale studies in children (12). While some retrospective case series have noted non-specific gastrointestinal complaints such as abdominal pain, diarrhoea, or dyspepsia after surgery, there is currently no conclusive evidence establishing a direct association with long-term complications such as post-cholecystectomy syndrome, colon cancer or persistent symptoms. Future research could focus on investigating the relationship between stone analysis results and long-term postoperative symptoms, as well as gathering data on post-cholecystectomy syndrome in children (13,14).

Therefore, future research should aim to address these knowledge gaps by incorporating prospective, longitudinal follow-up protocols, ideally with standardized symptom questionnaires, imaging modalities, and biochemical monitoring. In addition, evaluating the potential relationship between GS composition and long-term postoperative outcomes may provide valuable insights in this field. Determining whether specific stone types are associated with a higher risk of complications could contribute to the development of future risk stratification models, follow-up strategies, and personalized treatment plans. Therefore, we are considering this topic as one of the focus areas for our future research.

The S3 guidelines recommend UDCA treatment in asymptomatic patients (15). All patients referred from pediatric gastroenterology to our clinic were started on UDCA for litholysis, and no significant difference was observed between the symptomatic and asymptomatic patients. Although Corte et al. (16) reported significant relief in symptomatic cases, they argued that UDCA does not offer a 100% cure for GS treatment. A study by Baran et al. (17) on 74 children supported these findings, suggesting that UDCA treatment could be initiated preoperatively in asymptomatic patients without haematologic diseases (17).

Table II. Comparison of patients according to stone type

Parameters	Calcium stones	Mixed stones	Cholesterol stones
n (%)	104 (56.5)	67 (36.5)	13 (7.0)
Female gender, n (%)	50 (48.1)	43 (64.1)	12 (92.3)
Mean age, mean ± SD, years (range)	8.3±4.4 (0.5-18)	14.1±2.7 (7-19)	14.7±2.04 (11-17)
Obesity, (>90th percentile), n (%)	11 (10.5)	25 (37.3)	10 (76.9)
Haemolytic disease (Hereditary spherocytosis, ALL, AML, thalassemia major, G6PD deficiency), n (%)	31 (29.8)	None	None
UDCA use, n (%)	104 (100)	67 (100)	13 (100)

SD: Standard deviation, ALL: Acute myeloid leukaemia AML: Acute lymphoblastic leukaemia, G6PD: Glucose-6-phosphate dehydrogenase, UDCA: Ursodeoxycholic acid

It is important to note that there is still no clear evidence on whether certain specific characteristics of GS, such as their size, number, or composition, are influenced by the duration of UDCA treatment. While our study included patients who received a standardized dosage, the variation in treatment durations and the limited longitudinal data preclude any definitive conclusions on this matter. Further prospective studies with longer follow-ups, incorporating serial imaging and biochemical monitoring are needed to clarify these potential associations in order to better evaluate the effects of preoperative UDCA, thereby providing stronger evidence for its use in pediatric patients. In conclusion, the treatment of GSs in pediatric patients remains a topic of ongoing debate (17).

Study Limitations

This study has several limitations which should be acknowledged. First, due to its retrospective design and the fact that some patients were referred to our centre after initial diagnosis, complete preoperative clinical and laboratory data were not available for all cases. Specifically, cholesterol and triglyceride levels were not routinely measured across the entire cohort, which limited our ability to comprehensively evaluate certain metabolic risk factors. Additionally, consistent data regarding the duration of UDCA therapy prior to cholecystectomy were not available. Although all patients received UDCA at a standardized dose of 30 mg/kg/day, due to insufficient documentation, the variability in treatment duration could not be assessed. Consequently, it was not possible to determine whether the length of medical therapy had any effect on the GS characteristics, such as their size, number, or their chemical composition. Another important limitation was the lack of height data for most patients, which made it impossible to calculate BMI and Z-scores which precluded obesity classifications based on BMI percentiles. Instead, we used age-appropriate weight percentiles in order to assess nutritional status. While a high BMI is a known risk factor in adult populations, both elevated weight percentiles and haematologic disorders are recognized contributors to cholelithiasis in children (6,18). Finally, cholecystectomy rates increase with age due to risk factors such as haematologic diseases, a family history of GS, cystic fibrosis, cephalosporin treatment, and obesity (16,19). Although we investigated these risk factors, information regarding a family history of cholelithiasis was not available in this study. These limitations highlight the need for future prospective studies with standardized data collection and long-term follow-ups.

Conclusion

Our study was a single-centre study with the longest duration and the highest number of patients regarding the value of stone analysis on determining etiology which had been conducted to date. Consequently, in our series, it was shown that cholesterol stones were more common in overweight children and calcium bilirubinate stones were more common in haemolytic diseases. These findings were found to align with the literature, and it was observed that the content of the stones could be an important clue into understanding the etiology of cholelithiasis.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Ethical Review Committee of Ege University Faculty of Medicine (approval no.: 2024-2772 24-4.1T/49, date: 25.04.2024).

Informed Consent: All admissions, surgical procedures were performed after informed consent of the family/parents/caregivers.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.C., Ü.Ç., A.Ç., M.O.E., Concept: M.C., A.Ç., M.O.E., Design: M.C., M.O.E., Data Collection or Processing: M.C., Ü.Ç., T.K., A.Ç., M.O.E., Analysis or Interpretation: M.C., T.K., M.O.E., Literature Search: M.C., Writing: M.O.E.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

Gestational Age Matters: Dissecting Outcomes in Late Preterm Births

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ABSTRACT

Aim: The proportion of late preterm babies, defined as neonates born between 34+0/7 and 36+6/7 weeks of gestation, among the total number of babies born is increasing due to increasing technological possibilities and changing maternal factors in modern life. While attention is paid to preterm babies, ignoring these babies as term babies results in increased morbidity and mortality. This causes a significant burden on the health system, especially in places like our country where the number of births is high. However, this burden can be reduced with more care and less cost in late preterm babies as opposed to preterm babies.

Materials and Methods: In this retrospective cohort study, all late preterm infants admitted within the first 28 days of life over a five-year period were evaluated. Maternal and neonatal data were collected from patient records. Infants were classified into 3 groups to emphasize differences between gestational ages (34, 35 and 36 gestational weeks).

Results: Four hundred twenty-one infants were analyzed, and hyperbilirubinemia was the most frequent complication (47.5%), followed by respiratory difficulties (33.7%) and sepsis (24.2%). Infants delivered at 34 weeks showed a higher incidence of respiratory complications and required longer hospital stays than those born at 35 and 36 weeks. Moreover, differences in the occurrence of hypoglycemia and feeding intolerance further emphasized the unique vulnerability of the youngest subgroup.

Conclusion: Even within the late preterm category, distinct morbidity patterns exist based on gestational age. The findings underscore the necessity for tailored clinical management strategies to address the specific risks faced by the younger late preterm infants. Future studies should focus on refining care approaches and examining long-term outcomes in this population.

Keywords: Late preterm, maternal morbidity, neonatal morbidity, neonatal mortality

Introduction

Prematurity, traditionally defined as birth before 37 weeks of gestation, encompasses a wide range of neonatal outcomes and risks (1,2). Within this broad categorization, infants are further classified into early and late preterms, acknowledging the significant clinical and prognostic differences across this spectrum (3). The designation of "late preterm" specifically refers to infants born between 34+0/7 and 36+6/7 weeks of gestation. Despite their apparent maturity compared to earlier preterms, late preterm infants face considerable risks, including respiratory, metabolic, and neurological complications. While differences between

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34, 35, and 36-week infants exist and may influence management strategies, these distinctions are often overlooked in clinical practice.

The increasing incidence of late preterm births is a global concern, linked to heightened risks of neonatal morbidity and mortality. In the United States, the proportion of late preterm births has seen a notable rise, from 9.68% in 1990 to 12.81% in 2006, eventually reaching 20% by 2009 (4). Developing countries such as India have also reported rising preterm birth rates, largely due to limited access to maternal healthcare and high rates of infections during pregnancy (5). These trends reflect broader shifts in obstetric practices, including more frequent use of induction and cesarean delivery before full term, alongside demographic changes such as older maternal age and an increase in multiple gestations.

In Türkiye, it is estimated that out of approximately 1.3 million annual births, around 100,000 are late preterm. Despite the variability in reported rates across different healthcare settings, the prevalence generally falls between 9% and 15%, highlighting a significant public health issue (5,6). The morbidity and mortality associated with late preterm births, although lower than those for extremely preterm infants, are nevertheless substantially higher than for those born at term. Studies from various countries, including the UK, the US, and Canada, have consistently demonstrated increased risks for these infants (1-3).

Recent epidemiological data indicate notable shifts in preterm birth rates during and following the Coronavirus disease 2019 pandemic. Although some studies reported a temporary reduction in overall preterm births linked to lockdown measures and altered healthcare utilization, more nuanced patterns emerged for late preterm births, defined as infants born between 34+0/7 and 36+6/7 weeks of gestation. Specifically, Yalçın et al. (7) observed variable trends in Türkiye, where pandemic-related changes in prenatal care, maternal stress, and healthcare-seeking behaviors influenced birth outcomes differently across gestational ages, highlighting an increased vulnerability among late preterm infants. Similarly, a nationwide analysis from South Korea and a study from Germany demonstrated shifts in neonatal outcomes, emphasizing the importance of understanding regional and gestational-specific trends (8,9). Given these complex dynamics, close monitoring and tailored clinical management of late preterm infants have become increasingly crucial to mitigate morbidity and mortality risks exacerbated by pandemic-related disruptions.

This study aims to bridge the gap in understanding the unique characteristics and outcomes of late preterm infants, specifically examining differences between 34, 35, and 36 weeks of gestation. By evaluating local birth rates, neonatal intensive care needs, and morbidity and mortality patterns, it seeks to provide valuable insights for improving care strategies and advancing outcomes for this vulnerable group.

Materials and Methods

Study Design and Population

The retrospective cohort study, conducted between 2014 and 2019 in a tertiary neonatal intensive care unit (NICU), included all infants born between 34+0/7 and 36+6/7 weeks of gestation and admitted during the neonatal period (0-28 days). Its primary objective was to evaluate morbidity and mortality rates in late preterm infants, assess maternal and neonatal risk factors, and investigate differences among the subgroups of 34, 35, and 36 weeks to highlight their distinct clinical characteristics and outcomes.

The clinical data for this study were collected retrospectively from the hospital's electronic medical records. Eligible infants were identified based on gestational age at birth, and maternal data were obtained from both obstetric and neonatal records. All data were anonymized to protect patient confidentiality.

This study was approved by the Non-Interventional Research Ethics Committee of Dokuz Eylül University (approval no.: 2020/08-26, date: 27.04.2020).

Definitions and Interventions

Maternal risk factors such as chorioamnionitis (both clinical and histologic), premature rupture of membranes (PROM), preeclampsia, gestational diabetes mellitus (GDM), oligohydramnios, polyhydramnios, and thrombophilia were evaluated for their potential effects on neonatal outcomes.

Neonatal morbidities were classified system by system in this study

Respiratory system: Respiratory morbidities included conditions such as respiratory distress syndrome (RDS), pneumonia, transient tachypnea of the newborn (TTN), and air leak syndromes. These were managed with respiratory support, mechanical ventilation, and oxygen therapy.

Gastrointestinal system: Necrotizing enterocolitis (NEC) was identified using modified Bell's criteria, with management focusing on preventing further intestinal damage and controlling infection. In addition, infants

who presented with feeding intolerance or experienced significant weight loss were classified under gastrointestinal morbidities.

Hypoglycemia was defined with specific glucose thresholds: ≤40 mg/dL for symptomatic infants on the first day, and ≤50 mg/dL for subsequent days.

Hyperbilirubinemia was another key metabolic issue, managed using the Turkish Neonatology Society's 2014 guidelines for phototherapy thresholds, depending on gestational age and associated risk factors.

Neurological system: Neurological morbidity was defined as the presence of clinical seizures, the need for antiepileptic therapy, intraventricular hemorrhage (IVH), hypoxic-ischemic encephalopathy (HIE), or periventricular leukomalacia (PVL). In cases of suspected clinical seizures, standard 30-60 minute video electroencephalography recordings were performed using the international 10-20 electrode placement system (with 20 electrodes) to confirm electrographic seizure activity. HIE diagnosis and management-including the use of therapeutic hypothermia-were guided by the Turkish Neonatal Society's national recommendations (10). IVH was graded according to Papile's classification, and PVL was assessed via cranial ultrasonography using the de Vries criteria.

Infectious diseases: Infections, particularly sepsis, were a significant concern among late preterm infants. Sepsis was classified into early-onset sepsis, defined as infection occurring within the first 72 hours of life, and late-onset sepsis, which was diagnosed after 72 hours. Diagnosis of sepsis was confirmed through positive blood cultures, with treatment initiated based on systemic signs of infection.

Neonatal morbidity and mortality management adhered to the most up-to-date recommendations from the Turkish Neonatology Society and other contemporary publications during the study period (10-16).

Statistical Analysis

Data analysis was conducted using Statistical Package for the Social Sciences software (version 24.0). Continuous variables were described either as mean ± standard deviation for normally distributed data or as median (minimum-maximum) for non-normally distributed data. Normality was assessed using the Shapiro-Wilk test. To compare two groups for parametric variables, Independent Samples t-tests were utilized, while the Kruskal-Wallis test was employed for non-parametric variables. Categorical variables were analyzed using the chi-square test, and when relevant, relative risk calculations were conducted. Statistical significance was set at a p-value <0.05, with all tests performed as two-tailed to account for potential confounding factors.

Results

Study Population

During the study period, from June 1, 2014, to May 31, 2019, there were 6,545 live births at the hospital. Of these, 11% (n=727) were classified as late preterm. A total of 38.9% (n=283) of these late preterm newborns were admitted to the NICU for specific reasons. Additionally, 149 late preterm infants born at other centers were transferred to our hospital, representing 34% of the total admitted late preterm population. Eleven infants were excluded due to missing data, bringing the total number of cases included in the study to 421.

Maternal Demographic Results

Maternal demographic data were collected from obstetrics and gynecology clinic records. The average maternal age was 30±6 years, and no significant difference in maternal age was found when grouped by gestational weeks (p=0.53). Most pregnancies were second pregnancies, with no statistical difference in gestational age across different pregnancy orders (p=0.49). Multiple pregnancies comprised 12.1% of the sample, with 35-week gestations significantly more frequent than 34 or 36 weeks (p=0.019). Assisted reproductive technology was used in 4.4% of pregnancies, with no statistical difference among gestational age groups (p=0.83). Antenatal steroid administration occurred in 20 cases, with fewer cases at 36 weeks compared to 34 and 35 weeks (p=0.018) (Table I).

Regarding maternal morbidities, gestational hypertensive disorders were the most common (15.9%, n=62), with preeclampsia accounting for 81% of these cases, though no differences were observed among gestational ages (p=0.71). GDM was present in 12.6% of mothers, with no significant differences across gestational ages (p=0.42). Hypothyroidism was noted in 10% of mothers, and its prevalence was significantly higher in those who delivered at 36 weeks (p=0.024). Oligohydramnios was seen in 7.4% of pregnancies, with a lower frequency at 35 weeks (p=0.03). Prolonged PROM occurred in 8.2%, without significant variation by gestational age (p=0.29). Smoking during pregnancy was reported in 3.3% of cases, with no significant differences among groups (p=0.29).

Neonatal Demographic Results

Among the 421 neonates in the study, 23.8% (n=100) were born at 34 weeks, 32.8% (n=138) at 35 weeks, and

Table I. Maternal and neonatal characteristics and outcomes across the gestational age groups in late preterm infants

	34 GW	35 GW	36 GW	p-value
Total number of mothers, n	91	124	175	-
Average maternal age (years)	30.49±6.89	29.73±6.12	29.86±6.04	0.53
Number of multiple pregnancies, n (%)	12 (13.1)	21 (16.9)	14 (8)	**0.02**
Oligohydramnios, n (%)	11 (12.1)	6 (4.8)	12 (6.8)	0.03
Antenatal steroid, n (%)	8 (8.7)	9 (7.2)	3 (1.7)	0.018
Gestational hypertensive disorder, n (%)	17 (18.6)	18 (14.5)	27 (15.4)	0.71
Gestational diabetes, n (%)	15 (16.4)	15 (12.1)	19 (10.8)	0.42
Fetal growth restriction, n (%)	4 (4.3)	10 (8.1)	14 (8)	0.50
PPROM, n (%)	7 (7.6)	14 (11.3)	11 (6.3)	0.29
Mode of delivery (C/S), n (%)	79 (86.8)	106 (85.5)	133 (76)	0.21
Total number of babies, n	100	138	183	-
Birth weight, g	2.356±472	2.512±486	2.672±453	**0.001**
SGA, n (%)	9 (9)	22 (15.9)	32 (17.5)	0.15
LGA, n (%)	15 (15)	17 (12.3)	14 (7.6)	0.73
Female gender, n (%)	42 (42)	62 (44.9)	79 (43.1)	0.94
Apgar score 1st minute 5th minute	 9 (1-10) 9 (4-10)	 9 (1-10) 9 (7-10)	 9 (1-10) 9 (4-10)	 0.50 0.30
PPV in the delivery room, n (%)	32 (32)	36 (26)	34 (18.6)	0.090

Continuous variables are displayed as mean ± standard deviation or as median (minimum-maximum) where appropriate, while categorical variables are expressed as frequencies (n) and percentages (%). Statistical significance was assessed with a p-value <0.05 (bold values)
PPROM: Preterm premature rupture of membranes, LGA: Large for gestational age, SGA: Small for gestational PPV: Positive pressure ventilation

43.5% (n=183) at 36 weeks, with an average gestational age of 35.2±0.8 weeks. Males accounted for 56.5% (n=238) of the cohort. The average birth weight was 2544±484 grams, varying across gestational ages, with 36-week neonates being heavier. Apgar scores at 1 and 5 minutes showed no significant differences. Median hospital stay was 5 days, with 36-week neonates having shorter durations (p=0.001).

Neonatal morbidities: Among neonatal morbidities, respiratory morbidities were the most frequently observed, while hyperbilirubinemia was the most common specific condition documented, as presented in Figure 1.

Respiratory morbidities: Respiratory morbidities were observed in 33.7% (n=142) of the infants, with the highest frequency at 34 and 35 weeks. Infants born at 36 weeks had significantly fewer respiratory issues (p=0.014). TTN was the most common condition, seen in 18.1% of the cohort and 53.5% of those with respiratory morbidities. RDS and congenital pneumonia were also prevalent. Non-invasive ventilation was required in 32% of cases, while 12.8% required invasive ventilation, with no significant differences in ventilation duration across gestational weeks (Table II).

C/S: Caesarean section Gastrointestinal morbidities were observed in 15.4% (n=65) of the infants (Table III). The majority (58 cases) presented with isolated feeding intolerance, while other causes included intestinal atresia (4 cases), direct hyperbilirubinemia (2 cases), and NEC (1 case). Feeding intolerance was consistent across gestational weeks, but neonates born at 36 weeks required significantly shorter intravenous therapy (p=0.039). Total parenteral nutrition (TPN) was needed by 30.2% of infants, with 36-week infants requiring less TPN compared to younger gestational ages (p=0.001).

Metabolic morbidities: In this study, 23.9 (n=101) of infants were monitored for hypoglycemia, with the highest incidence observed in those born at 35 weeks (p=0.003). Intravenous dextrose was required for an average of 4 days, with no significant differences between gestational ages. Hyperbilirubinemia, requiring treatment in 47.5% (n=200) of infants, was the most common morbidity. Phototherapy was administered most frequently to 34-week infants, and 36-week infants had significantly shorter hospital stays (p=0.001). Risk factors included ABO and Rh incompatibility, though no significant differences were found between groups (Table III).

