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İçindekiler / Contents

ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Improving Early Identification of Microbial Etiology in Severe Pediatric Pneumonia by Using Inflammatory Profiles: A Cross-sectional Study

Enflamatuvar Profiller Kullanılarak Ağır Çocukluk Çağı Pnömonisinde Mikrobiyal Etiyolojinin Erken Belirlenmesinin İyileştirilmesi: Kesitsel Bir Çalışma

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Abstract

Introduction: Pediatric pneumonia can result from bacterial or viral pathogens, presenting with overlapping clinical features, which makes accurate differentiation challenging. In developing countries, where access to microbiological diagnostics is limited, timely identification of the etiology is crucial to guide treatment. Basic inflammatory markers such as absolute neutrophil count (ANC), neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein (CRP) may help distinguish bacterial from viral infections. This study evaluates the diagnostic value of routine inflammatory markers in severe pneumonia.

Materials and Methods: This cross-sectional study included 61 children aged 2 months to 5 years with severe pneumonia at Children's Hospital 1, Vietnam. Bacterial etiology was confirmed using real-time polymerase chain reaction from tracheal aspirates; viral pneumonia was identified by detecting respiratory viruses in the absence of bacteria. Clinical characteristics and inflammatory markers were collected. Comparative and receiver operating characteristic (ROC) curve analyses were performed to assess diagnostic performance.

Results: 51 children (83.6%) had bacterial pneumonia, and 10 (16.4%) had viral pneumonia. Bacterial pneumonia was more common with recurrent pneumonia and high fever ($p < 0.05$). ANC ($p < 0.005$), NLR ($p = 0.0002$), and CRP ($p = 0.01$) were significantly elevated in bacterial cases. Area Under the ROC Curve (AUROC) showed NLR had the highest discriminatory value (AUROC = 0.87). The optimal NLR cut-off value (≥ 0.8) yielded 78.4% sensitivity and 90% specificity. Combining NLR and CRP with clinical symptoms increased specificity but reduced sensitivity. A moderate positive correlation was observed between NLR and CRP (Spearman's rho = 0.514, $p < 0.0001$).

Conclusion: NLR and other inflammatory markers offer practical value in distinguishing severe bacterial pneumonia, particularly in resource-limited settings. Nevertheless, interpretation should always be guided by clinical context.

Keywords
Severe pneumonia, inflammatory markers, neutrophil-to-lymphocyte ratio, early diagnosis, microbiology.

Anahtar kelimeler
Ağır pnömoni, enflamatuvar belirteçler, nötrofil/lenfosit oranı (NLR), erken tanı, mikrobiyoloji

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Öz

Giriş: Gelişmekte olan ülkelerde mikrobiyolojik tanı olanaklarının sınırlı olduğu durumlarda, çocuklarda bakteriyel ve viral pnömoniyi hızla ayırt etmek güçtür. Bu çalışmanın amacı, ağır pnömonisi olan çocuklarda mutlak nötrofil sayısı (MNS), nötrofil/lenfosit oranı (NLR) ve C-reaktif protein (CRP) gibi rutin inflamatuvar belirteçlerin etiyolojik ayırıcı tanıdaki değerini değerlendirmektir.

Gereç ve Yöntem: Bu kesitsel çalışma, Vietnam Çocuk Hastanesi 1'de ağır pnömoni tanısı ile izlenen 61 çocuğu (yaş: 2 ay–5 yaş) kapsamaktadır. Bakteriyel etiyoloji, trakeal aspiratlardan gerçek zamanlı polimeraz zincir reaksiyonu (rt-PCR) ile doğrulandı; viral pnömoni ise bakteriyel etken saptanmaksızın solunum virüslerinin gösterilmesiyle tanımlandı. Klinik özellikler ve inflamatuvar belirteçler kaydedildi. Gruplar arası karşılaştırmalar ve ROC eğrisi analizleri yapılarak tanısal performans değerlendirildi.