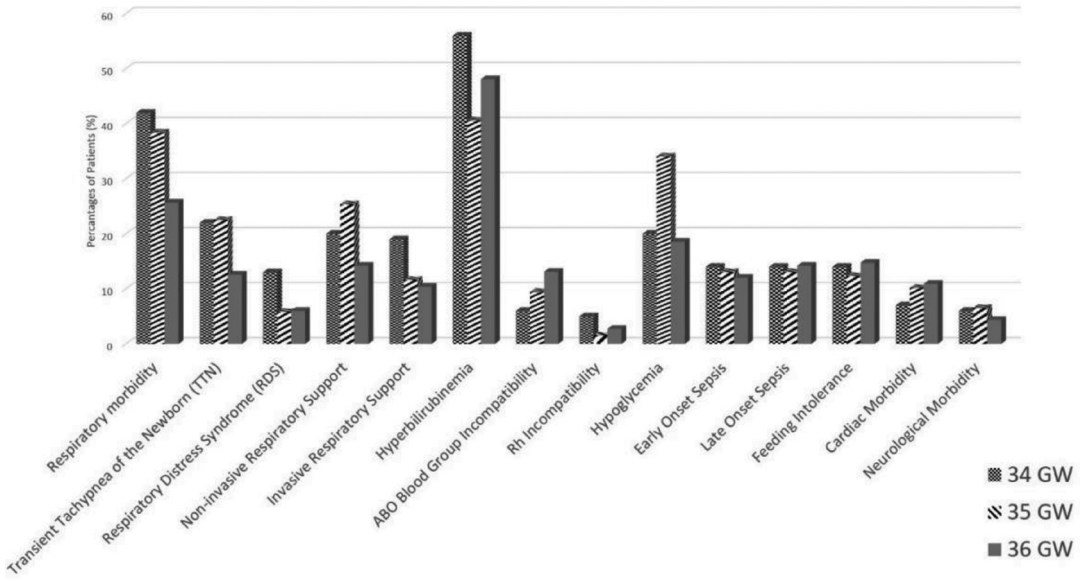

Figure 1. Distribution of respiratory, metabolic, infectious, and interventional outcomes among hospitalized late preterm infants by gestational week. This figure illustrates the percentage of hospitalized late preterm infants (34, 35, and 36 weeks) affected by various morbidities, metabolic disturbances, infections, and the need for respiratory interventions. Parameters include both clinical diagnoses (e.g., TTN, RDS, sepsis) and treatment indicators (e.g., non-invasive/invasive support), as well as underlying etiologies (e.g., ABO/Rh incompatibility)
TTN: Transient tachypnea of the newborn, RDS: Respiratory distress syndrome

Table II. Respiratory morbidities and ventilation support in late preterm infants across the gestational weeks

	34 GW	35 GW	36 GW	p-value
Respiratory morbidity, n (%)	42 (42)	53 (38.4)	47 (25.6)	**0.014**
TTN, n (%)	22 (22)	31 (22.4)	23 (12.6)	**0.035**
RDS, n (%)	13 (13)	8 (5.8)	11 (6.1)	**0.034**
Pneumonia, n (%)	6 (6)	8 (5.8)	6 (3.2)	0.46
Apnea, n (%)	4 (4)	7 (5.1)	7 (3.8)	0.84
Pneumothorax, n (%)	2 (2)	1 (0.7)	2 (1.1)	0.67
Non-invasive ventilation support, n (%)	20 (20)	35 (25.3)	26 (14.2)	**0.024**
Intubation, n (%)	19 (19)	16 (11.6)	19 (10.4)	0.10
Ventilation time, days (total)	7 (1-37)	7 (1-55)	5 (2-21)	0.46
Ventilation time, days (intubated)	2 (1-20)	2.5 (1-55)	5 (1-21)	0.29

Continuous variables are displayed as mean ± standard deviation or as median (minimum-maximum) where appropriate, while categorical variables are expressed as frequencies (n) and percentages (%). Statistical significance was assessed with a p-value <0.05 (bold values)
TTN: Transient tachypnea of the newborn, RDS: Respiratory distress syndrome

Neurological morbidities: Neurological complications were observed in 5.2% (n=22) of the cohort. Seizures requiring antiepileptic treatment occurred in 3.6% (n=15) of infants, without significant differences between gestational ages. IVH was detected in 1.7% (n=7), with 71% occurring in 34-week infants, a statistically significant finding (p=0.008) (Table III). HIE was seen in 1.7% (n=7) of patients, and 57.1% of these cases required antiepileptic treatment. The median hospital stay for these infants was 17 days, significantly longer compared to other patients (p=0.001). Mortality was recorded in 21.8% (n=5) of neurologically affected infants.

Congenital anomalies: The most common congenital anomaly observed was cardiac anomalies, present in 9.7% (n=41) of the infants. Atrial septal defect (ASD) was the most frequent cardiac anomaly, followed by patent ductus arteriosus (PDA) and critical congenital heart disease. Congenital anomalies of the kidneys and urinary tract (CAKUT) were identified in 1.9% (n=8) of the infants.

Table III. Different morbidities and mortality in late preterm infants across the gestational weeks

	34 GW	35 GW	36 GW	p-value
Feeding intolerance, n (%)	14 (14)	17 (12.3)	27 (14.8)	0.82
TPN requirement, n (%)	42 (42)	49 (35.5)	36 (19.7)	**0.001**
TPN duration, (days)	5 (1-28)	6 (1-57)	5 (1-33)	0.62
Hypoglycemia, n (%)	20 (20)	47 (34.1)	34 (18.6)	**0.003**
Hyperbilirubinemia, n (%)	56 (56)	56 (40.5)	88 (48.1)	0.06
ABO group incompatibility, n (%)	6 (6)	13 (9.4)	24 (13.1)	0.07
Rh incompatibility, n (%)	5 (5)	2 (1.4)	5 (2.7)	0.51
Exchange transfusion, n (%)	1 (1)	1 (0.7)	0	0.45
Neurological morbidity, n (%)	6 (6)	9 (6.5)	8 (4.3)	0.68
Intraventricular hemorrhage, n (%)	5 (5)	0	2 (1.1)	**0.008**
HIE, n (%)	0	3 (2.1)	4 (2.1)	0.32
Congenital metabolic diseases, n (%)	3 (0.7)	1 (1)	0	-
Sepsis, n (%)	28 (28)	36 (26.1)	38 (20.7)	0.33
Early sepsis, n (%)	14 (14)	18 (13.1)	22 (12.1)	0.89
Late sepsis, n (%)	14 (14)	18 (13.1)	16 (8.7)	0.32
Early sepsis duration of antibiotic use, (days)	7 (5-7)	7 (5-14)	7 (5-10)	0.06
Late sepsis duration of antibiotic use, (days)	10 (3-14)	10 (5-30)	6 (3-21)	0.09
Length of hospital stay, (days)	8 (1-53)	7 (1-67)	4 (1-42)	**0.001**
Mortality, n (%)	3 (3)	2 (1.4)	5 (2.7)	0.99

Continuous variables are displayed as mean ± standard deviation or as median (minimum–maximum) where appropriate, while categorical variables are expressed as frequencies (n) and percentages (%). Statistical significance was assessed with a p-value < 0.05 (bold values)
TPN: Total parenteral nutrition, HIE: Hypoxic-ischemic encephalopathy

Additionally, 0.7% (n=3) had congenital metabolic diseases. Infants with critical congenital heart disease had longer hospital stays and later transitions to full enteral feeding.

Infectious morbidities: Sepsis was identified in 24.2% (n=102) of the infants, with early-onset sepsis occurring in 53% of cases and late-onset sepsis in 47% (Table III). Culture-positive sepsis was found in 15.2% of cases, with coagulase-negative staphylococci being the most frequent pathogen. The median length of hospital stay for septic infants was 12.5 days, significantly longer than for non-septic infants (p=0.001). IV therapy duration was longer in septic cases (p=0.04). Mortality was observed in 4.9% of the sepsis cases, with one death related to *Candida parapsilosis* infection.

Neonatal mortality: In this study, mortality was observed in 2.4% (n=10) of late preterm infants, with no significant difference between gestational weeks (p=0.99). Among the deaths, three occurred in 34-week infants, two in 35-week, and five in 36-week infants. The most common cause of death was cardiac-related, followed by sepsis and disseminated intravascular coagulation. Other causes included respiratory failure, hydrops fetalis, and severe neurological anomalies. The average time to mortality was 13 days (range: 2-55 days).

Discussion

Late preterm births, defined as deliveries occurring between 34+0/7 and 36+6/7 weeks of gestation, account for a significant proportion of neonatal admissions globally. These infants face increased risks of morbidity and mortality compared to term counterparts, primarily due to physiological immaturity. This study evaluated the outcomes of late preterm infants admitted to a tertiary care center, emphasizing the differences among gestational age subgroups (34, 35, and 36 weeks). The findings highlight distinct patterns of morbidity and neonatal care requirements, underlining the importance of tailored management strategies for each gestational subgroup.

In our study, late preterm births accounted for 11% of live deliveries over a five-year period, a finding consistent with reported rates of 7%-12% in developed countries and 9%-20% in developing nations (1,2). Factors contributing

to this increasing prevalence include advanced maternal age, widespread use of assisted reproductive technologies, and improvements in obstetric care. Notably, 39% of these infants required hospitalization, underlining the burden of morbidity in this population.

Maternal factors significantly influenced late preterm births in this study. The average maternal age was 30 years, and multiple pregnancies accounted for 12% of the cases. Hypertensive disorders (15.9%), gestational diabetes (12.6%), and hypothyroidism (10%) emerged as the most common maternal morbidities, consistent with prior studies. For example, Helvacı et al. (17) reported preeclampsia at 9.3% and gestational diabetes at 6.7%. The higher prevalence observed in this study may reflect the tertiary referral nature of the hospital, which manages a greater proportion of high-risk pregnancies.

In terms of neonatal outcomes, the most frequent morbidities observed in our cohort were hyperbilirubinemia (47.5%), respiratory morbidities (33.7%), and sepsis (24.2%). The high rate of hyperbilirubinemia is consistent with the literature, where studies have shown that late preterm infants are more susceptible to jaundice due to immaturity in bilirubin metabolism delayed feeding, and hemolytic conditions such as ABO and Rh incompatibilities (17,18). Although phototherapy remained the primary treatment modality, its duration was uniform across gestational ages, suggesting standardized care practices.

Respiratory morbidities, particularly TTN and RDS, were observed in 33.7% of the infants, with a significantly lower incidence in those born at 36 weeks compared to those born at 34 and 35 weeks reflecting incomplete alveolar development and surfactant deficiency (p=0.014). The most common respiratory complication was TTN, accounting for 53% of the respiratory cases. RDS was observed in 22.5% of the respiratory cases, while congenital pneumonia was identified in 14%. These findings align with studies showing a gradual reduction in respiratory complications as gestational maturity increases (19). For example, Kitsommart et al. (20) reported a TTN rate of 47% and an RDS rate of 37.3% in late preterm infants.

Our study also found that sepsis was a major contributor to morbidity, affecting 24.2% of the infants, with early-onset sepsis accounting for 53% of cases and late-onset sepsis for 47%. Culture-positive sepsis was identified in 15% of the cases, with coagulase-negative staphylococci being the most frequently isolated pathogen. Similar findings have been reported in other studies, with rates of sepsis in late preterm infants ranging from 15% to 28% (20,21). Notably, no significant differences were observed in sepsis rates among the gestational age subgroups. The prolonged length of hospital stay and the need for extended intravenous therapy underscore the importance of early identification and prompt treatment of infections in this vulnerable population.

Metabolic and gastrointestinal complications were also prominent. Hypoglycemia, another common metabolic issue in late preterm infants, was observed in 24% of the infants in our study, with 46.5% of the cases occurring in infants born at 35 weeks. This aligns with the literature, where hypoglycemia is frequently reported in late preterm infants due to immature glucose regulatory mechanisms (22,23). In our unit, infants born at 34 weeks are typically admitted to the NICU for close observation during the early days of life, unless both their clinical condition and birth weight are clearly adequate. On the other hand, 35-week infants are more often followed in the postnatal ward with their mothers unless specific concerns are noted. This variation in early monitoring practices may help explain the higher hypoglycemia rate observed among the 35-week group. While NICU-admitted infants undergo more frequent glucose checks, allowing for early detection and treatment of hypoglycemia, those monitored in the postnatal setting may not be screened as consistently. As a result, hypoglycemia in these infants might go unrecognized initially and only come to attention when symptoms emerge, potentially leading to later NICU admission. Even when 34-week infants are kept with their mothers, they are generally monitored more closely and early interventions are more likely to be initiated. In light of these findings, and in alignment with recent guideline updates, our unit has begun working on revising its protocols to ensure more uniform and proactive monitoring strategies across the late preterm population. The median duration of intravenous dextrose therapy was four days, with no significant differences between gestational age groups.

Gastrointestinal morbidities were observed in 15.4% of the infants, with feeding intolerance being the most common issue, affecting 58 infants. Feeding intolerance is a well-recognized challenge in late preterm infants, as they often have difficulty with coordinated sucking and swallowing (24,25). Our study also identified four cases of congenital intestinal atresia and one case of NEC, consistent with the low incidence of NEC reported in recent years due to improved feeding practices and the promotion of breast milk feeding (26).

Neurological morbidities, including HIE, seizures and intracranial hemorrhages, were noted in 5% of infants. Intracranial hemorrhage was significantly more common among infants born at 34 weeks, likely due to the fragility of the germinal matrix at earlier gestations (16). HIE was identified in seven infants, and therapeutic hypothermia was required in four cases.

Congenital anomalies, particularly involving the cardiovascular and renal systems, are prominent concerns in late preterm infants. ASD and PDA frequently emerge as significant cardiac anomalies in this population. This is in line with findings from studies such as that of Swenson et al. (27), where major cardiac anomalies were identified in late preterm infants at similar rates. While ASDs often remain asymptomatic initially, PDAs can exacerbate respiratory distress and feeding challenges, requiring timely medical or surgical management to mitigate complications. Similarly, CAKUT represent critical morbidities, with risks of infections and potential long-term renal impairment.

Mortality in our cohort was 2.4%, with no significant differences between gestational age groups. The leading causes of death were cardiac anomalies and sepsis. This mortality rate is lower than those reported in studies from the United States, where late preterm mortality rates of up to 10% have been documented (28). The relatively lower mortality rate in our study may reflect the high quality of neonatal care provided at our tertiary care center.

Study Limitations

This study was designed to evaluate early morbidities and mortality specifically among hospitalized late preterm infants, with the goal of supporting protocol development and clinical decision-making in our unit. As such, infants who did not require NICU admission were not included, which may limit the generalizability of our findings to the broader late preterm population. While long-term outcomes such as neurodevelopment or later health status are undoubtedly important, they were beyond the scope of this retrospective study and were mentioned in the abstract only as a suggestion for future research. Additionally, because our aim was to describe the overall frequency of a wide range of neonatal morbidities rather than focus on specific associations, we did not perform multivariate regression analysis. Given the diversity of outcomes and relatively small subgroup sizes, we felt that such an analysis would not yield sufficiently reliable or meaningful results in this context.

Conclusion

This study highlights the significant morbidity and mortality associated with late preterm births. These infants require close monitoring and specialized care to address common complications such as hyperbilirubinemia, respiratory distress, sepsis, hypoglycemia, and feeding intolerance. Particularly, smaller late preterm infants (e.g., 34-35 weeks) demand more attention for respiratory support and feeding challenges, whereas all late preterm infants share similar risks for issues like hyperbilirubinemia and sepsis. Our findings underscore the importance of adhering to evidence-based guidelines for the management of late preterm infants to improve their outcomes. Further research is needed to explore long-term outcomes in this population.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Non-Interventional Research Ethics Committee of Dokuz Eylül University Faculty of Medicine.

Informed Consent: Informant consent was obtained in accordance with ethical standards.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: O.B., C.A., F.E., N.D., H.O., Concept: O.B., F.E., N.D., H.O., Design: O.B., F.E., N.D., H.O., Data Collection or Processing: O.B., K.A.C.B., Analysis or Interpretation: C.A., F.E., H.O., Literature Search: O.B., K.A.C.B., F.E., Writing: O.B., C.A., N.D.

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Original Article

The Effect of Aminoglycoside Use on the Hearing of Children with Cystic Fibrosis

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ABSTRACT

Aim: This study aimed to examine the effects of aminoglycoside (AG) antibiotics on hearing in children with cystic fibrosis (CF), to determine the risk factors for ototoxicity and the most appropriate audiological tests.

Materials and Methods: This was a retrospective observational study. Hearing tests of CF patients who were regularly followed up in our pediatric chest disease clinic and who had undergone hearing tests between January 2017 and December 2021 were evaluated. All patients underwent standard pure tone audiometry (PTA), extended high-frequency (EHF) PTA, and distortion product otoacoustic emission tests.

Results: This study included 65 patients, aged 5-18 years, who were diagnosed with CF in two groups, one being a study group treated with AG (n=40) and the other being a control group not exposed to AG (n=25). Ototoxicity was determined in 30% of the patients treated with intravenous AG and in 4% of the control group. There was seen to be a high risk of ototoxicity in those patients who received ≥8 cycles of AG. The hearing thresholds at high frequencies, such as 16,000 hertz, were determined to be higher in the right and left ears of the AG treated group in comparison to the control group (p=0.025, p=0.001). Ototoxicity was determined in 2 more patients at high frequency which could not be determined in PTA.

Conclusion: Patients with CF for whom AG antibiotics are frequently used should be followed up at certain intervals with EHF PTA, which is more sensitive, even when there are no complaints.

Keywords: Cystic fibrosis, aminoglycoside, hearing loss

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Introduction

Cystic fibrosis (CF) is a chronic disease with autosomal recessive transmission and usually has respiratory tract involvement. The frequency of *Pseudomonas aeruginosa (P. aeruginosa)* infection has been reported to be approximately 29% between the ages of 0 and 10 years, and 43% in the 11-17 years age group. Aminoglycoside (AG) group antibiotics are administered intravenously (IV) and in nebulized form in *P. aeruginosa* infections. One of the most common causes of ototoxicity is AG use, and when it is considered that these drugs are widely used in CF patients, it has been reported that these patients constitute a high-risk group with respect to ototoxicity.

AG antibiotics are often used in patients with CF (1). They are administered in systemic and nebulized form, especially in *P. aeruginosa* infections (1). The inhalation form of tobramycin is used for the eradication of chronic *P. aeruginosa* colonization in patients aged >6 years (2). IV forms are used in flare-ups of acute infection and the inhalation form of tobramycin is used for long-term eradication in children age ≥6 years. Hearing loss caused by AG depends on the cumulative dose (3,4). Hearing loss may emerge after a single dose, can be bilateral and irreversible, and may require cochlear implantation (5-7).

Ototoxic drugs generally cause hearing and/or vestibular problems (8,9). The prevalence of ototoxicity shows variability (10-12). Our aim in this study was to examine the effects of AG group antibiotics on hearing in children with CF and to determine the most suitable hearing test.

Materials and Methods

Our study was a retrospective cohort study at a pediatric pulmonology department between January 2017 and December 2021. Approval for this study was granted by the Ege University Medical Research Ethics Committee (decision no.: 23-3.IT/38, dated: 23.03.2023). The inclusion criteria of the patients were as follows; I) patients whose ages ranged from 5 to 18, and who were regularly followed up with a diagnosis of CF [This diagnosis was based on the European Cystic Fibrosis Society Patient Registry inclusion criteria and included patients who fulfilled the diagnostic criteria: (a) two sweat tests greater than 60 mmol/L chloride, and (b) one sweat test greater than 60 mmol/L chloride and DNA analysis with two identified disease causing CF mutations]. II) Hearing test given due to AG use. Those patients who received IV AG were determined as the study group and a control group of those who did not receive any AG was also formed. The exclusion criteria of patients were as follows; I) being between the ages of 0-5, II) patients who did not comply with the hearing tests or whose tests could not be evaluated [the standard pure tone audiometry (PTA), expanded high-frequency (EHF) PTA, and distortion product otoacoustic emission (DPOAE) tests were applied]. III) patients who were diagnosed with hearing problems due to another cause or had a family history of hearing loss were also excluded. There is no consensus in the literature on when to perform a hearing test after AG use. The hearing tests of all patients were evaluated retrospectively by an otolaryngologist. The patients were separated into 2 groups as follows: 40 patients who received IV AG antibiotic treatment and a control group of 25 patients who had never received IV AG. The American Speech-Language-Hearing-Association classification was used for hearing loss evaluation (13-15).

Amikacin was administered as the IV AG antibiotic and usage for 10 days was accepted as 1 cycle. Demographic and clinical characteristics were compared between the groups with and without ototoxicity. Chronic bacterial colonization of the respiratory tract was examined (16). The patients' sweat tests, genetic mutations, cumulative AG doses, and hearing test results were recorded.

Statistical Analysis

All data were analysed using Statistical Package for the Social Sciences (SPSS) software (version 25.0) (SPSS Inc., Chicago, USA). Descriptive analyses, including plots of mean and standard deviation or median (interquartile range-IQR), and minimum-maximum (min.-max.) of the audiological assessments, were performed. For the comparison of groups, the chi-square test was used for categorical data with or Fisher's exact test being used where appropriate, and the Mann-Whitney U test was used for continuous but non-normally distributed data. Further analysis of the risk factors of each of the audiological tests was performed using multivariable linear regression analysis in order to confirm which factors were significantly associated with ototoxicity. Spearman's rho correlation test was performed in order to test the correlation between the average lung function forced expiratory volume (FEV) 1% predicted and several IV AG courses received and between the type of AG used and the occurrence of HF hearing loss. The receiver operating characteristic (ROC) curve was used to determine the cumulative AG dose in those patients with ototoxicity. The cumulative AG area under the curve (AUC) was calculated from the ROC. All tests of significance were two-tailed, and p-values of <0.05 were considered statistically significant.

Results

PTA, EHF PTA, and DPOAE tests were performed on 65 (52.4%) of the 124 CF patients followed up in our clinic. Of

all of the patients, 54.3% were female and their median age was 110 (min.: 60-max.: 216) months. There were 40 Patients who used IV AG. Ototoxicity in PTA was determined in 12 (30%) patients who used IV AG. Hearing loss in PTA was determined in 8 (20%) of 40 patients using IV AG. The hearing losses were in the range of 6,000-8,000 hertz (Hz). Hearing loss was bilateral in 7 (87.5%) patients and unilateral in 1 (12.5%). The numbers of patients in both groups who were determined to have impairments in the audiological tests are shown in Figure 1.

In the comparisons of the DPOAE thresholds of both groups, the hearing thresholds at 1,000 and 4,000 Hz in both ears were determined to be significantly higher in those patients who used IV AG. Comparisons of DPOAE test hearing thresholds of those patients either receiving or not receiving AG are shown in Table I.

At 16,000 kilo-Hz, the median hearing threshold value was 15 (min.: 10-max.: 50) decibel (dB) in the right ear for those who used IV AG, 5 (min.: 0-max.: 20) dB in those who did not use IV AG (p=0.025), and a median of 20 dB in the left ear of those who used IV AG and 5.5 dB in those who did not use IV AG (p=0.001). Comparisons of the hearing thresholds in the standard PTA and EHF PTA tests are shown in Table II.

The 40 patients who received IV AG antibiotics were separated into two subgroups, namely those determined with ototoxicity and those without ototoxicity. The demographic and clinical characteristics were compared

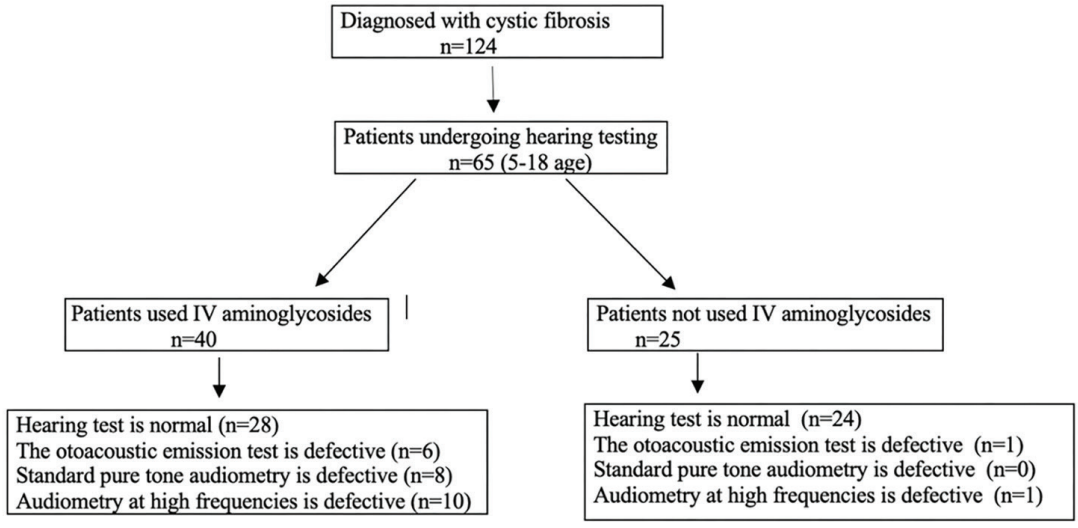

Figure 1. Hearing test results of patients
IV: Intravenously

Table I. Comparison of otoacoustic emission test hearing thresholds of patients receiving and those not receiving IV AG

Frequency (Hz)	Ear (median) (min.-max.)	Patients who used AG (n=40) (dB)	Patients who did not use AG (n=25) (dB)	p-value
1,000	Right Left	12.3 (5.2-15.9) 11.4 (6.1-14.3)	9.6 (5.6-12.8) 9.9 (7.9-10.3)	0.041 0.028
1,400	Right Left	8.1 (4.5-12.3) 8.7 (7.9-16.5)	10.2 (6.1-14.2) 9.2 (6.1-13.7)	0.312 0.224
2,000	Right Left	19.9 (3.2-14.3) 8.7 (3.4-15.1)	12.1 (6.9-13.7) 3.2 (9.2-17.1)	0.412 0.540
2,800	Right Left	10.9 (5.7-14.8) 7.8 (4.3-11.3)	12.1 (5.2-13.8) 6.5 (4.2-9.6)	0.379 0.265
4,000	Right Left	10.1 (2.5-16.1) 12.3 (6.8-14.9)	8.2 (6.1-13.6) 11.6 (9.4-13.5)	0.004 0.047
6,000	Right Left	11.2 (5.1-13.4) 10.7 (5.2-14.3)	8.7 (4.5-14.4) 9.5 (3.4-13.9)	0.103 0.329

dB: Decibel, Hz: Hertz, AG: Aminoglycoside, IV: Intravenous, min.-max.: Minimum-maximum

between these two groups, and no difference was determined with respect to their age or gender. The delta f508 mutation was seen more frequently in the group with ototoxicity, but this difference was not statistically significant (p=0.321). The m1555a> g mutation, which is associated with the development of ototoxicity in the literature, was examined in 5 (12.5%) patients in the group receiving IV AG and was not detected in any. *P. aeruginosa* colonization was determined at higher rates in the group with ototoxicity (p=0.004). In the examination of exposure to AG, the median cumulative AG dose was 354 mg/kg in the group with ototoxicity and 213 mg/kg in the group without ototoxicity (p=0.001). The number of AG cycles had a median of 6 (min.: 3-max.: 20) in the group with ototoxicity and in the group without ototoxicity (p=0.012).

The number of days of receiving AG was greater in the group with ototoxicity but this difference between the groups was not statistically significant (p=0.060). The use of nebulized tobramycin was determined to be 78.9% in the group with ototoxicity and 38.1% in the other group (p=0.030). The use of vancomycin was determined at a higher rate in the group with ototoxicity but this difference between the groups was not statistically significant (p=0.217). Spirometry values were compared between the groups, and the mean FEV1%, forced vital capacity %, and mid expiratory flow 25-75% values were lower in the group with ototoxicity but not to a level of statistical significance.

The risk factors for ototoxicity of the 40 patients using AG are shown in Table III. The use of nebulized tobramycin was found to be higher in the ototoxicity group (p=0.003). *P. aeruginosa* colonization, the number of AG cycles, and the cumulative AG dose were determined to be high. As a result of univariate and multivariate logistic regression analyses of these potential risk factors, only the cumulative AG dose and the number of cycles were determined to be risk factors for ototoxicity. For a cumulative AG dose of ≥390 mg/kg,

Table II. Comparison of standard pure tone audiometry and expanded high-frequency audiometry hearing thresholds of patients who received and those who did not receive IV AG

Frequency (Hz)	Ear (median) (min.-max.)	Patients who used AG (n=40) (dB)	Patients who did not use AG (n=25) (dB)	p-value
250	Right Left	5 (5-15) 5 (5-10)	6 (4-10) 4 (5-15)	0.063 0.208
500	Right Left	10 (5-30) 10 (5-20)	4 (5-15) 8 (5-25)	0.008 0.118
1,000	Right Left	12.5 (5-25) 12.5 (7.5-20)	10 (5-20) 15 (5-20)	0.430 0.567
2,000	Right Left	15 (10-40) 10 (15-30)	10 (7.5-30) 10 (5-20)	0.930 0.230
3,000	Right Left	7.5 (5-20) 10 (5-20)	12.5 (5-30) 12.5 (2.5-20)	0.268 0.531
4,000	Right Left	5 (2.5-10) 2.5 (0-7.5)	5 (2.5-7.5) 5 (2.5-10)	0.578 0.251
6,000	Right Left	15 (0-30) 10 (5-25)	10 (5-40) 7.5 (5-20)	0.411 0.620
8,000	Right Left	15 (5-40) 10 (5-35)	10 (5-20) 5 (0-20)	0.278 0.322
9,000	Right Left	10 (7.5-30) 7.5 (5-30)	10 (5-25) 5 (2.5-15)	0.211 0.256
10,000	Right Left	10 (0-40) 10 (5-45)	10 (5-25) 5 (2.5-12.5)	0.080 0.094
12,000	Right Left	12.5 (10-55) 10 (5-60)	10 (5-20) 7.5 (0-15)	0.112 0.233
14,000	Right Left	15 (10-55) 12.5 (5-40)	5(0-20) 5.5 (5-30)	0.003 0.008
16,000	Right Left	15 (10-50) 20 (5-70)	5 (0-15) 5.5 (0-25)	0.025 0.001

dB: Decibel, Hz: Hertz, AG: Aminoglycoside, IV: Intravenous, min.-max.: Minimum-maximum

the OR (95%) was determined to be 5.140 (min.: 4.801-max.: 10.388) (p=0.003). For the number of AG cycles ≥8, the OR (95%) was determined to be 8.333 (min.: 5.556-max.: 11.334) (p<0.001). Table IV shows the risk factors for hearing loss.

The cut-off value for the cumulative AG dose causing ototoxicity was calculated from the ROC curve as 390 mg/kg (AUC: 0.798, sensitivity 57%, specificity 82%). The cut-off value for the number of AG cycles causing ototoxicity was calculated from the ROC curve as 8 (AUC: 0.822, sensitivity 59%, specificity 81%), and the cut-off value for the number of days of AG was determined to be 45 (AUC: 0.792, sensitivity 48%, specificity 85%). The ROC curve of the AG dose, the number of cycles, and the days causing ototoxicity is shown in Figure 2.

Table III. Comparison of clinical features of patients with and without ototoxicity

n=40	**Ototoxicity (n=12)**	**Non-ototoxicity (n=28)**	**p-value**
Age (months) (median) (IQR) (min.-max.)	120 (60-216)	109 (36-214)	0.596
Sex (M/F)	7/5	15/13	0.809
Mutation, n (%) p.F508del	 7 (58.3)	 13 (46.4)	 0.321
Colonization, n (%) *P. aeruginosa* *S. aureus*	 9 (75.0) 3 (25.0)	 7 (25.0) 3 (10.7)	 0.004 0.074
IV AG exposure (median) (IQR) (min.-max.) Total dose AG (mg/kg) Total AG days Total AG cycles	 354 (44.6-2150) 40.0 (10.0-200.0) 6.0 (3.0-20.0)	 213 (18.1-1023) 20.0 (10.0-80.0) 2.0 (1.0-6.0)	 0.023 0.060 0.012
Nebulized tobramycin, n (%)	11 (91.6)	8 (38.1)	0.003
IV vancomycin, n (%)	10 (83.3)	13 (61.9)	0.217
Oral azithromycin, n (%)	5 (41.6)	6 (21.4)	0.425
Spirometry values (median) (IQR) (min.-max.) FEV1% FVC% FEV1/FVC%	 62.1 (20.2-82.1) 65.3 (38.4-86.2) 68.7 (29.1-87.0)	 64.4 (25.3-86.5) 68.2 (37.5-84.2) 69.4 (32.6-85.9)	 0.241 0.467 0.352

IQR: Interquartile range, min.-max.: Minimum-maximum, AG: Aminoglycoside, IV: Intravenous, FEV1: Forced expiratory volume in 1, FVC: Forced vital capacity, *S. aureus: Staphylococcus aureus, P. aeruginosa: Pseudomonas aeruginosa*

Table IV. Univariate and multivariable logistic regression analyses for ototoxicity

Variable	**Univariate analysis**		**Multivariate analysis**	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Age	0.013 (0.001, 0.029)	0.253		
Sex	0.019 (0.002, 0.054)	0.123		
P. aeruginosa colonization	0.823 (0.356, 0.788)	0.680		
Mutation (Delta f508)	0.549 (0.356, 1.223)	0.267		
Nebulized tobramycin	0.119 (0.056, 2.373)	0.061		
AG cycles >8 cycle	7.544 (0.229, 0.948)	0.001	8.333 (5.556, 11.334)	<0.001
Cumulative AG dose >390 mg/kg	7.272 (6.354, 8.343)	0.006	5.140 (4.801, 10.388)	0.003
IV vancomycin	0.378 (0.234, 1.755)	0.192		
Oral azithromycin use	0.017 (0.072, 0.924)	0.083		

AG: Aminoglycoside, IV: Intravenous, *P. aeruginosa: Pseudomonas aeruginosa*

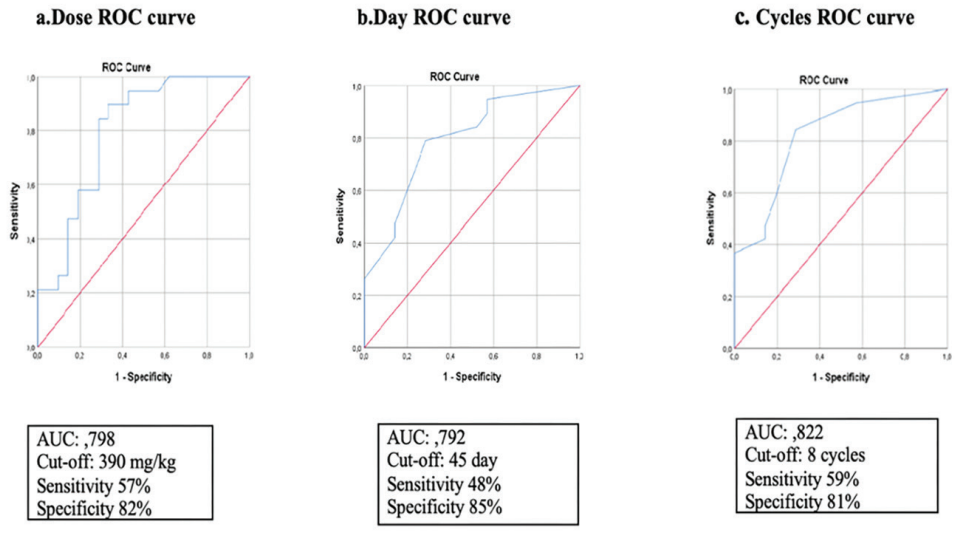

Figure 2. (a, b, c) ROC curve and AUC ROC of total aminoglycoside causing ototoxicity cumulative dose, number of days and cycles
ROC: Receiver operating characteristic, AUC: Area under the curve

Discussion

In the current study, ototoxicity was determined at a rate of 30% in the group receiving AG antibiotics. This rate has been reported in the literature as being 43% by Cheng et al. (17), 24% by Al-Malky et al. (18) and 17% by Martins et al. (19). In a report on the patient records of the Cystic Fibrosis Foundation, the prevalence of hearing loss was reported to be 1.3% in all children (<18 years) with CF (20). In a systematic review which examined studies of AG ototoxicity in children with CF between 1970 and 2014, sensorineural hearing loss was reported to vary between 0% and 29% in 44% of patients receiving 0-10 cycles of AG (21). In a screening of 9,939 children aged 0-6 years in France, the frequency of hearing loss was found to be 10.9% (22).

In the group receiving AG, a difference was found at 500 Hz compared to the control group, and at high frequencies, the difference was determined to be at 14,000 and 16,000 Hz. In a study by Weigert et al. (23), a difference was determined at 10,000 and 16,000 Hz. These differences at high frequencies suggest that there could be subclinical hearing loss even when the patients have no complaints.

There was no difference determined between the current study patients with or without ototoxicity with respect to their age, gender, or CF genetic mutations. *P. aeruginosa* colonization was determined at a significantly higher rate in the group with ototoxicity, which can be attributed to the frequent use of AG antibiotics in acute flare-ups of *P. aeruginosa* infections and the use of nebulized tobramycin in chronic *P. aeruginosa* colonization. The total AG dose, AG dose per kilo, and the number of AG cycles were determined to be significantly higher in the group with ototoxicity. The m1555a>g mutation, which has been associated with the development of ototoxicity in the literature, even at low-dose AG exposure, was not detected in any of the current study patients. Since our study was planned retrospectively, we could not examine the m1555a>g mutation in all patients. The use of nebulized tobramycin was higher in the group with ototoxicity. However, the difficulty in statistically determining the time and amount of usage by the patients is among the limitations of our study. The cumulative AG dose and the number of cycles were found to be risk factors for ototoxicity in the current study. This suggests that care should be taken in the repeated use of AG in patients with CF. Previous studies have also shown that AG ototoxicity is proportional to the number of cycles and the cumulative dose (24,25). In the current study, the use of IV AG for 8 cycles or more was found to increase the risk of ototoxicity. The results of the logistic regression analysis showed that the cumulative AG dose (7.5-fold) and number of cycles (8.7-fold) were risk factors for ototoxicity. Therefore, care should be taken in the repeated use of AG in CF patients. This rate was reported to be 10 cycles in a study by Geyer et al. (25). The minimum number of cycles was 3 AG cycles in the ototoxicity group. In another study of children receiving at least 3 cycles of AG, hearing loss was determined at a rate of 12.5% (26). In a study by Elson et al. (27), audiogram abnormalities were determined in 63% of patients exposed to IV AG, and in 53% of patients exposed to nebulized AG, and a strong correlation was reported between IV AG usage and hearing loss.

Study Limitations

The limitations of this study were its retrospective, cross-sectional design, and that there were no basal hearing tests of the patients before they received AG. However, a significant difference was determined between the results of those patients with CF who did not receive AG.

Conclusion

In conclusion, CF is a disease in which AG group antibiotics, known to have nephrotoxic and ototoxic side effects, are often used. Even when there are no clinical findings suggesting ototoxicity, such as hearing loss, the evaluation of CF patients by means of different hearing tests, especially HF audiometry, at regular intervals after the first use of AG, especially for those using high-dose (cumulative 390 mg/kg) AG antibiotics for more than 8 cycles, is important for the early detection of ototoxicity. When it is considered that the life expectancy of CF patients is being extended with newly developed treatment methods, hearing loss in these patients is extremely important and care must be taken in the use of AG antibiotics. As AG group antibiotics are frequently used in children with CF, these patients must be followed up in collaboration with the ear, nose, and throat clinic even when there are no complaints such as hearing loss or balance problems, and audiological tests should be performed via annual otoscopic examinations.

Ethics

Ethics Committee Approval: This study was approved by the Ege University Medical Research Ethics Committee (approval no.: 23-3.IT/38, dated: 23.03.2023).

Informed Consent: This study was designed retrospective study.

Authorship Contributions

Surgical and Medical Practices: M.M.Ö., G.T., M.F.Ö., H.D.Ş., M.B., F.Ç., G.K.Ö., B.G.D., F.G., E.D., Concept: M.M.Ö., H.D.Ş., F.G., E.D., Design: M.M.Ö., G.T., M.F.Ö. H.D.Ş., F.Ç., F.G., E.D., Data Collection and/or Processing: M.M.Ö., G.T., M.F.Ö., Analysis and/or Interpretation: M.M.Ö., G.T., B.G.D., Literature Search: M.M.Ö., M.B., G.K.Ö., Writing: M.M.Ö., M.F.Ö., G.K.Ö., F.G., E.D.

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Original Article

Emergency Admissions Due to Respiratory Problems in Children Change with Extend of Air Pollution

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ABSTRACT

Aim: Outdoor air pollution can cause many acute or chronic diseases in childhood, with respiratory tract diseases being the leading outcome. Very little childhood data exists to investigate the levels of exposure to pollution. This study aimed to reveal the relationship between pollution and acute respiratory disease in children.

Materials and Methods: This study involved 38,696 patients admitted to pediatric emergency services with respiratory complaints. PM_{10} and SO_2 were selected as indicators of air pollution. Daily data on these indicators were obtained from the province's Air Quality Monitoring Stations website. Data were assessed using descriptive statistics, Pearson's correlation test, and logistic regression.

Results: Among the admitted children, 44.8% were female, and 55.2% were male, with the majority (42.3%) aged 0-3 years. PM_{10} levels exceeded the World Health Organization daily limit (50 μg/m³) on 314 days, with a mean value of 76.54±28.13 μg/m³. SO_2 levels exceeded the 20 μg/m³ limit on 17 days, with a mean of 9.99±5.79 μg/m³. Positive correlations were found between PM_{10} and SO_2 with respect to hospital admissions ($p<0.01$). Logistic regression revealed significant associations between PM_{10} and all respiratory conditions, while SO_2 was linked to acute nasopharyngitis, upper respiratory infections, bronchiolitis, and asthma ($p<0.01$).

Conclusion: Parameters regarding outdoor air pollution positively correlated with acute respiratory tract findings in childhood and acute exacerbation of chronic diseases. Therefore, outdoor air pollution should be considered the most important environmental risk factor for childhood respiratory tract health.

Keywords: Air pollution, respiratory tract diseases, PM_{10}, SO_2

Introduction

Air pollution is a significant public health hazard, especially in urban areas (1,2). Current scientific evidence suggests a potential relationship between urban air pollution and adverse health effects, especially on the respiratory system (3,4). Children are among the most vulnerable populations (5,6).

Some pollutants found in the air are emitted directly from a source. These are called primary pollutants. The other pollutants, known as secondary pollutants, are formed when primary pollutants react in the atmosphere with other pollutants. In urban regions, the most important secondary pollutant is ozone (O_3), formed due to an atmospheric reaction between nitrogen oxides (NOx), and

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volatile organic compounds in the presence of sunlight. When considered from this point of view, the "critical air pollutants" are O_3, carbon monoxide (CO), NOx, sulfur dioxide (SO_2), lead (Pb), and particulate matter (PM) (7). Solid (dust, ash, Pb) or liquid (haze, smoke, oil, acids, etc.) particles which are larger than gas molecule sizes (0.0002-0.0003 gm) and suspended in the air for a while are classified as PM. PM_{10} (PM with an aerodynamic diameter of 10 micrometers or less) is a major air pollutant composed of suspended solid or liquid particles. Due to their respirable nature, they can penetrate deep into the lower respiratory tract, potentially causing adverse health effects (8). The potential of PM to cause health problems is strongly influenced by its size, as smaller particles can penetrate deeper into the respiratory tract and reach the alveolar regions.

Many studies have revealed that children are more susceptible to air pollution's acute and chronic effects (9-12). For children, the primary air pollutants are PM_{10}, NOx, SOx, CO, and O_3 (13). Despite air pollution and increasing concern about the number of respiratory tract infection cases, especially in metropolitan areas, research on the effects of pollutants on the upper respiratory tract is relatively limited. Epidemiological studies on children and adolescents have shown the impact of pollutants in general without assessing the actual effects on different age groups (14-16). This study aimed to analyze the relationship between the main parameters of air pollution in the city center of Manisa and acute respiratory diseases, which are one of the reasons for the emergency admission of children living in this region.

Materials and Methods

Study Population

The study was conducted with 38,696 patients in total, 8,840 of whom were admitted to the Pediatric Emergency Department of Manisa Celal Bayar University Hospital (CBUH) with respiratory complaints and 29,856 of whom were admitted to the Pediatric Emergency Department of Manisa Merkez Efendi Hospital (MMEH) between the dates of January 1st, 2017 and December 31st, 2017. This research was approved by the Celal Bayar University Hospital Ethics Committee (approval no.: 20.478.486, dated; 14.03.2018). All procedures were conducted in accordance with the ethical standards outlined in the Declaration of Helsinki. The families of all patients were informed about the objectives of this study and the potential publication of medical data, and written informed consent was obtained from the patients' parents.

Patients diagnosed with one of the acute respiratory tract diseases aged between 0-17 years were included in this study. Patients with International Statistical Classification of Diseases and Related Health Problems diagnosis codes J00, J45, J06, H66, J20, and J21 were screened. Acute respiratory tract diseases were classified as acute nasopharyngitis, asthma, acute upper respiratory tract infection, otitis media, acute bronchitis, or acute bronchiolitis. The first admission of those patients admitted more than once were included in this study. Those cases with chronic systemic disease of another system, those patients with incomplete data, re-admissions, or underlying chronic conditions were excluded.

Study Design and Data Collection

This study was planned as a cross-sectional research. Information on age, gender, date of admission, and diagnosis of the cases were obtained from the patient files. Any further data not included in the patient files were obtained via phone call. The first admission of those patients admitted more than once were included in this study.

Atmospheric Air Pollution Parameters

The data on air pollution in the city center of Manisa were obtained from the Website of Air Quality Monitoring Stations operated by the Ministry of Environment and Urbanization. According to the air pollution data of Manisa city center, the pollutants measured at the air quality monitoring station were PM_{10} and SO_2, and daily average values were determined in order to estimate the air pollution value for each admission with regard to these pollutants.

Statistical Analysis

Analysis was performed using Statistical Package for the Social Sciences for Windows, version 25.0 (IBM Inc., Armonk, NY, USA). Descriptive statistics are reported as mean ± standard deviation for normally distributed variables and median (range) for skewed data. The data were analyzed using descriptive statistics (frequency, percentage distribution, mean, and standard deviation), Pearson's correlation test, and logistic regression analysis.

Results

Of the children who applied to the pediatric emergency clinic with respiratory complaints, 44.8% were girls, and 55.2% were boys. 42.3% of the cases were between the ages of 0-3, 23.4% were between the ages of 4-6, 26% were between the ages of 7-12, and 8.3% were between the ages of 13-17. Of the cases, there were some smokers in the 13-17 age group, and their ratio to all patients was 1%. While

the most frequent diagnosis in girls was bronchitis, it was upper respiratory tract infection in boys. The most frequent age range at diagnosis was 0-3, both in girls and boys. Similarly, the most frequent age range at diagnosis for all the patients was 0-3. Diagnoses by gender and age groups are summarized in Table I.

When analyzing the distribution of diagnoses by months, it was detected that acute nasopharyngitis and acute upper respiratory tract infection were most frequently seen in October, acute bronchitis and acute bronchiolitis were most frequently seen in February, otitis media was most frequently seen in March, and asthma was most frequently seen in May (Table II).

During the study period, the level of PM_{10} measured at the station was above the limit value, which was set at daily 50 μg/m³ by World Health Organization (WHO), for 314 days out of the 365 days, and the measured mean PM_{10} value was 76.54±28.13 μg/m³. It is seen in the monthly assessments that the PM_{10} value reached its highest level in November with 118.80±6.55 μg/m³. During the same period, the daily SO_2 limit, which was set as 20 μg/m³ by WHO, was exceeded at the station for 17 days out of the 365 days, and the mean SO_2 value was 9.99±5.79 μg/m³. It can be seen in the monthly assessments that the SO_2 value reached its highest level in November at 16.00±1.14 μg/m³. The mean PM_{10} and SO_2 values by month are given in Table III.

When the number of patients admitted to pediatric emergency services was assessed month by month, it was detected that the maximum number of admissions to CBUH was in January with 1,166 children, and the maximum admission to MMEH was in October with 3,332 children. When considering the total number of admissions, October had the highest admission rate with 4,144 children.

Significant results were achieved in the correlation analysis conducted to assess the relationship between PM_{10} and SO_2 concentrations and the number of hospital admissions to pediatric emergency departments. Accordingly, there were significant positive correlations between [PM_{10} and CBUH admissions ($r=0.280$, $p<0.01$), PM_{10} and MMEH admissions ($r=0.404$, $p<0.01$), PM_{10} and total admissions ($r=0.407$, $p<0.01$)]. Similarly, significant positive correlations existed between SO_2 and CBUH, MMEH, and the total number of admissions (SO_2 and CBUH admissions ($r=0.379$, $p<0.01$), SO_2 and MMEH admissions ($r=0.467$, $p<0.01$), SO_2 and total admissions ($r=0.407$, $p<0.01$)]. These correlation results are summarized in Table IV.

In the logistic regression analysis conducted to observe the effects of PM_{10} and SO_2 on diagnoses relating to the respiratory system, it was detected that PM_{10} and SO_2 affected diagnosis. Accordingly, acute nasopharyngitis, acute upper respiratory tract infection, acute bronchitis, acute bronchiolitis, otitis media, and asthma increased as

Table I. Diagnoses by gender and age groups

Age groups		Diagnosis						Total
		Acute nasopharyngitis	Acute upper respiratory tract infection	Acute bronchitis	Acute bronchiolitis	Otitis media	Asthma	
Girl	0-3	1,042	3,277	1,324	466	1,034	29	7,172
	4-6	572	1,868	770	246	604	22	4,082
	7-12	654	2,095	841	291	655	25	4,561
	13-17	227	674	282	99	209	15	1506
	All ages	2,495	7,914	3217	1102	2,502	91	17,321
Boy	0-3	1,326	4,197	1,703	572	1,349	47	9,194
	4-6	740	2,261	907	326	705	30	4,969
	7-12	799	2,499	1,030	355	792	27	5,502
	13-17	234	798	315	105	254	4	1,710
	All ages	3,099	9,755	3,955	1,358	3,100	108	21,375
All patients	0-3	2,368	7,474	3,027	1,038	2,383	76	16,366
	4-6	1,312	4,129	1,677	572	1,309	52	9,051
	7-12	1,453	4,594	1,871	646	1,447	52	10,063
	13-17	461	1,472	597	204	463	19	3,216
	All ages	5,594	17,669	7,172	2,460	5,602	199	38,696

Table II. Seasonal diagnosis percentages

Season	Acute nasopharyngitis	Acute upper respiratory tract infection	Acute bronchitis	Acute bronchiolitis	Otitis media	Asthma
Fall	17.8%	49.8%	16.5%	4.5%	10.7%	0.4%
Winter	13.6%	40.8%	22%	7.6%	15.2%	0.49%
Spring	12%	41%	20.4%	7.8%	17.8%	0.69%
Summer	13.4%	53.4%	13%	5%	14.5%	0.34%

Table III. Mean PM_{10} and SO_2 values by month

Month	PM_{10} (µg/m³)	SO_2 (µg/m³)
January	78.46±6.24	8.46±0.90
February	74.50±5.80	7.18±0.60
March	84.23±3.51	10.10±0.86
April	72.17±3.28	9.57±0.79
May	71.48±3.98	7.03±0.64
June	62.33±3.79	7.62±0.57
July	60.68±1.52	8.42±0.63
August	63.97±1.14	7.48±0.53
September	71.10±2.82	11.62±0.81
October	69.81±2.64	10.03±0.88
November	118.40±6.55	16.00±1.14
December	99.14±9.30	15.58±1.14

PM_{10}: Particulate matter having particle size 10 micrometers or less in diameter, SO_2: Sulfur dioxide, Unit: µg/m³

Table IV. The relationship between PM_{10}-SO_2 and the number of admissions to the pediatric emergency department

	PM_{10}	SO_2	CBUH	MMEH	Total
PM_{10}	1	0.853**	0.280**	0.404**	0.407**
SO_2		1	0.140**	0.467**	0.379**
CBUH			1	0.558*	0.760**
MMEH				1	0.963**
Total					1

*p<0.05 and **p<0.01
PM_{10}: Particulate matter having particle size 10 micrometers or less in diameter, SO_2: Sulfur dioxide, CBUH: Celal Bayar University Hafsa Sultan Hospital, MMEH: Manisa Merkez Efendi Hospital

PM_{10} levels increased. Additionally, acute nasopharyngitis, acute upper respiratory tract infection, acute bronchiolitis, and asthma increased in line with increases in SO_2. The odds ratio (OR), confidence interval (CI), and p-values are given in Table V. The highest effect of PM_{10} [OR; 95% CI 0.131 (1.19-1.44); p<0.01], and SO_2 [OR; 95% CI 1.27 (1.12-1.42); p<0.01] on diagnoses was for the diagnosis of acute upper respiratory tract infection.

Table V. The effect of PM_{10} and SO_2 on diagnosis relating respiratory system

	PM_{10} OR (95% CI)	SO_2 OR (95% CI)
Acute nasopharyngitis	1.16 (1.06-1.26)**	1.19 (1.09-1.30)**
Acute upper respiratory tract infection	1.31 (1.19-1.44)**	1.27 (1.12-1.42)**
Acute bronchitis	1.14 (1.02-1.28)*	1.20 (1.06-1.31)
Acute bronchiolitis,	1.17 (1.03-1.33)*	1.14 (0.99-1.29)**
Otitis media	1.03 (0.88-1.16)*	0.97 (0.81-1.08)
Asthma	1.18 (1.07-1.3)**	1.24 (1.14-1.34)*

**p<0.01 and *p<0.05 Pearson's correlation test. unit: µg/m³
PM_{10}: Particulate matter having particle size 10 micrometers or less in diameter, SO_2: Sulfur dioxide, OR: Odds ratio, CI: Confidence interval

Discussion

In the present study, we investigated the relationships between pediatric respiratory conditions, air pollution, and seasonal variations. Our results demonstrated a significant correlation between the number of patients admitted to the pediatric emergency department with respiratory complaints and PM_{10} and SO_2 levels, which were considered as being the key air pollutants in this research. The number of admissions was also at its highest level in line with the highest levels of air pollution, especially in November and December. Also, it was revealed that air pollution significantly affected all respiratory system diseases. This study was conducted based on establishing a link between air pollution and seasonal factors with the prevalence of respiratory illnesses in pediatric populations. Hence, strengthening preventive health services in areas with intense air pollution may reduce the frequency of respiratory diseases in the pediatric population.

Among the pediatric cases evaluated, the distribution of respiratory complaints demonstrates significant age and gender variations. Boys constituted 55.2% of the cases, while girls accounted for 44.8%. The majority of cases (42.3%) were in the 0-3 age group, emphasizing the vulnerability of younger children to respiratory illnesses. This aligns

with previous research, which has established that younger children are at a higher risk of respiratory diseases due to their immature immune systems and narrower airways (17).

Seasonal analysis revealed distinct patterns in the occurrence of respiratory illnesses. Acute nasopharyngitis and acute upper respiratory tract infections were most prevalent in October, corresponding to the fall months, whereas acute bronchitis and bronchiolitis peaked in February during the winter. Otitis media was most frequently diagnosed in March, and asthma exacerbations were highest in May. These findings are consistent with seasonal fluctuations in respiratory virus activity and allergen levels, as well as variations in ambient air pollution during the colder months (18,19).

In many studies, PM_{10} and SO_2 are considered significant and frequently analyzed pollutants for assessing health risks caused by air pollution (20-22). They are also frequently used indicators in studies evaluating the relationship between air pollution and respiratory system diseases (2). Based on previous research, PM_{10} and SO_2 were also selected as air-pollution indicators in this study. Our results showed that air pollution, measured in terms of PM_{10} and SO_2 concentrations, had a significant impact on pediatric respiratory health. This study reported a mean PM_{10} value of 76.54 μg/m³, exceeding the WHO daily limit of 50 μg/m³ on 314 days of the year. Similarly, SO_2 concentrations surpassed the WHO daily limit on 17 days. High PM_{10} levels were observed in November, while SO_2 peaked during the same month. These results align with earlier studies which demonstrated that increased air pollution levels correlate with higher rates of pediatric emergency admissions for respiratory conditions (23,24). The positive correlations between PM_{10}, SO_2, and hospital admissions emphasize the critical role of air quality in exacerbating respiratory conditions, particularly in vulnerable populations. Similarly, it was detected in the research conducted by Farhat et al. (25) between August 1996 and August 1997 on 43,635 children admitted to the respiratory emergency department of Sao Paulo University Hospital that there were significant correlations between the number of admissions and the levels of PM_{10}, SO_2, NO_2, and CO.

In the scope of our research, it was revealed via logistical regression analysis conducted to observe the effects of PM_{10} and SO_2 on diagnoses relating to the respiratory system that PM_{10} and SO_2 affected these diagnoses. Accordingly, acute nasopharyngitis, acute upper respiratory tract infection, acute bronchitis, acute bronchiolitis, otitis media, and asthma increased as PM_{10} levels increased. Additionally, acute nasopharyngitis, acute upper respiratory tract infection, acute bronchiolitis, and asthma increased in line with increasing levels of SO_2. PM_{10} and SO_2 had the most significant effect on acute upper respiratory tract infection diagnoses. In another study by Sunyer et al. (26), it was shown that emergency department visits due to adult chronic obstructive pulmonary disease were correlated with air pollution. An analysis of adults and children in London revealed that PM_{10} and SO_2 had significant effects on asthma and other lower respiratory tract diseases (27). These findings underscore the need for stringent air quality regulations and public health interventions in order to mitigate the adverse effects of air pollution on children's respiratory health (28,29).

Study Limitations

This study has several limitations. Firstly, its retrospective design limits the ability to establish a direct causal relationship between air pollution and pediatric respiratory diseases. Secondly, other environmental and socioeconomic factors, such as indoor air pollution, household smoking, and pre-existing medical conditions, were not accounted for, potentially affecting the observed associations. Furthermore, this study only focused on PM_{10} and SO_2 as primary pollutants, while other air pollutants, such as NO_2 and O_3, which may also contribute to respiratory illnesses, were not included in the analysis. Future research incorporating more comprehensive air quality monitoring and individual-level exposure assessments is needed in order to further elucidate these associations.

Conclusion

It was observed that there was a significant correlation between the number of patients admitted to the pediatric emergency department with respiratory complaints and PM_{10} and SO_2 levels, which were considered as the main air pollutants in this research. The number of admissions was also at its highest level in line with the highest levels of air pollution, especially in November and December. Also, it was revealed that air pollution had significant effects on all respiratory system diseases. Even if it is hard to isolate the effect of PM_{10} and SO_2, as many air pollutants cause respiratory complaints, our findings showed that air pollution is a significant public health problem in Manisa. This study provides compelling evidence linking air pollution and seasonal factors to the prevalence of respiratory illnesses in pediatric populations. Effective public health measures, including air quality control, vaccination programs, and increased awareness among parents and caregivers are essential in order to reduce the incidence

and severity of these conditions. This study also highlights a critical link between air pollution, seasonal variation, and the healthcare burden. It underscores the importance of implementing real-time air quality monitoring and public advisories during periods of high pollution in order to reduce the burden on the healthcare system.

Ethics

Ethics Committee Approval: The research was approved by the Manisa Celal Bayar University Hospital Ethics Committee (approval no.: 20.478.486, dated; 14.03.2018).

Informed Consent: The families of all patients were informed about the objectives of the study and the potential publication of medical data, and written informed consent was obtained from the patients' parents.

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Footnotes

Authorship Contributions

Concept: B.K., Design: B.K., H.Y., Data Collection or Processing: Ö.Y., Analysis or Interpretation: Ö.Y., Literature Search: H.Y., Writing: B.K., Ö.Y.

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

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Original Article

Demographic and Clinical Characteristics of Childhood Autoimmune Thyroiditis: Single-Center Study

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ABSTRACT

Aim: This study aimed to evaluate the clinical characteristics of pediatric patients diagnosed with autoimmune thyroiditis (AIT) at a tertiary healthcare center.

Materials and Methods: We conducted a retrospective study of 155 children diagnosed with AIT at a pediatric endocrinology clinic between January 1st, 2014 and December 31st, 2022. Clinical data were obtained through a comprehensive medical record review.

Results: The study population showed a strong female predominance (87.7%), with most patients (78.1%) being 10 years or older at diagnosis. The most common presenting symptom was neck swelling (23.2%), while 38.7% were asymptomatic at diagnosis. A family history of thyroid disease was present in 37.4% of the cases, and the majority of patients (76.0%) were pubertal at diagnosis. Thyroid function at presentation revealed subclinical hypothyroidism in 40.0%, euthyroidism in 33.5%, overt hypothyroidism in 22.6%, and hyperthyroidism in 3.9% of the patients. Anti-thyroid antibodies (anti-thyroid peroxidase and anti-thyroglobulin) were positive in 67.1% of the patients for both antibodies, with 92.9% positive for at least one antibody. Thyroid ultrasonography showed features compatible with AIT in 93.1% of those patients who underwent imaging. L-thyroxine treatment was initiated in 68.4% of the patients either at diagnosis or during follow-up. After a median follow-up period of 1.79 years (range 0-8.93), treatment was discontinued in five patients with overt hypothyroidism, three of whom achieved sustained euthyroidism while one developed subclinical hypothyroidism. Some patients with subclinical hypothyroidism showed spontaneous recovery of thyroid function.

Conclusion: Pediatric AIT demonstrates variable presentations and dynamic thyroid function changes, necessitating personalized monitoring.

Keywords: Autoimmune thyroiditis, Hashimoto's thyroiditis, autoimmunity, thyroid dysfunction

Introduction

Autoimmune thyroiditis (AIT) is the leading cause of hypothyroidism in iodine-sufficient regions worldwide (1). It represents the most common etiology of acquired thyroid dysfunction in the pediatric population, especially after the age of six years (2). The prevalence of chronic AIT in childhood peaks in early to mid-adolescence, with a female-to-male predominance of approximately 2:1. Although presentation before three years of age is rare, cases have been documented even in infancy (3).

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AIT develops in genetically predisposed individuals due to environmental triggers. A strong genetic component is evident, with antibody positivity observed in approximately 50% of first-degree relatives and concordance rates of 30-60% reported in monozygotic twins. The autoimmune process is mediated by antibodies targeting thyroid antigens, primarily anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg), while thyroid-stimulating hormone (TSH) receptor-blocking antibodies are detected less frequently. The histopathological hallmarks of AIT include lymphocytic infiltration, lymphoid germinal centers, and the destruction of thyroid follicles, with intrathyroidal lymphocytes consisting predominantly of T and B cells (2).

Patients with AIT often present with an asymptomatic goiter. In many cases, abnormal thyroid function is discovered incidentally during laboratory screening. Affected individuals may be euthyroid, hypothyroid or, less commonly, hyperthyroid (2,3). Although AIT diagnosis is typically based on the clinical features of hypothyroidism and thyroid autoantibody positivity, seronegative forms occur in 5-10% of cases. In such instances, thyroid ultrasonography plays a critical role in diagnosis (4). Characteristic ultrasonographic findings include decreased echogenicity, parenchymal heterogeneity, increased vascularity, and small cystic formations (5).

We aimed to evaluate the auxological, biochemical, and radiological findings and treatment responses of children and adolescents with AIT at a tertiary health center. Patients were categorized based on their thyroid function tests and pubertal status in order to compare their clinical and laboratory characteristics among subgroups.

Materials and Methods

This retrospective study was conducted at a tertiary care center and included 155 pediatric patients diagnosed with AIT between January 1st, 2014, and December 31st, 2022. The study protocol was approved by the Fırat University Non-Interventional Research Ethics Committee (decision no.: 23529; dated: 04.04.2024). Informed consent was waived due to the retrospective design of this study.

Auxological, biochemical, radiological, and treatment-related data were extracted from the medical records. The collected variables included age at presentation, sex, presenting symptoms, family history of thyroid disease, coexisting autoimmune conditions, body weight standard deviation scores (SDS), height SDS, body mass index (BMI) SDS, pubertal stage, goiter grade, thyroid function tests [TSH, free thyroxine (FT4)], anti-Tg, anti-TPO, thyrotropin receptor antibody (TRAb), thyroid ultrasonographic findings, treatment details, and follow-up outcomes.

Height, weight, and BMI SDS were calculated using national reference data for Turkish children (6). Pubertal staging was assessed according to the Tanner criteria. Thyroid gland size was evaluated by palpation and classified by goiter grading. Institutional laboratory reference intervals were 0.89-1.76 ng/dL for FT4 and 0.5-5.5 mIU/L for TSH.

The diagnosis of AIT was established based on the presence of thyroid autoantibodies (anti-TPO and/or anti-Tg) and/or characteristic ultrasonographic findings. In seronegative cases, typical sonographic features (e.g., decreased echogenicity, parenchymal heterogeneity, pseudonodular appearance, or increased vascularity) supported the diagnosis. For those patients presenting with hyperthyroidism, TRAb levels were measured in order to differentiate AIT from Graves' disease.

The patients were classified into four groups based on their thyroid function at presentation; overt hypothyroidism, subclinical hypothyroidism, euthyroidism, or hyperthyroidism. Due to the small number of hyperthyroid cases, overt and subclinical hyperthyroidism were combined into a single group for analysis. Pubertal status was recorded, and the participants were stratified into prepubertal and pubertal subgroups for comparative analyses.

L-thyroxine (L-T4) treatment was initiated in those patients with overt or subclinical hypothyroidism, as well as euthyroid cases with compressive symptoms or significant goiter. Discontinuation of L-T4 therapy was considered in three scenarios: (1) patients maintained on very low-dose L-T4 with normalized TSH after titration; (2) non-adherent patients with normal thyroid function tests after discontinuation; or (3) euthyroid patients treated for goiter who showed regression of thyroid enlargement.

Statistical Analysis

Data were analyzed using IBM Statistical Package for the Social Sciences (version 22.0). Normally distributed continuous variables were expressed as mean ± standard deviation, non-normally distributed variables as median (range), and categorical variables as frequencies (%). Group comparisons were performed using the Mann-Whitney U test (non-parametric data), the chi-square test (categorical variables), and Kruskal-Wallis test. A p-value <0.05 was considered statistically significant.

Results

Among the 155 children diagnosed with AIT, 136 (87.7%) were female, resulting in a female-to-male ratio of 7.2:1. The majority of the patients (78.1%) were over 10 years of age with the median age at presentation being 13.1 years (range: 1.2-17.9).

The most common presenting complaints were abnormal thyroid function tests or the detection of thyroid autoantibodies during routine screening (60 patients, 38.7%). Other commonly seen symptoms were neck swelling (36 patients, 23.2%), hair loss (15 patients, 9.7%), fatigue (8 patients, 5.2%), weight gain (6 patients, 3.9%), as well as other symptoms such as tachycardia, tremor, irritability, or short stature (23 patients, 14.8%).

An evaluation of comorbidities showed that 106 patients (68.4%) had no accompanying diseases. The most common associated conditions included type 1 diabetes mellitus (6 patients, 3.9%), vitiligo (4 patients, 2.6%), asthma (4 patients, 2.6%), alopecia areata (3 patients, 1.9%), Down's syndrome (3 patients, 1.9%), epilepsy (3 patients, 1.9%), celiac disease (2 patients, 1.3%), autoimmune polyglandular syndrome (1 patient, 0.6%), and other disorders (21 patients, 13.6%).

A positive family history of thyroid disease was identified in 37.4% of the patients. Among these, the most frequently reported conditions were goiter (56.9%), AIT (17.2%), hypothyroidism (12.0%), unspecified thyroid disorders (6.9%), hyperthyroidism (5.2%), and thyroid nodules (1.7%).

The median weight SDS was 0.14 (range: -2.10 to 3.77), median height SDS was -0.15 (range: -2.85 to 2.51), and median BMI SDS was 0.23 (range: -0.85 to 3.23). A total of 15 patients (9.7%) had a BMI SDS >2. On initial examination, goiter was detected in 80 patients (53.3%) and was absent in 70 patients (46.6%). The patient characteristics, including auxological parameters and thyroid function status at diagnosis, are summarized in Table I.

Thyroid function status at admission was categorized as subclinical hypothyroidism in 62 patients (40.0%), euthyroidism in 52 patients (33.5%), overt hypothyroidism in 35 patients (22.6%), and hyperthyroidism in 6 patients (3.9%) (Table I).

Table I. Characteristics of patients according to auxologic data and thyroid function tests at diagnosis

Parameter	Euthyroidism (n=52)	Subclinical hypothyroidism (n=62)	Overt hypothyroidism (n=35)	Hyperthyroidism (n=6)	p-value
Female/male	41/11	60/2	32/3	3/3	0.001
Age, years	13.7 (4.65-17.9)	12.5 (1.23-17.8)	13.3 (4.17-17)	9.7 (5.83-16.5)	0.084
Height SDS	-0.05 (-2.85-2.36)	-0.15 (-2.31-2.51)	-0.27 (-2.05-1.51)	-0.95 (-1.85-0.41)	0.328
Weight SDS	0.19 (-2.10-2.61)	0.10 (-1.71-3.77)	0.25 (-1.74-2.76)	-0,53 (-1.84-1.32)	0.686
BMI SDS	0.31 (-0.83-2.29)	0.18 (-0.82-3.23)	0.40 (-0.85-2.83)	-0.50 (-0.50-1.68)	0.409
TSH	3.22 (0.65-5.47)	9.6 (5.71-60.6)	89.7 (6.46-150)	0.01 (0.01-0.20)	<0.001
Free T4	1.17 (0.71-1.57)	1.05 (0.86-2.14)	0.61 (0.01-0.84)	1.72 (1.10-3.21)	<0.001
Anti-TPO positivity (n, %)	42 (80.8)	54 (87.1)	32 (91.4)	5 (83.3)	0.612
Anti-Tg positivity (n, %)	38 (73.1)	49 (79)	22 (62.9)	6 (100)	0.322
Pubertal (n, %)	38 (73.1)	45 (72.5)	22 (68)	3 (50)	0.140

BMI: Body mass index, SDS: Standard deviation score, Anti-TPO: Anti-thyroid peroxidase, Anti-Tg: Anti-thyroglobulin, TSH: Thyroid-stimulating hormone

Table II. Characteristics of patients in prepubertal and pubertal groups at diagnosis

Parameter	Prepubertal (n=35)	Pubertal (n=108)	p-value
Female/male	28/7	100/8	0.010
Age, years	8.02 (1.23-11.7)	13.9 (8.32-17.9)	<0.001
Height SDS	-0.10 (-2.31-2.51)	-0.16 (-2.05-2.36)	0.604
Weight SDS	0.17 (-1.84-2.28)	0.13 (-2.10-3.77)	0.807
BMI SDS	0.28 (-0.80-3.23)	0.19 (-0.85-3.14)	0.924
TSH	10.8 (0.01-150)	7.37 (0.01-150)	0.054
Free T4	1.05 (1.05-0.24)	1.04 (0.01-2.14)	0.807
Anti-TPO positivity (n, %)	31 (88.6)	92 (85.2)	0.189
Anti-Tg positivity (n, %)	25 (71.4)	81 (75)	0.691

BMI: Body mass index, SDS: Standard deviation score, Anti-TPO: Anti-thyroid peroxidase, Anti-Tg: Anti-thyroglobulin, TSH: Thyroid-stimulating hormone

Pubertal status at presentation was as follows: 35 patients (24%) were prepubertal, and 108 patients (76%) were pubertal. Goiter staging differed significantly between groups, with prepubertal patients most frequently having stage 2 goiter (22.9%) and pubertal patients predominantly exhibiting stage 1b (25.9%). This difference was statistically significant ($p<0.001$). However, no significant differences were observed in TSH levels, free T4, autoantibody presence, or ultrasonographic findings (Table II).

Thyroid autoantibody results at diagnosis revealed that anti-TPO antibodies were positive in 133 patients (85.8%), anti-Tg antibodies were positive in 115 patients (74.2%), and concurrent anti-TPO and anti-Tg positivity was observed in 104 patients (67.1%). At least one antibody was positive in 144 patients (92.9%). Notably, none of the hyperthyroid patients had detectable TRAb antibodies.

Thyroid ultrasonography was performed in 87 patients (56.1%) at presentation. Among these, 81 (52.3% of the total cohort) exhibited sonographic features consistent with AIT, yielding a positivity rate of 93.1% among those examined.

The median follow-up duration was 1.76 years (range: 0-8.93). L-T4 treatment was initiated in 68.4% of the patients, including all overt hypothyroid patients, 53 subclinical hypothyroid patients (85.4%), and 18 euthyroid patients (34.6%).

Among the 35 overt hypothyroid patients, 5 were evaluated during a treatment-free interval. Three (8.6%) achieved euthyroidism, 1 (2.9%) remained subclinically hypothyroid, and 1 required treatment reinitiation due to overt hypothyroidism. Of the 53 subclinical hypothyroid patients started on treatment, discontinuation was attempted in 7. Five achieved normalized thyroid function, while 2 persisted with subclinical hypothyroidism. Among the 9 untreated subclinical hypothyroid patients (TSH: 5.83-6.78 mIU/L), 4 became euthyroid and 5 remained subclinically hypothyroid. Of the 9 hyperthyroid patients at diagnosis, 7 achieved euthyroidism by their 3-month follow-up, while 2 developed subclinical hypothyroidism

Discussion

This study provides an extensive review of the clinical, biochemical, and ultrasonographic presentations of pediatric patients diagnosed with AIT over a nine-year period at a tertiary care center. Our results confirm well-documented patterns in the literature while also offering insights into the disease spectrum and its real-world management.

Consistent with previous reports, we observed a female predominance, with most patients being pubertal at diagnosis (median age of 13.1 years) (1-3). Approximately half of our patients presented with goiter, aligning with literature reports of 50-90% prevalence in pediatric AIT cases (7). Similar studies from Türkiye reported goiter in 54.9% and 49.4% of AIT cases (8,9). These findings underscore the importance of thorough physical examination and maintaining clinical suspicion for AIT even in asymptomatic children.

A family history of thyroid disease was present in nearly half of our patients, comparable to rates of 41.1% and 52% in other series (8,10). This reinforces the established genetic predisposition in AIT pathogenesis, likely resulting from complex gene-environment interactions (11). These findings highlight the importance of family screening and health education for first-degree relatives, potentially enabling earlier diagnoses. However, current guidelines lack definitive recommendations for AIT screening in at-risk children, suggesting that these patients should instead undergo regular monitoring during routine health visits.

Thyroid function at diagnosis varied among the patients. Subclinical hypothyroidism was most common, followed by euthyroidism and overt hypothyroidism, while hyperthyroidism was observed in very few cases. This distribution matches previous reports demonstrating that subclinical or overt hypothyroidism predominates in pediatric AIT (8,10,12-15). Notably, over half of our patients were hypothyroid at diagnosis, reflecting the often-insidious disease course and supporting periodic thyroid function screening in high-risk populations.

Autoantibodies are critical for making the diagnosis but are occasionally negative in a small percentage of patients. In our series, 7.1% of the patients were seronegative at the time of diagnosis but exhibited ultrasonographic features consistent with AIT. This again emphasizes the diagnostic use of thyroid ultrasonography, particularly in seronegative patients (5,15). Ultrasonographic findings typical of AIT, such as diffuse hypoechogenicity and heterogeneous parenchymal echotexture with a micronodular pattern, were observed in nearly all of those patients who were imaged at diagnosis, in accordance with superior rates of previously noted positivity of between 20 and 95%, depending on the diagnostic criteria and disease stage (8,16). In this study, 56.1% of the patients were imaged with ultrasound (US), and 52.3% of the sample had positive AIT features. These results are important in showing the value of US in supporting the diagnosis, especially when antibody testing is unremarkable.

Approximately one-third of patients had comorbid chronic conditions, particularly autoimmune disorders such as type 1 diabetes and vitiligo. This association supports the autoimmune pathogenesis of AIT and necessitates multidisciplinary management with screening for additional autoimmune diseases (7-9).

Regarding treatment, 68.4% received L-T4, similar to previous reports of 40-70% treatment rates in pediatric AIT (17-20). Indications primarily included overt or significant subclinical hypothyroidism, with some euthyroid patients treated for symptomatic goiter. Most treated hypothyroid patients achieved euthyroidism within months, while some untreated subclinical hypothyroid cases showed spontaneous recovery-though relapses occurred. These findings mirror prior studies demonstrating fluctuating thyroid function in pediatric AIT, highlighting the need for individualized long-term follow-up (10).

Study Limitations

This study's strengths include the large single-center cohort with extended observation periods, comprehensive analysis of auxological, biochemical, and ultrasonographic data, and clinically relevant stratification by pubertal status and thyroid function. Its limitations include its retrospective design which risks incomplete data and reporting bias, inconsistent baseline imaging/antibody testing which may affect diagnostic classification, and variable follow-up durations and attrition which limit its long-term outcome assessments.

Conclusion

In conclusion, this study demonstrates the heterogeneous clinical and biochemical presentation of pediatric AIT. The observed fluctuations in thyroid function, including spontaneous normalization in some hypothyroid patients, suggest that regular thyroid function monitoring is essential and temporary L-T4 discontinuation may be considered in selected cases under close supervision. An individualized, dynamic approach to treatment and follow-up is recommended for optimal pediatric AIT management.

Ethics

Ethics Committee Approval: Ethics approval was obtained from the Fırat University Non-Interventional Research Ethics Committee (approval no.: 23529 date: 04.04.2024).

Informed Consent: Informed consent was waived due to the retrospective design.

Footnotes

Authorship Contributions

Concept: E.Y., İ.E., D.Ö., Design: E.Y., İ.E., Data Collection or Processing: E.Y., Analysis or Interpretation: E.Y., İ.E., D.Ö., Literature Search: E.Y., Writing: E.Y., İ.E., D.Ö.

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Original Article

Childhood Epilepsies with Occipital Discharges: Evaluation of 84 Patients

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ABSTRACT

Aim: Childhood epilepsy with occipital discharges encompasses various subtypes, including childhood occipital visual epilepsy (COVE), self-limited epilepsy with autonomic seizures (SeLEAS), photosensitive occipital lobe epilepsy, symptomatic epilepsy, and unclassified cases. The primary aim of this study was to analyze the clinical characteristics of pediatric epilepsy patients with occipital discharges based on their etiological classification and to compare any differences between these subgroups. Additionally, this study sought to identify prognostic factors by comparing patients who achieved remission within 36 months (Group 1) with those who did not respond within the same period (Group 2).

Materials and Methods: This study included 84 children diagnosed with occipital discharge-related epilepsy. A comprehensive review of their medical records was conducted, assessing their demographic data, ictal symptoms, neurological examination findings, electroencephalography and magnetic resonance imaging results, family history, febrile seizures, and treatment responses.

Results: Of the total cohort, 32% (n=27) were classified as Group 1, while 68% (n=57) were in Group 2. Structural brain abnormalities were significantly more prevalent in Group 2. The age at diagnosis was significantly younger in Group 2 compared to Group 1 (p=0.003), and the rate of intellectual disability was higher in Group 2 (p=0.05). The presence of systemic diseases and the use of multiple anti-epileptic drugs were significantly more frequent in Group 2 (p=0.021, p=0.018). The duration of epilepsy follow-up was notably longer in Group 2 (p<0.001). COVE and SeLEAS were more commonly found in the early remission group (p=0.012, p=0.034), while no cases of symptomatic occipital epilepsy achieved remission within the first 36 months (p=0.001).

Conclusion: The majority of children with occipital epilepsy did not achieve remission within 36 months. Younger age at onset and the presence of intellectual disability were associated with longer periods of non-remission. COVE and SeLEAS were more likely to achieve early remission, whereas symptomatic occipital epilepsies showed no remission within the first 36 months. These findings underline the importance of early diagnosis and highlight the potential impact of structural brain abnormalities and cognitive impairments on the prognosis of childhood occipital epilepsy.

Keywords: Occipital epilepsy, children, prognostic factors, remission

Introduction

Occipital lobe epilepsies (OLE) represent a diverse group of epileptic syndromes with distinct clinical features, etiologies, and prognostic outcomes. These epilepsies, which are relatively rare in children, can be broadly categorized into idiopathic and symptomatic types. Idiopathic OLE include syndromes such as childhood occipital visual epilepsy (COVE), self-limited epilepsy with autonomic seizures

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(SeLEAS), and photosensitive occipital lobe epilepsy (POLE), whereas symptomatic occipital epilepsies are associated with structural brain abnormalities, metabolic disturbances, or other underlying conditions.

The classification of occipital lobe epilepsy is essential in order to determine treatment approaches and predict prognosis. According to the International League Against Epilepsy (ILAE), the major subtypes of occipital lobe epilepsy in children are: COVE, SeLEAS, POLE, and symptomatic occipital lobe epilepsy. COVE and SeLEAS are typically characterized by self-limited, benign courses, with seizure onset often occurring between the ages of 3 and 16 years. POLE, in contrast, is marked by photosensitivity and focal seizures originating in the occipital lobe. Symptomatic occipital epilepsies, which are associated with identifiable brain lesions or systemic conditions, tend to have worse prognoses (1).

Despite significant progress in the understanding of occipital lobe epilepsies, identifying prognostic factors for treatment response remains a clinical challenge. It is known that the prognosis for children with occipital lobe epilepsy varies considerably depending on the subtype and the presence of structural abnormalities. Previous studies have shown that idiopathic occipital epilepsies, such as SeLEAS, typically exhibit remission within the first two years, whereas symptomatic occipital epilepsies have a much lower rate of remission and often require long-term management (1). Additionally, factors such as age at onset, the presence of cognitive impairments, and the use of multiple anti-epileptic drugs (AEDs) have been shown to influence the outcome (2).

While there is a growing body of literature addressing pediatric occipital epilepsy, studies focusing specifically on the comparison of clinical features and treatment outcomes across different subtypes are limited. Understanding these differences is crucial for developing more tailored treatment strategies and improving outcomes for affected children. Moreover, identifying early prognostic markers could guide clinicians in predicting the likelihood of remission and customizing treatment regimens accordingly.

Interestingly, prior pediatric case series involving occipital discharges have reported that remission is commonly observed within 1-2 years, and no patients exhibited symptoms after the age of 12 years (3,4). In contrast, adult studies have shown significantly lower rates of remission, highlighting the importance of age-dependent differences in the disease course (5). Additionally, differences in prognosis and clinical characteristics between subtypes such as COVE and SeLEAS, despite both being classified as idiopathic, have also been emphasized in the literature (3,6).

In this study, we aimed to analyze the clinical and imaging characteristics of 84 children diagnosed with occipital discharge-related epilepsy. We also sought to identify factors associated with early remission and treatment failure, comparing patients who achieved remission within 36 months (Group 1) with those who did not (Group 2). By examining the relationship between these factors, we hope to provide more insights into the management of pediatric occipital lobe epilepsy and improve our understanding of the factors influencing treatment response.

Materials and Methods

This retrospective cohort study included a total of 84 children aged 0-17 years who were diagnosed with occipital epilepsy between 2018 and 2023. Cases with a follow-up period of less than 6 months, those with generalized discharges on electroencephalography (EEG), those with dominant abnormal discharges detected in areas other than the occipital lobe, and cases with irregular follow-up exceeding one year or those non-compliant with treatment were excluded. Patients who were diagnosed with occipital epilepsy but did not receive anti-epileptic drug therapy were also excluded from this study.

This study was approved by the İzmir Bakırçay University Non-Interventional Clinical Research Ethics Committee (approval no.: 1056, date: 05.24.2023).

The clinical and laboratory features, EEG, and magnetic resonance imaging (MRI) results of the patients were analyzed. The demographic data of the patients (age at epilepsy diagnosis, current age, gender, parental consanguinity), family history of epilepsy, history of febrile convulsions, presence of other systemic diseases, AEDs used and their number, the duration of seizure control with anti-epileptic drug therapy, EEG findings, subtype of occipital lobe epilepsy (COVE, POLE, SeLEAS, symptomatic, unclassified), duration of epilepsy follow-up, MRI findings, additional neurological findings, and psychiatric disorders were recorded.

Patients with occipital pathological discharges on EEG (high-amplitude sharp and/or spike discharges) who met the clinical criteria for occipital epilepsy syndromes, including COVE, POLE, SeLEAS, and symptomatic occipital epilepsy, were classified under separate diagnoses according to the ILAE classification system and included in this study as part of the idiopathic epilepsy group.

Those patients with occipital lesions and occipital discharges on EEG were diagnosed with symptomatic occipital epilepsy.

Patients with occipital lobe discharges but not meeting the clinical features of any defined occipital lobe epilepsy syndrome were classified as unclassified epilepsies.

In our study, those patients who had not experienced seizures within the prior six months or who had normal EEG findings despite receiving one or more anti-epileptic drugs, or those who were treated for epilepsy and had completed treatment with drug withdrawal within 36 months, were classified as responders to treatment (Group 1). Patients were classified as non-responders to treatment (Group 2) if they met at least one of the following criteria: (1) they had never experienced a seizure-free period longer than six months; (2) they had experienced a seizure-free period longer than six months, but occipital discharges persisted on EEG; or (3) both of these conditions were present (Group 2).

Statistical Analysis

Statistical analyses were performed using Jeffreys's Amazing Statistics Program and Jamovi software. Descriptive statistics are presented as frequencies (percentages) for categorical variables and medians (minimum-maximum) for numerical variables. Pearson's chi-square, Fisher's exact, or Fisher-Freeman-Halton tests, and the Mann-Whitney U test were used, and p-values were calculated.

Results

The total group of 84 patients was divided into two groups based on their characteristics. Group 1 (n=27) included patients with a shorter duration of epilepsy follow-up, while Group 2 (n=57) had a longer follow-up period. Statistical analysis revealed significant differences between the groups in several variables (Table I).

The epilepsy follow-up duration was significantly shorter in Group 1 [27.0 months (8.0-54.5)] compared to Group 2 [63.3 months (37.0-210.49)], with a p-value of <0.001. The age of epilepsy onset was also significantly different between the groups, with Group 1 having an average age of 5.88±3.88 years, while Group 2 had a lower average age of 4.10±3.80 years (p=0.024).

There was no significant difference between the groups in terms of sex distribution (p=0.308), family history of

Table I. Patient characteristics and group comparison based on treatment response

Variable	Total Group (n=84)	Group 1 (n=27)	Group 2 (n=57)	p-value
Follow-up duration (months)	49.3 (8.0-210.4)	27.0 (8.0-54.5)	63.3 (37-210.4)	<0.001
Age of epilepsy onset (years)	5.07±4.16	5.88±3.88	4.10±3.80	0.024
Sex female/male	36/48	26/31	10/17	0.308
Family history of epilepsy n (%)	20/84 (23.8)	6/27 (22.2)	14/57 (24.5)	0.523
Automatisms, n (%)	21 (25)	4 (14.8)	17 (29.8)	0.225
Visual symptoms, n (%)	34 (40.5)	12 (44.4)	22 (38.6)	0.391
Intellectual disability n (%)	8 (9.5)	0 (0)	8 (14.03)	0.038
Neurological findings, n (%)	13 (15.5)	3 (11.1)	10 (17.5)	0.535
Longest seizure-free period (months)	24.0 (2.0-60.0)	16.5 (2.0-60.0)	24.0 (4.0-60.0)	0.030
MRI abnormalities, n (%)	18 (21.4)	1 (3.7)	17 (29.8)	0.015
Use of two or more anti-epileptic drugs, n (%)	29 (34.5)	4 (14.8)	25 (43.9)	0.018
Febrile seizures, n (%)	16 (19.0)	2 (7.4)	14 (24.6)	0.116
Occipital lobe epilepsy subtypes, n (%)				
- COVE	11 (13.1)	5 (18.5)	6 (10.5)	0.012
- POLE	5 (6.0)	2 (7.4)	3 (5.3)	0.424
- SeLEAS	26 (31.0)	13 (48.1)	13 (22.8)	0.034
- Symptomatic	11 (13.1)	0 (0.0)	11 (19.3)	0.001
- Unclassified	31 (36.9)	7 (25.9)	24 (42.1)	0.322

MRI: Magnetic resonance imaging, COVE: Childhood occipital visual epilepsy, POLE: Photosensitive occipital lobe epilepsy, SeLEAS: Self-limited epilepsy with autonomic seizures

epilepsy (p=0.523) or automatisms (p=0.225). Similarly, no significant difference was found in visual symptoms (p=0.391) or neurological findings (p=0.535).

The longest seizure-free period was shorter in Group 1 [16.5 months (2.0-60.0)] compared to Group 2 [24.0 months (4.0-60.0)], with a significant difference (p=0.030). MRI abnormalities of the patients were significantly more common in Group 2 (29.8%) than in Group 1 (3.7%) with a p-value of 0.015. Only one patient in the group who achieved remission within the first 36 months (Group 1) showed bilateral ventricular enlargement. In contrast, among those patients who did not achieve remission within 36 months (Group 2), MRI abnormalities were detected in 17 cases. These included 4 cases of cortical dysplasia, 6 cases of periventricular leukomalacia, 2 cases of occipital hypoglycemia sequelae, and 5 cases of non-specific ventricular enlargement. The use of two or more AEDs was more prevalent in Group 2 (43.9%) compared to Group 1 (14.8%), with a statistically significant difference (p=0.018).

Regarding febrile seizures, the occurrence was higher in Group 2 (24.6%) compared to Group 1 (7.4%), but this difference did not reach statistical significance (p=0.116).

In terms of epilepsy subtypes, there were notable differences between the groups. The frequency of occipital lobe epilepsy subtypes was significantly different between the groups. COVE was more frequent in Group 1 (18.5%) than Group 2 (10.5%) (p=0.012), while SeLEAS was more prevalent in Group 1 (48.1%) than in Group 2 (22.8%) (p=0.034). Symptomatic epilepsy was significantly more common in Group 2 (19.3%) than in Group 1 (0.0%) (p=0.001). No significant differences were found for POLE (p=0.424) and the unclassified subtypes (p=0.322).

These findings highlight key differences in clinical characteristics, seizure control, and epilepsy subtypes between the two groups.

Discussion

OLE consist of idiopathic (POLE, COVE, SeLEAS), symptomatic (cortical dysplasia, hypoglycemia, infarction, etc.), and unclassified groups. It has been reported that 1.2-2.6% of newly diagnosed epileptic patients have occipital epilepsy (7). In pediatric patients, one of the most common questions after clinical diagnosis is when the disease will improve. In search of an answer to this question, we aimed to identify some prognostic factors which could assist at the time of diagnosis. We compared the characteristics of those patients who achieved remission within the first 36 months with those who did not.

We set the limit for early remission at 36 months in this study. It was found that those patients who did not achieve remission had an average treatment duration of 63.3 months. This finding suggests that identifying prognostic factors and making predictions from the time of diagnosis are crucial for both the patient's expectations and the patient's trust in the physician.

Early onset of epilepsy has been found to be a negative prognostic factor for early remission and recovery. In a similar study, early diagnosis age in OLE was related to abnormalities in brain MRI findings (8). Although that study did not identify robust predictors for seizure outcome, our data suggest that early MRI abnormalities and younger age at onset may also be linked to poorer long-term seizure control. Together, these findings underscore the clinical importance of integrating neuroimaging and semiological features when evaluating prognosis in pediatric occipital epilepsy. Symptomatic epilepsy is often associated with earlier onset, and given its generally poorer prognosis compared to idiopathic epilepsy, early onset itself emerges as a risk factor for poor treatment response. The presence of MRI abnormalities, early age at seizure onset, and symptomatic etiology appear to be interrelated factors, collectively contributing to the clinical significance of the observed outcomes. The greater the extent of structural abnormality on brain MRI, the higher the likelihood of drug-resistant occipital lobe epilepsy. A systematic review and meta-analysis reported that the presence of a lesion on preoperative MRI increases the odds of medical treatment failure by approximately 3.24-fold in OLE (9). Our findings align with this literature: Group 2 demonstrated a significantly higher rate of MRI abnormalities (29.8%, p=0.015) and correspondingly poorer remission outcomes.

In our study, the frequency of automatisms was found to be 25%. There are only a limited number of studies in the literature reporting on the prevalence of automatisms in occipital lobe epilepsies. Salanova et al. (10) reported that approximately 50% of patients with occipital lobe epilepsy exhibit automatisms resembling those seen in temporal lobe epilepsy. Similarly, Wong et al. (11) emphasized that the presence of automatisms may indicate temporal spread of epileptic activity. In our cohort, those patients in Group 2 were older, and although not statistically significant, automatisms were more frequent in this group. Oguni (12) showed that occipital EEG foci tend to evolve with age,

shifting toward the centro-parietotemporal and frontopolar regions, with this transformation continuing up to the age of 12-16 years. Considering that automatisms are primarily associated with temporal lobe activity, the older age and persistent occipital discharges observed in Group 2 suggest that the clinical presentation in these children may have gradually transitioned from occipital to a temporal lobe epilepsy semiology.

In a prospective study by Ko and Holmes (13) involving 343 pediatric patients, intellectual disability was shown to be a significant risk factor for drug-resistant epilepsy. In our study, 14% (8 patients) of the patients in Group 2 had intellectual disability, and the difference between the groups was statistically significant (p=0.038).

In pediatric patients, if the appropriate drug and dose are administered, seizure control is achieved with monotherapy in 65-70% of cases (14). Although polytherapy is generally avoided, it has been reported that 30-50% of cases require polytherapy (15). In a study by Datta and Wirrell (16), it was reported that the number of AEDs negatively affects prognosis. In our study, 29 patients (34.5%) were on polytherapy, with 25 of them (43.9%) being in Group 2 and 4 of them (14.8%) being in Group 1. A statistically significant difference was found between the groups in terms of the likelihood of using two or more AEDs (p=0.018).

The median value of the longest seizure-free period was 24 months for patients in Group 2. The longest seizure-free period in Group 2 was significantly longer than in Group 1 (p=0.030). Patients in Group 2 had not been seizure-free for more than six months or continued to show abnormal occipital discharges on EEG after 36 months of treatment. Interestingly, there were patients who had been seizure-free for 48 months, but their EEGs remained pathological.

In a study by Gherpelli et al. (17), the presence of sharp waves, spikes, multiple spikes, and spike-slow wave patterns on EEG before drug withdrawal was found to increase the risk of seizure recurrence. In another meta-analysis, the relative risk between abnormal EEG patterns prior to drug withdrawal and recurrence was found to be 1.45 (18). Interictal EEG abnormalities are directly proportional to the presence of clinical seizures and serve as an indicator of poor prognosis before treatment termination. Therefore, a careful decision must be made regarding treatment withdrawal in patients with persistent EEG abnormalities (19). In our clinic, recovery is defined as both seizure freedom and complete resolution of EEG abnormalities. As a result, our recovery times are longer compared to the literature.

In our study, there were no patients in the symptomatic group who achieved remission. The SeLEAS group was the most promising group with the quickest recovery, with 48% of patients achieving remission within the first 36 months of treatment. These results are consistent with the literature, which reports symptomatic OLE and POLE subtypes as the groups with the longest time to response and the highest recurrence rates (20).

Study Limitations

This study has several limitations which should be acknowledged. First, its retrospective design inherently limits the ability to establish causality between clinical features and treatment outcomes. Second, although the study cohort included a relatively large sample of pediatric patients with occipital lobe epilepsy, the subgroup sizes (e.g., SeLEAS, symptomatic, POLE) were modest, which may limit the statistical power of certain comparisons and restrict the generalizability of subtype-specific conclusions. Third, follow-up durations varied across patients, and the minimum follow-up period of six months might have been insufficient to detect long-term remission or relapse in some cases. Fourth, EEG interpretation was not centrally reviewed and may have been subject to inter-observer variability. Prospective, multicenter studies with standardized imaging protocols and extended follow-ups are needed to validate and expand upon these findings.

Conclusion

This study provides valuable insights into the clinical and prognostic factors of OLE in pediatric patients. The findings suggest that early onset of epilepsy and the presence of symptomatic epilepsy are associated with a less favorable treatment response. In particular, those patients with early onset epilepsy, as well as those with MRI abnormalities or symptomatic forms of epilepsy, tend to have longer treatment durations and more persistent seizure activity. Conversely, idiopathic epilepsies, such as SeLEAS, show better outcomes, with a higher rate of remission within the first 36 months of treatment.

Additionally, the use of polytherapy and the presence of cognitive impairments, such as intellectual disability, were found to be significant factors contributing to poor prognosis in this cohort. These results emphasize the importance of the early identification of prognostic factors which can help guide treatment strategies and improve the management of pediatric occipital lobe epilepsy.

In conclusion, understanding the clinical and imaging characteristics associated with different OLE subtypes

is crucial in predicting patient outcomes and tailoring individualized treatment plans. Further research is needed to identify additional factors influencing treatment response and to develop more effective therapeutic approaches for pediatric patients with occipital lobe epilepsy.

Ethics

Ethics Committee Approval: This study was approved by the İzmir Bakırçay University Non-Interventional Clinical Research Ethics Committee (approval no.: 1056, dated: 24.05.2023).

Informed Consent: Informed consent was obtained from the patients and their parents.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.G.T., Concept: H.G.T., Design: H.G.T., Data Collection or Processing: D.Ö., Analysis or Interpretation: H.G.T., Literature Search: D.Ö., Writing: H.G.T., D.Ö.

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Original Article

Control of Coagulation Abnormalities with Sodium Benzoate in Patients with Argininemia

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ABSTRACT

Aim: This study aimed to evaluate coagulation disorders in patients with argininemia associated with *arginase* 1 gene mutations and the control of these disorders with sodium benzoate treatment.

Materials and Methods: Five argininemia patients followed up in the Pediatric Metabolism Clinic in University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, were included in this study. The patients initially received protein-restricted diet treatment, while their ammonia, platelet count, liver enzymes and coagulation parameters were measured regularly. Later, sodium benzoate was added to the treatment and the same parameters were measured at 1-month intervals.

Results: In the coagulation parameters measured after sodium benzoate treatment, one out of the five patients showed complete improvement, three had partial improvement, and one had no change. In the patients with coagulation disorders, factor VII and IX levels were low, while arginine levels remained above 250 µmol/L.

Conclusion: The pathophysiology of coagulation disorders in patients with argininemia has not yet been fully elucidated, but it is thought that high arginine levels may affect the synthesis of short-lived coagulation factors. Adding sodium benzoate to dietary therapy may contribute to both the control of arginine levels and an improvement in coagulation parameters. This study demonstrates the importance of coagulation monitoring in those patients with argininemia and the potential therapeutic role of sodium benzoate.

Keywords: Argininemia, coagulation disturbance, factor deficiency, sodium benzoate

Introduction

Argininemia [arginase 1 deficiency (ARG1-D), or hyperargininemia; Online Mendelian Inheritance in Man 207800] is an autosomal recessive inherited disease caused by the deficiency of arginase 1, which is a rare type of urea cycle disorder (UCD) (1). It is caused by mutations in the *ARG1* gene located on chromosome 6q23 (2). The UCD consortium study from Europe and the USA reported that the incidence of ARG1 deficiency was estimated to be approximately 1 per 950,000 births (3), accounting for 3.5% of all UCD patients (4). Unlike other UCDs, clinical presentations are complicated and lack specificity, including progressive spastic paraplegia, hyperactivity of deep tendon reflexes, intellectual developmental disability, failure to thrive, seizures, microcephaly and ataxia in late infancy or the pre-school age (5-6). Additionally, neonatal hyperammonaemia and encephalopathy are not common

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features of this disorder. Liver damage ranges from a mild elevation of transaminases to liver failure (7). In addition, coagulation dysfunction is characteristic of argininemia, which is not accompanied by life-threatening haemorrhagic complications, and its mechanism is still unclear (8).

Coagulation disturbances have been reported in ARG1-D patients (8,9). Coagulation dysfunction is characteristic of argininemia without life-threatening haemorrhagic complications, and low levels of factor (F) VII and FIX have been demonstrated, although this mechanism is still unclear (8). Most of the coagulation factors are proteins with a serine protease structure. The activity of serine proteases is controlled by plasmatic serine protease inhibitors (10). Serine protease recognizes a specific region (P1-P10) in the serpin molecule. Most often, arginine is the amino acid at position P1. This interaction can be competitively inhibited by the arginine functional group, free arginine or free guanidine (11). L-arginine (or guanidine) has been shown to inhibit the activation of haemostasis (12).

Previous studies have not reported an effective drug treatment for coagulation disturbances in patients with argininemia. The effectiveness of vitamin K therapy has not been demonstrated in these patients (8,13). In our study, we examined coagulation dysfunction in our patients with argininemia and the effects of sodium benzoate on coagulation dysfunction in addition to the traditional treatment of dietary therapy.

Materials and Methods

Five argininemia patients followed up by Pediatric Metabolism Clinic in University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, whose diagnoses were confirmed by *ARG1* gene sequence analysis, were determined as the study group. This study was approved by the Ethics Committee of the University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital (approval no.: 2022.01.35, date: 26.01.2022). Informed consent was obtained from the legal guardians of all participants prior to their inclusion in this study. Procedures were carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Ammonia levels, platelet counts, liver function tests, and coagulation parameters [prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), clotting factor levels] were taken from the patients while they were on a protein-restricted diet only. After sodium benzoate was added to their treatment, the same laboratory tests were repeated at 1-month intervals. Parameters measured before and after sodium benzoate treatment were compared.

Statistical Analysis

Due to the small sample size in this study, formal statistical analyses were not conducted. Instead, the data are presented using descriptive statistics, expressed as mean ± standard deviation (SD).

Results

The summary of the clinical features of the patients is presented in Table I. Cases 1 and 2 and Cases 3 and 4 were siblings. There was consanguinity between the parents. Cases 1 and 2 were of Syrian origin and the family could communicate in Turkish.

The first case was diagnosed late at the 14 years. The patient had severe spastic paraplegia and mental-motor retardation. Height and weight percentiles were quite low (<-2 SD score). She could not walk or speak. Since her oral feeding was inadequate, orogastric tube feeding treatment was applied. At the time of diagnosis, liver transaminases, arginine levels and coagulation parameters were found to be high. With the diagnosis of liver failure, the patient was treated with fresh frozen plasma, N-acetylcysteine and high-dose vitamin K. Although the transaminase values improved with low-protein diet treatment, the coagulation parameters continued to be impaired. However, after the patient was started on sodium benzoate treatment, the INR value returned to normal levels (Figure 1, Table II).

The second case was the sibling of the first case and was diagnosed at the age of 1 through family screening. No clinical findings were detected at the time of diagnosis. A low-protein diet was started. However, the patient could not comply with the diet treatment. During the follow-up, deterioration in transaminase and coagulation parameters was observed. Sodium benzoate was added

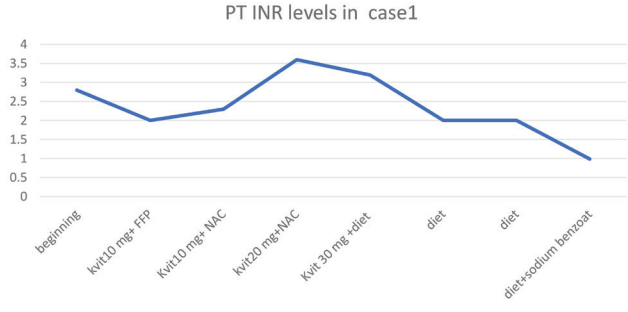

Figure 1. PT INR levels in case 1

PT: Prothrombin time, INR: International normalized ratio, FFP: Fresh frozen plasma

Table I. Clinical characteristics of five patients with arginemia

	Gender (years)	Age at presentation	Current ages (years)	Consanguinity	Coagulation dysfunction	Bleeding sign	Variant of ARG1/ inheritance	Physical examination
Case 1	14	5 years	14	Yes	Yes	No	c.58-3C>G homozygous	Spastic paraplegia; intellectual developmental disability
Case 2	3	1 years	3	Yes	Yes	No	c.58-3C>G homozygous	Hyperreflexia borderline intellectual developmental disability;
Case 3	6	1 years	6	Yes	Yes	No	c.306C>G (p.Ser102ARG) homozygous	Hyperreflexia borderline intelligence
Case 4	2	Neonatal	2	Yes	No	No	c.306C>G (p.Ser102ARG) homozygous	Hyperreflexia language decite
Case 5	6	3 years	6	Yes	Yes	No	c.130+1G>A homozygous	Hyperreflexia borderline intelligence language decite

ARG1: Arginase 1

Table II. Laboratory data before and after sodium benzoate treatment

Variables	**Ref**	**Case 1**		**Case 2**		**Case 3**		**Case 4**		**Case 5**	
Sodium benzoate		**Before**	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**
PT (s)	8.4-10.6	**11.2**	8.8	**11.5**	**11.9**	**12**	**11.2**	8.7	8.452	**13.5**	**12.99**
aPTT (s)	23.9-33.2	**35.5**	24.5	**39**	**38.2**	**37.9**	**36.1**	30	28.8	**41**	**38.36**
INR	0.8-1.2	**2.5**	0.996	**1.40**	**1.41**	**1.42**	**1.38**	0.92	0.98	**2.2**	**1.46**
FVII, %	50-150	**22**	86.2	**26**	**32**	**38**	**40**	100	100	**25.88**	**28**
FIX, %	50-150	**23.2**	90	**25.8**	**30**	**35.4**	**35**	78.6	82	**20.1**	**25**
AST (IU/L)	0-52	43	32.6	**81**	**78.2**	**55**	**57.6**	41	39.4	**157**	**161.8**
ALT (IU/L)	0-29	38	25.6	**55.4**	**52.8**	**48**	**50.6**	23	17.6	**75**	**72.6**
Albumin (gr/L)	34-54	31.5	32.5	36	40.6	40	38.4	35	37.8	39	44.6
T. bilirubin (µm/L)	0.3-1	0.11	0.15	0.20	0.25	0,27	0.35	0.20	0.15	0.10	0.36
Arginine (µm/L)	18-110	**220**	**195**	**371.6**	**368.5**	**309.8**	**313.2**	**236.6**	**245.3**	**309.3**	**289.3**
Ammoniac (µm/L)	11-51	50	46.4	31	36.31	29	23.5	38	46.4	30	33.7
Effect		Complete improvement		Partial improvement		Partial improvement		No abnormality		Partial improvement	

The distribution of laboratory parameters before and after sodium benzoate treatment is presented in Table II. Sodium benzoate treatment resulted in complete improvement in coagulation parameters (PT, aPTT, INR) in Case 1, and partial improvement in Cases 2, 3, and 5. No abnormal coagulation findings were observed in Case 4. Factor VII and IX levels were low before treatment in Cases 1, 2, 3, and 5, with a post-treatment increase noted, although levels did not fully normalize. Arginine levels remained elevated in cases with coagulation disorders. No significant changes were observed in other liver function tests (AST, ALT, albumin, bilirubin) or in ammonia levels.

PT: Prothrombin time, aPTT: Activated partial thromboplastin time, INR: International normalized ratio, F: Factor, AST: Aspartete aminotransferase, ALT: Alanine aminotransferase, T.bilirubin: Total bilirubin

to the treatment without making any changes to the diet treatment he received. A partial improvement in the INR value was observed after one month (Table II).

The third case was diagnosed at the age of 1. Liver transaminases and coagulation parameters, which were normal at the time of diagnosis, began to deteriorate in the sixth year. However, partial improvement in coagulation parameters was observed with the addition of sodium benzoate (Table II).

The fourth case was diagnosed in the neonatal period. Liver transaminases and coagulation parameters remained

normal from the time of diagnosis and throughout the study. Sodium benzoate was administered as part of the study. INR values were evaluated as normal before and after sodium benzoate.

The fifth case was diagnosed at the age of 3 years. At the time of diagnosis, liver transaminases and coagulation parameters were high and were evaluated as liver failure. Despite vitamin K, frozen plasma and low protein diet treatment, the PT INR value remained constant at 2. After the patient was started on sodium benzoate treatment within the scope of the study, a near-normal improvement in the INR value was observed (Table II).

In our study, FVII and IX levels were found to be low in the first, second, third and fifth cases, while other factor levels were normal (Table II).

Arginine levels were below 250 µmol/L in our patients without coagulation disorders. However, arginine levels in 3 patients with coagulation disorders remained above 250 µmol/L despite conventional treatment. Hyperammonemia was not observed in any of our patients with coagulation disorders. No significant change was observed in albumin and total bilirubin values in any patient. Platelet counts were normal. No major or minor bleeding findings were observed in patients with coagulation disorders.

Discussion

While the clinical presentation of ARG1-D varies by individual, most patients appear to have normal development from birth to toddlerhood, with symptoms beginning sometime between the ages of 1-3 years (14). Coagulation dysfunction is also a characteristic of argininemia, however, this symptom is not accompanied with life-threatening haemorrhagic complications and the underlying mechanisms remain unclear (8).

Liver disease in UCDs likely results from chronic accumulation of amino acids such as glutamine, toxic products such as argininosuccinate and guanidino compounds, ongoing steatosis and glycogen deposition, a deficiency of essential amino acids and nitric oxide, and a failure of adequate adenosine triphosphate production consequent to mitochondrial dysfunction (15,16).

The liver is the most important organ where all coagulation factors are synthesized. In chronic liver diseases (CLD), almost all coagulation factors and inhibitors are reduced. In acute liver failure (ALF), FV and FVII, which have short half-lives, decrease first, followed by FII and FX. FIX and FXI levels are normal in ALF and low in CLD (16).

In our study, we found low levels of factors VII and IX in our patients with impaired coagulation. Other factors were normal. There were no signs in our patients of minor or major bleeding, which are symptoms of clotting factor deficiency. In a recent study similar to our study, FVII and FIX levels were found to be low, while other factors related to vitamin K, such as factors II and X, were found to be normal. Contrary to our study, petechiae and ecchymosis, which are signs of minor bleeding, were observed in some of the patients in another study. In that same study, no hyperammonemia was observed in any of the patients, which is similar to our study (8). Laemmle et al.'s (17) study demonstrated increased PT INR unresponsive to vitamin K during elevated ammonia measurements in ornithine transcarbamylas cases with ALF. They suggested that hyperammonemia may affect the synthesis of short-lived clotting factors (17).

The main goal of long-term management for ARG1-D patients is to lower the levels of plasma arginine. The current standard of care is dietary restriction, aimed at limiting arginine and protein intake through a low-protein diet, often supplemented by essential amino acids (1,14). Although dietary modifications can produce modest reductions in plasma arginine, levels remain markedly elevated in most patients, as arginine flux is largely due to whole body protein turnover and minimally affected by dietary intake (15). In our 3 patients with impaired coagulation, their blood arginine levels remained above 250 µmol/L throughout the study. There was a moderate elevation in liver transaminase values. In one of our patients whose coagulation parameters improved, the plasma arginine level remained below 200 µmol/L. In a study by Cui et al. (9), the range of blood arginine concentrations was 187-810 µmol/L, with an average of 459±209 µmol/L. While liver transaminases were elevated in nine patients, no significant changes were observed in albumin and total bilirubin, and platelet counts were normal. Results from coagulation analysis showed that PT was prolonged, PT INR increased in nine patients, and aPTT was significantly prolonged (>10 s) in five patients (9).

Sodium benzoate is a widely used food and drink preservative and is also an established and accepted adjunctive treatment in the European guidelines for UCDs and all causes of hyperammonemia (14,18). Nitrogen scavenger drugs such as sodium benzoate, sodium phenylacetate and glycerol phenylbutyrate may also be used to reduce the risk of hyperammonemia by removing excess nitrogen through an alternative pathway but have no effect on arginine levels

(15). Levels of guanidino compounds are increased even when arginine is minimally increased or normal. Therefore, dietary arginine restriction does not appear to be sufficient for metabolic control. Sodium benzoate can bind to glycine and reduce the substrate concentration (19). In our study, we thought that in addition to reducing arginine levels with diet, applying sodium benzoate as a glycine scavenger could reduce guanidinoacetate compounds and have a positive effect on coagulation in addition to its nitrogen scavenger effect. We observed that coagulation parameters were completely improved in one of our patients with the addition of sodium benzoate treatment, and that coagulation disorders were limited in our other patients.

Liver transplantation effectively treats ARG1-D in the liver, normalizing arginine and ammonia levels and stopping neurological deterioration, making strict protein restriction and nitrogen scavengers unnecessary (20). It constitutes the ultimate treatment option for patients with recurrent attacks of hyperammonemia (9). However, it is a high-risk operation, especially for those with ALF or encephalopathy. Enzyme replacement therapy is another treatment option which is currently under investigation, involving intravenous injections of pegylated human recombinant arginase 1 (pegzilarginase) (21).

Study Limitations

This study has several limitations. Firstly, the small sample size limits the generalizability of the findings and reduces the statistical power to detect significant differences. Due to the rarity of ARG1 deficiency, recruiting a larger cohort was challenging. Additionally, dietary compliance varied among the participants, which may have influenced the biochemical and clinical outcomes. Finally, some laboratory parameters, such as guanidino compounds and nitric oxide metabolites, were not measured, limiting insight into the underlying pathophysiological mechanisms. Future studies with larger sample sizes and longer follow-up periods are warranted to better understand coagulation disorders in ARG1 deficiency and the therapeutic role of sodium benzoate.

Conclusion

In conclusion, it should be emphasised that ARG1-D patients have coagulation disorders in addition to their known clinical findings. Coagulation tests and factor levels should be included among the follow-up parameters of ARG1-D patients. No effective treatment has been reported for the treatment of coagulation disorders in these patients. Although it has been reported that peak plasma arginine levels may be effective in the development of coagulation abnormalities, further research is needed on its underlying mechanisms and treatments. We report that sodium benzoate treatment can be used in addition to diet therapy in the control of coagulation parameters in ARG1-D patients, even if ammonia levels are not high.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of the University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital (approval no.: 35, dated; 26.01.2022).

Informed Consent: Informed consent was obtained from the legal guardians of all participants prior to their inclusion in the study.

Footnotes

Authorship Contributions

Concept: N.Ü.E., Design: N.Ü.E., H.Ö., Data Collection or Processing: N.Ü.E., A.G., Analysis or Interpretation: N.Ü.E., Literature Search: N.Ü.E., Writing: N.Ü.E.

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Case Report

Tocilizumab in Dengue/Flavivirus-Associated Acute Necrotizing Encephalopathy: Two Pediatric Cases

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ABSTRACT

Acute necrotizing encephalopathy of childhood (ANEC) is a rare, rapidly progressive neurological disorder predominantly affecting children. It is often triggered by viral infections such as influenza. Dengue virus may also be a trigger. The hallmark of ANEC is cytokine storm-induced inflammation, leading to symmetrical necrotizing lesions in the thalami, brainstem, and cerebellum. Tocilizumab, an anti-interleukin 6 (IL-6) receptor antibody, has emerged as a promising therapy for cytokine-mediated damage. Here, we present 2 cases of dengue/flavivirus encephalopathy, "with magnetic resonance imaging findings suggestive of the classic features of ANEC", the symmetric bilateral lesions affecting the thalami. Two previously healthy children presented with acute febrile illness and neurological symptoms, requiring admission to a paediatric intensive care unit. The first case was a 5-year-old girl with a 3-day history of high fever, followed by seizures for 2 days and subsequent unconsciousness. Upon admission, she was critically ill, unconscious with a Glasgow Coma Scale score of E1M2V1, and in respiratory failure. Her acute necrotizing encephalitis severity score (ANE-SS) was 7/9. She was managed with ventilatory support, intravenous (IV) fluids, IV antibiotics, and other supportive care. The second case involved an 8-year-old boy with a 2-day history of fever, accompanied by headache, vomiting, and drowsiness. On admission, he was lethargic and drowsy, showing signs of meningeal irritation. His ANE-SS was 4/9. Both cases were treated with tocilizumab, an IL-6 receptor inhibitor, as a single dose of 12 mg/kg infusion over 1 hour, along with antiepileptics, corticosteroids, IV immunoglobulins, and other supportive management. Both patients recovered dramatically. Repeat neuroimaging on day 5 showed significant reductions in the sizes and severities of the lesions in both cases. The efficacy of tocilizumab in these two cases highlights its potential as a targeted therapy for cytokine-mediated neurological damage in ANEC.

Keywords: ANEC, dengue/flavivirus, tocilizumab

Introduction

Dengue is a mosquito-borne viral illness which affects millions globally, particularly in tropical regions. While it primarily manifests with fever, rash, and thrombocytopenia, dengue can also cause severe neurological complications, including encephalitis, myelitis, and, more rarely, acute necrotizing encephalopathy of childhood (ANEC) (1). ANEC is an rare but severe condition marked by rapid neurological decline and distinctive neuroimaging findings (2-4).

ANEC has a poor prognosis, with high mortality and severe neurological sequelae in survivors. The pathophysiology of ANEC involves a hyperimmune response to viral infections, characterized by a "cytokine storm" which disrupts the blood-brain barrier, leading to widespread brain damage. Tocilizumab, a monoclonal antibody which inhibits the interleukin-6 (IL-6) receptor, has been used in treating cytokine storm syndromes, and its role in managing ANEC associated with dengue is a promising new avenue (5,6).

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Case Report 1

A 5-year-old girl, previously healthy, presented with a high fever of 3 days duration, followed by seizures for 2 days with multiple episodes, followed by unconsciousness for 1 day. At the time of admission, the child was very sick, unconscious, with E1M2V1, and with respiratory failure. The patient was admitted to the paediatric intensive care unit. Treated with ventilatory support, intravenous (IV) fluids, IV antibiotics, and other supportive management. Investigations revealed hemogram (Hb) [Hb 10.2 gr %, packed cell volume (PCV) 27%, red blood cells (RBC) 4.2 million/cumm, white blood cells (WBC) 4,100 cells/cumm, (P47, L50, E03), platelets 197,000/cumm]. D-dimers 2,510 ng/mL, lactate dehydrogenase (LDH) 688 IU/L, procalcitonin 10.99 ng/mL, ferritin 442.5 ng/mL, IL-6 3.4 pg/mL, s. calcium 7.2 mg/dL, blood sugar 84 mg/dL, CRP 4.7 mg/L, s. sodium 132 mmol/L, s. potassium 4.0 mmol/L, s. chloride 99 mmol/L, s. creatinine 0.7 mg/dL, PT 12.8 sec, aPTT 32.6 sec, INR 0.9, s. bilirubin total 0.7 mg/dL and direct 0.4 mg/dL, serum glutamic-oxaloacetic transaminase (SGOT) 108 IU/L, serum glutamic-pyruvic transaminase (SGPT) 97 IU/L, alkaline phosphatase 81 IU/L, total protein 6.9 gr/dL, and albumin 3.8 gr/dL. Dengue enzyme-linked immunosorbent assay (ELISA) was positive for IgM. Electrocardiogram (ECG) and echocardiography (ECHO) were normal. Abdominal ultrasonography (USG) showed minimal ascites.

Neuroimaging via magnetic resonance imaging (MRI) revealed classic features of ANEC, with symmetric bilateral lesions affecting the thalami, cerebellar vermis, paravermian cerebellar hemisphere, right hippocampus, and left paraventricular region (differentials dengue/flaviviral encephalitis) (Figures 1, 2). Cerebrospinal fluid (CSF) analysis showed mildly elevated protein levels but no evidence of bacterial or other viral infections. Electroencephalogram (EEG) showed focal sharp discharges and slowing, diffuse monomorphic theta activity, poor sleep patterns, and diffuse cerebral dysfunction. The acute necrotizing encephalitis severity score (ANE-SS) was 7/9 [ANE-SS ranges from 0 to 9 points, with 3 points for the existence of shock, 2 points for brain stem lesions, 2 points for age over 48 months, 1 point for a platelet count below 100,000/µL, and 1 point for CSF protein above 60 mg/dL. Patients are classed as low risk (ANE-SS 0-1 points), medium risk (ANE-SS 2-4 points), or high risk (ANE-SS 5-9 points)] (7).

Despite standard supportive care, including antiepileptics, corticosteroids (methylprednisolone 30 mg/kg for 5 days), and IV immunoglobulins (2 gr/kg over 2 days), the child's condition continued to deteriorate. Given

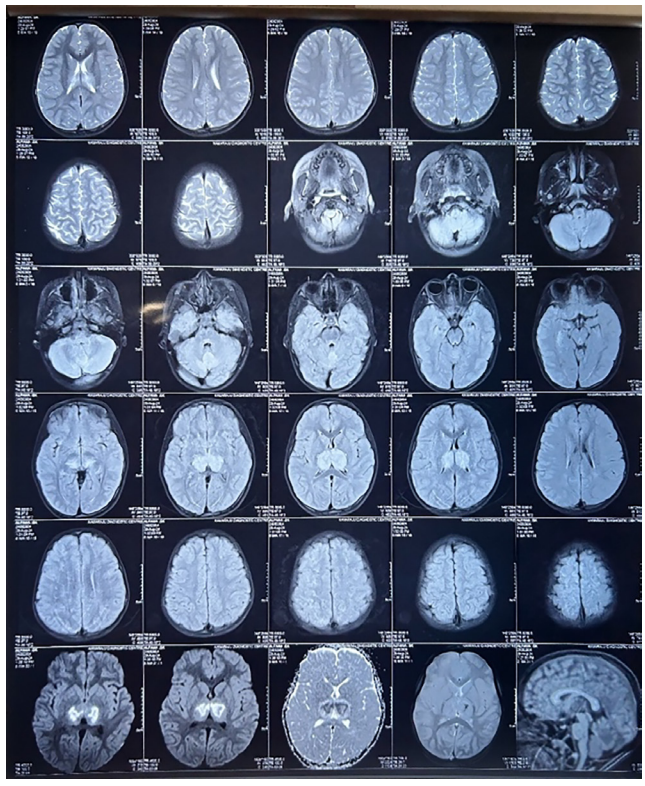

Figure 1. Areas of altered signal in thalami, cerebellar vermis, paravermian cerebellar hemisphere, right hippocampus, and left paraventricular region showing T2, FLAIR hyperintensity, T1 hypointensity with areas of diffusion restriction
FLAIR: Fluid-attenuated inversion recovery

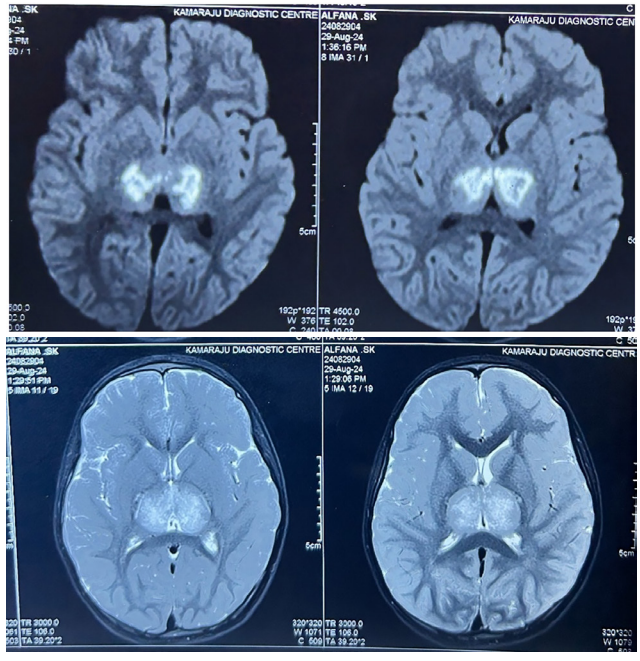

Figure 2. There are small foci of low signal on GE sequence in thalami suggesting hemorrhagic foci
GE: Gradient echo

the rapid progression of neurological damage and the suspected cytokine storm, the decision was made to initiate treatment with tocilizumab, an IL-6 receptor inhibitor. The patient received a single dose of 12 mg/kg of tocilizumab as an infusion over 1 hour. Within 36 hours, her seizures ceased, and her consciousness improved significantly. By day five, she was responsive, and her motor functions were gradually recovering. Repeat neuroimaging on day 5 showed a significant reduction in the size and severity of the lesions (Figure 3). The child was discharged with no significant neurological deficits and continued to do well on follow-up. After 1 month, she was completely normal with a normal MRI brain scan.

Case Report 2

An 8-year-old boy presented with a fever of 2 days duration, associated with headache, vomiting, and drowsiness. At the time of admission, the child was very sick, dull, drowsy, and with meningeal irritation. He was admitted to the paediatric intensive care unit. His ANE-SS was 4/9. He was treated with IV fluids, IV antibiotics, and other supportive management. Investigations revealed Hemogram [Hb 12.2 gr %, PCV 33%, RBC 4.4 million/cumm, WBC 5,900 cells/cumm, (P69, L28, E04), platelets 221,000/cumm].

D-dimers 5550 ng/mL, LDH 760 IU/L, Procalcitonin 22.82 ng/mL, ferritin 496.2 ng/mL, IL-6 2.0 pg/mL, s. calcium 7.2 mg/dL, blood sugar 116 mg/dL, CRP 8.9 mg/L, S. sodium 136 mmol/L, S. potassium 3.5 mmol/L, S. chloride 110 mmol/L, S. creatinine 0.7 mg/dL, PT 14.0 sec, aPTT 38.5 sec, INR 1.0, S. bilirubin total 0.6 mg/dL and direct 0.4 mg/dL, SGOT 29 IU/L, SGPT 22 IU/L, alkaline phosphatase 93 IU/L, total protein 6.9 gr/dL, and albumin 3.5 gr/dL. Dengue ELISA was positive for IgM. ECG and ECHO were normal. Abdominal USG showed minimal left hydronephrosis.

Neuroimaging via MRI revealed the classic features of ANEC, with symmetric bilateral lesions affecting the thalami (differentials dengue/flaviviral encephalitis) (Figure 4). CSF analysis showed a normal study. EEG showed

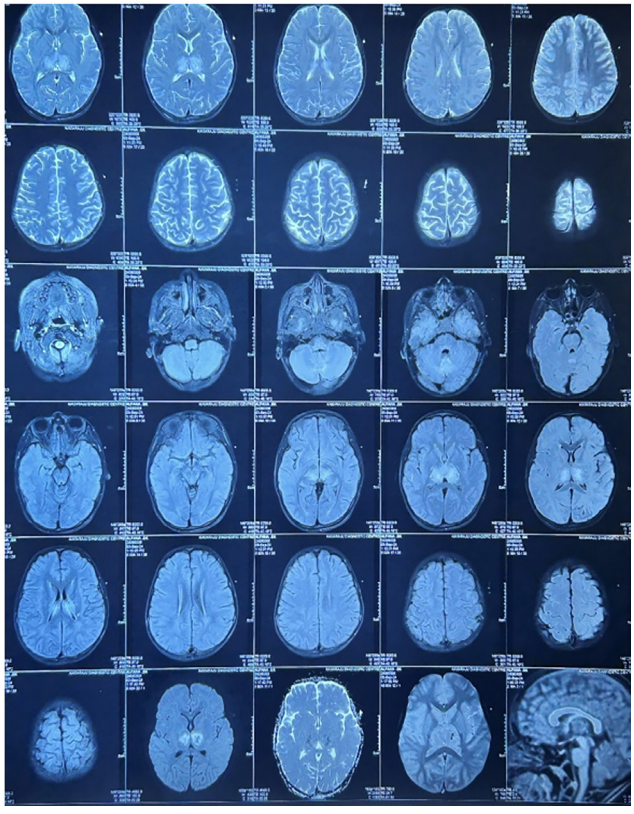

Figure 3. Areas of altered signal in the cerebrum and cerebellum. Partial resolution of signal changes in the cerebrum and cerebellum with no appearance of fresh changes

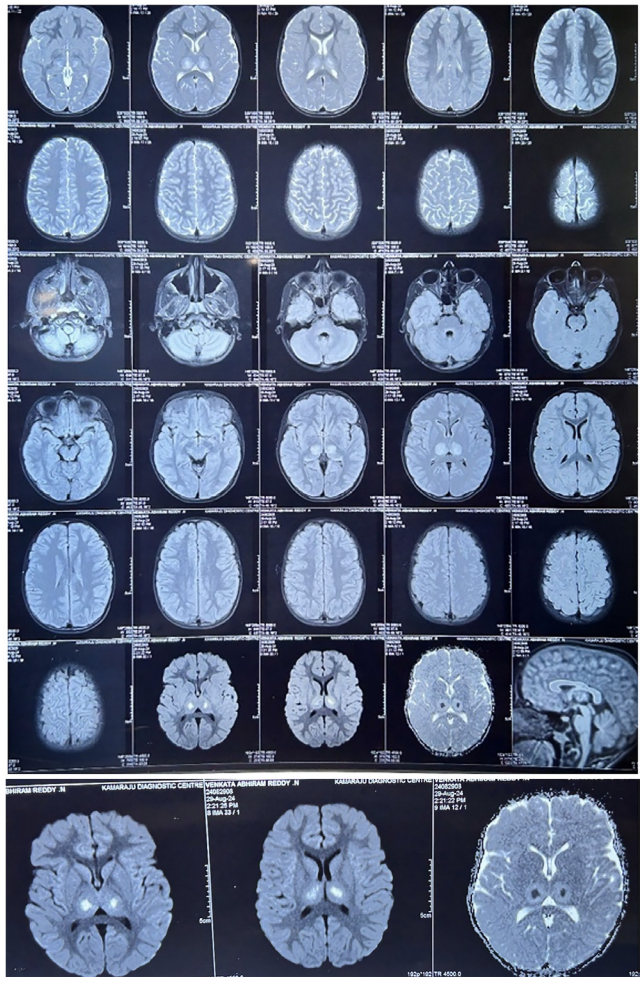

Figure 4. Bilateral relatively symmetrical areas of T2, FLAIR hyperintensity, T1 hypointensity with small areas of diffusion restriction in thalami
FLAIR: Fluid-attenuated inversion recovery

intermittent bursts of generalized slow-wave epileptiform discharges. Despite standard supportive care, including antiepileptics, corticosteroids (methylprednisolone 30 mg/kg for 5 days), and IV immunoglobulins (2 gr/kg over 2 days), the child's neurological condition deteriorated rapidly, likely due to a cytokine storm. As a result, the team administered a single dose of tocilizumab, an IL-6 receptor inhibitor, at 12 mg/kg as an infusion over 1 hour. Within 36 hours, the child's condition improved markedly, and by day 5, neuroimaging showed a significant reduction in lesion size and severity (Figure 5). The child was discharged without notable neurological deficits and continued to do well on follow-up.

Pathophysiology and Rationale for Tocilizumab

ANEC is thought to result from a hyperinflammatory response triggered by viral infections, which leads to excessive release of pro-inflammatory cytokines such as IL-6. This cytokine surge can compromise the blood-brain barrier, causing brain edema, haemorrhage, and necrosis, particularly affecting the thalami, brainstem, and cerebellum. The central role of the cytokine storm in ANEC's pathogenesis makes targeted immunotherapy a promising treatment approach. Tocilizumab, a monoclonal antibody which blocks IL-6 receptors, helps inhibit this cytokine surge and has shown positive outcomes in managing cytokine release syndromes in other conditions, such as coronavirus disease-2019 and autoimmune diseases. In these two cases, tocilizumab was administered early in dengue-associated ANEC, resulting in rapid neurological and radiological improvement, highlighting a novel therapeutic approach.

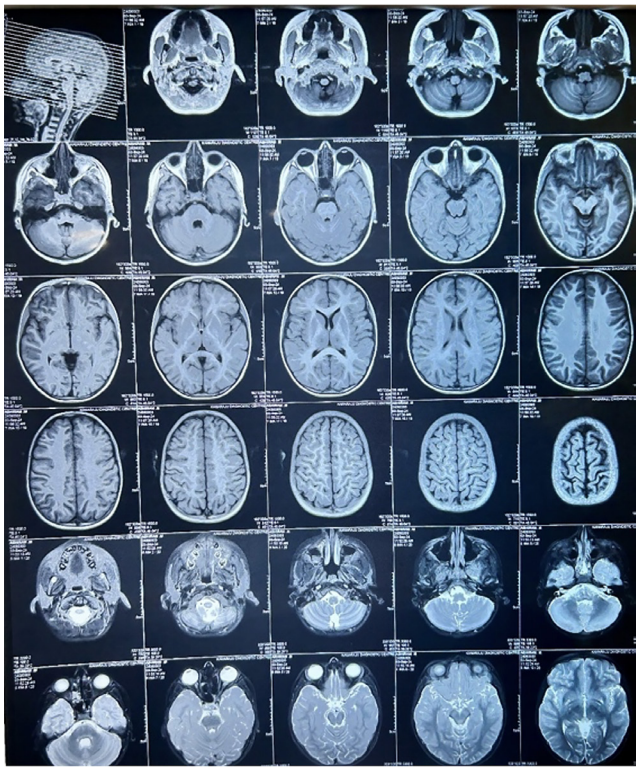

Figure 5. Reduction in the size of signal changes suggesting partial clearing

Tocilizumab is generally well tolerated. Its most common side effects include cough, sore throat, nasal congestion or runny nose, headache, dizziness, mouth ulcers, hypertension, hypercholesterolemia, allergic reactions, skin rashes, gastrointestinal symptoms, and haematological abnormalities such as cytopenias. It may also cause elevations in liver enzyme levels. Tocilizumab is contraindicated in individuals with known hypersensitivity to any of its components.

Management and Outcome

Both patients received standard supportive care, including antipyretics, fluid management, corticosteroids, and antiepileptic drugs. However, their neurological status continued to deteriorate until tocilizumab was introduced. In both cases, tocilizumab administration was followed by rapid clinical improvement, a stabilization of seizures, and a recovery of consciousness. Follow-up MRIs showed partial to significant resolution of the brain lesions, and both patients were discharged with minimal or no long-term neurological deficits.

The dramatic improvements seen in both patients underscore the potential role of tocilizumab in treating dengue-associated ANEC. Early intervention with tocilizumab may prevent the progression of brain injury and improve long-term neurological outcomes in this devastating condition.

Discussion

In our study, we demonstrated that early IL-6 blockade with tocilizumab in severe ANE is a safe treatment option and it may help improve outcomes. Our patients had thalamic lesions, which are key predictors of a high risk of death or severe disability based on the ANE severity score. Both patients showed excellent clinical and radiological recovery. By targeting the cytokine storm early, tocilizumab appears to reduce neurological damage and enable rapid clinical recovery. While corticosteroids are generally the first-line treatment used to decrease inflammation in ANEC, they may be insufficient in cases with intense cytokine storm activity.

Huang et al. (8), in their study, suggested that glucocorticoids and immunoglobulins may improve the prognosis of ANE. However, the underlying therapeutic mechanisms were not elaborated on, and both glucocorticoids and immunoglobulins lack specificity in the treatment of various critical illnesses. Therefore, their significance in the management of ANE remains questionable. In recent years, studies by Koh et al. (9) have reported the effective use of tocilizumab in mitigating cytokine storms.

Other studies have reported similar success with tocilizumab in treating severe neurological inflammation. Jaiswal et al. (10) described its use in a 24-month-old boy with acute leukoencephalopathy with restricted diffusion. On day 16 of treatment, the child received IV tocilizumab (8 mg/kg) after informed consent, leading to an improvement in sensorium and reduced irritability within 24 hours. The patient was then transitioned to oral prednisolone, tapered over three weeks. Similarly, Huang et al. (8) reported on a 2-year 10-month-old boy who developed ANE following a H1N1 (influenza A) infection. Post-tocilizumab treatment, the child experienced an improvement in consciousness, an absence of convulsions, enhanced limb mobility, and a significant reduction in encephalopathy lesions. Nguyen et al. (11) described the first known case of tocilizumab use in acute encephalopathy with biphasic seizures and restricted diffusion, involving a 21-month-old who received a single dose (120 mg) and achieved a normal outcome at six months.

In our study, we used tocilizumab at a dose of 12 mg/kg IV as a single dose. An open-label study by Mallalieu et al. (12) provided data on the pharmacokinetics, pharmacodynamics, and efficacy of tocilizumab 12 mg/kg IV in systemic juvenile idiopathic arthritis (sJIA) patients younger than 2 years, demonstrating comparability to patients aged 2 to 17 years. The safety profile was also similar, except for a higher incidence of serious hypersensitivity reactions in patients under 2 years of age.

Among other indications for tocilizumab use, Brunner et al. (13) conducted a 2-year clinical trial in patients aged 2 to 17 years with sJIA unresponsive to methotrexate. The patients received weight-based tocilizumab every 4 weeks, with responders at week 16 (n=166) randomized either to continue tocilizumab or switch to placebo until week 40, followed by open-label tocilizumab for all (n=160). At week 104, sustained therapeutic efficacy was demonstrated using JIA- American College of Rheumatology 50/70/90 response criteria (13).

Conclusion

ANEC is a rare but severe neurological complication of dengue fever, characterized by a cytokine storm which leads to rapid neurological deterioration with rapid onset encephalopathy and bilateral brain lesions. In this case report, two paediatric patients with dengue/flavivirus-associated ANEC improved dramatically after treatment with tocilizumab. These cases highlight the potential of IL-6 blockade to alter the course of this disease, offering hope for better outcomes in an otherwise grim prognosis. Further research and larger studies are warranted to explore the use of tocilizumab in this setting and to develop standardized treatment protocols for dengue-associated ANEC.

IL-6 blockade shows promise in managing severe dengue-associated ANEC: Tocilizumab, an IL-6 inhibitor, demonstrated significant clinical and radiological improvement in paediatric patients with dengue-associated ANEC, suggesting its potential to alter disease progression and improve outcomes in cases with a high risk of disability or mortality.

Rapid intervention can prevent further neurological deterioration: Early administration of tocilizumab helped manage cytokine storm-driven neurological damage, resulting in rapid improvement and underscoring the importance of timely intervention in cytokine-mediated encephalopathies.

Need for larger studies and standardized protocols: These cases underscore the urgent need for more research and larger studies in order to assess the efficacy and safety of tocilizumab in dengue-associated ANEC, ultimately contributing to the development of standardized treatment protocols to guide clinical practice.

Ethics

Informed Consent: Informed consent was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: L.B., Concept: L.B., Design: L.B., Data Collection or Processing: L.B., S.K., C.S.R.T., Analysis or Interpretation: L.B., S.K., C.S.R.T., Literature Search: L.B., S.K., C.S.R.T., Writing: L.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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Letter to the Editor

Chanarin-Dorfman Syndrome Presenting with Ichthyosis and Persistent Hypercreatinekinasemia: Value of the Peripheral Blood Smear

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Introduction

Chanarin-Dorfman syndrome (CDS) is a rare autosomal recessive non-lysosomal lipid storage disorder characterized by the accumulation of neutral lipids in various tissues such as the skin, skeletal muscle, liver, eye, ear, central nervous system, and bone marrow (1). The disease is caused by mutations in the [alpha/beta hydrolase domain 5 (ABHD5) -containing, comparative gene identification-58 (CGI-58)] gene located on the short arm of chromosome 3 (2). Diagnosis is based on the presence of ichthyosiform skin lesions and the demonstration of lipid vacuoles in neutrophils or monocytes in a peripheral blood smear. Defective lipolysis leads to intracellular triglyceride accumulation and the pathognomonic Jordans' anomaly in leukocytes (1,3). In this case report, we present a two-year-old girl with ichthyosis, muscle enzyme elevation, and vacuolated neutrophils, illustrating how a simple peripheral blood smear can direct timely molecular confirmation and counselling.

At one year of age, the patient developed scaly lesions beginning on the upper extremities and spreading to the whole body. Family history revealed second degree consanguinity. On physical examination, her height, weight, and head circumference were within normal percentiles. Systemic examination revealed marked skin dryness, hyperpigmented scaly patches on the back and trunk, and generalized hyperkeratosis (Figure 1). Neurological findings were normal. Laboratory tests showed elevated creatine kinase (CK) at 1.046 IU/L (reference: 0-190 IU/L). Muscle tissue associated enzymes, namely aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and aldolase, remained within reference limits. Thyroid, parathyroid, viral serologies, autoimmune panel, serum lipids, and a targeted inborn-error screen (plasma amino acids, acylcarnitine profile, urine organic acids) were unremarkable. Due to unexplained hyperCKemia and skin findings, a peripheral blood smear was performed, revealing marked vacuolization in neutrophils (Figure 2). Based on this finding, CDS was considered. The Denver developmental screening test, audiological and ophthalmological examinations, and metabolic workup were normal. Electromyography, echocardiography, and abdominal ultrasonography revealed no abnormalities. Muscle biopsy could not be performed due to a lack of consent. Genetic analysis revealed a homozygous ABHD5 (NM_016006): c. 594dupC (p.Arg199Glnfs*11) mutation.

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Figure 1. Marked dryness in the skin, hyperpigmented squamous lesions in places, hyperkeratosis appearance in the body skin

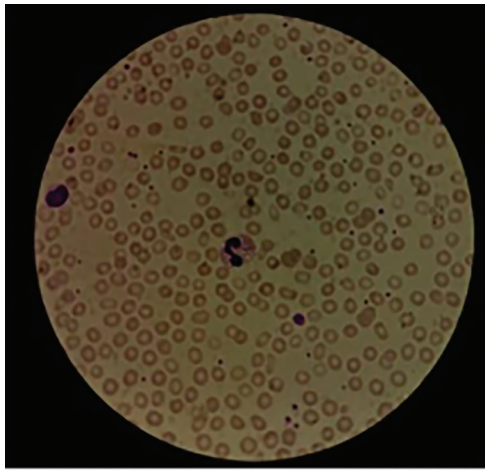

Figure 2. Marked vacuolization observed in neutrophils on the peripheral blood smear

CDS was first described by Jordan in 1953 through identification of lipid vacuoles in leukocytes in two brothers with progressive muscle disease. Later, Chanarin and Dorfman demonstrated that the condition involved defective intracellular triglyceride metabolism, with lipid accumulation in leukocytes, hepatocytes, and other cell types (1). The disorder results from a defect in the CGI-58 protein, essential for triglyceride lipase activation and triacylglycerol hydrolysis in adipose tissue (2). To date, around 120 cases of CDS have been reported in the literature, with higher prevalences found in regions such as the Mediterranean and Middle East, where consanguineous marriages are more common (1). Besides cutaneous manifestations, systemic involvement is frequent, including hepatomegaly, elevated transaminases (AST/ALT), steatosis, cataract, nystagmus, strabismus, sensorineural hearing loss, mental retardation, and myopathy (1,4). Cutaneous findings usually mimic non-bullous congenital ichthyosiform erythroderma. A collodion baby appearance may be present at birth, although hair, nails, mucosa, and teeth are typically spared (1). While serum lipid abnormalities are not common, some cases have shown elevated very low-density lipoprotein and reduced high-density lipoprotein levels (5).

CK elevation is a recognized clue; however, published cohorts frequently show concurrent rises in LDH and/or transaminases, likely reflecting subclinical myopathy or hepatic steatosis. Çetinarslan et al. (6) reported on four Turkish children in whom CK elevation coincided with increased LDH and/or AST/ALT. Our patient exhibited isolated CK elevation-an uncommon but noteworthy biochemical footprint-underscoring phenotypic heterogeneity.

Management focuses on early diagnosis, genetic counselling, surveillance for organ involvement, and nutritional measures: a diet low in long-chain fatty acids and enriched with medium-chain triglycerides may delay hepatic complications. Emerging data on systemic retinoids and lipid-lowering agents remain anecdotal.

This case underlines three teaching points: (i) persistent hyperCKemia in a child with ichthyosis should prompt a peripheral blood smear; (ii) Jordans' anomaly is a rapid, low-cost diagnostic gateway to CDS; and (iii) molecular confirmation enables tailored follow-up before irreversible hepatic or neuromuscular damage occurs. We advocate including CDS in the differential diagnosis of ichthyosis accompanied by muscle-enzyme elevation, even when LDH and transaminases are normal.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.T.T., Ö.D., Concept: B.T.T., Design: B.T.T., Data Collection or Processing: B.T.T., Ö.D., Analysis or Interpretation: B.T.T., Ö.D., Literature Search: B.T.T., Ö.D., Writing: B.T.T.

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