Bulgular: 51 çocukta (%83,6) bakteriyel, 10 çocukta (%16,4) viral pnömoni saptandı. Bakteriyel olgular rekürren pnömoni ve yüksek ateş ile daha sık ilişkiliydi ($p<0,05$). MNS ($p<0,005$), NLR ($p=0,0002$) ve CRP ($p=0,01$) bakteriyel olgularda anlamlı düzeyde daha yüksekti. NLR, en iyi ayırıcı gücü gösterdi (AUROC=0,87). NLR ≥0,8 eşik değeri için duyarlılık %78,4 ve özgüllük %90,0 bulundu. NLR + CRP'nin klinik bulgularla birlikte kullanımı özgüllüğü artırırken duyarlılığı bir miktar azalttı. NLR ile CRP arasında orta düzeyde pozitif korelasyon izlendi (Spearman rho=0,514; $p<0,0001$).

Sonuç: NLR başta olmak üzere temel inflamatuvar belirteçler, özellikle kaynakların kısıtlı olduğu ortamlarda ağır çocukluk çağı pnömonisinde bakteriyel-viral ayrımına pratik katkı sağlayabilir. Bununla birlikte, yorumlama her zaman klinik bağlam içinde yapılmalıdır.

Introduction

Community-acquired pneumonia (CAP) remains a leading cause of death in children under five, responsible for nearly 2 million deaths annually, according to the World Health Organization (WHO) and the United Nations International Children's Emergency Fund (UNICEF) (1). The primary causative agents are bacteria and viruses (2). In Vietnam, Tran Quang et al. (3) reported bacterial infections in 83.1% and viral infections in 50.5% of severe pneumonia cases.

Managing pediatric pneumonia in developing countries is challenging due to the high prevalence of severe cases, inconsistent diagnostic criteria, and limited access to microbiological tests needed to identify pathogens before initiating appropriate treatment (4). Notably, bacterial and viral pneumonia trigger distinct immune responses. Therefore, using accessible and affordable biomarkers that reflect these differences may aid in distinguishing between bacterial and viral etiologies, helping to reduce complications and mortality (5).

Numerous studies have attempted to distinguish clinical features and inflammatory markers to reduce reliance on microbiological testing, which is often unavailable in resource-limited settings. Moreover, pathogen culture results are time-consuming and thus unsuitable for managing severe pneumonia cases that require timely intervention. However, findings across studies remain inconsistent and continue to be a matter of debate. This article describes the clinical and paraclinical characteristics of severe bacterial versus viral pneumonia, while evaluating the diagnostic value of basic inflammatory markers in distinguishing between these two etiologies to improve the quality of pathogen identification in pediatric cases.

Materials and Methods

Study Design and Population

This cross-sectional descriptive study was conducted at a children's hospital in southern Vietnam, from December 2022 to November 2023, enrolling children aged 2 months to 5 years diagnosed with severe CAP. Inclusion criteria required: i) cough or difficulty breathing accompanied by at least one of the following signs: age-specific tachypnea, abnormal lung examination findings, or chest indrawing combined with radiographic evidence of pulmonary infiltrates on chest X-ray (1); ii) classification as severe CAP based on criteria from the British Thoracic Society (6), defined respiratory rate greater than 70 breaths per minute, severe chest indrawing, cyanosis, intermittent apnea, grunting, inability to feed, or capillary refill time ≥ 2 seconds; iii) availability of C-reactive protein (CRP) along with routine blood test results obtained within 24 hours of admission; iv) specimen collection and testing for respiratory pathogens within 24 hours of admission. Exclusion criteria included: i) underlying cardiopulmonary diseases; ii) recent hospitalization within 30 days; iii) prior antibiotic or immunosuppressive therapy within 1 month before admission; iv) absence of parental consent.

Data Collection Procedures

Children diagnosed with severe CAP were screened based on predefined inclusion and exclusion criteria. Eligible patients were enrolled consecutively, and demographic, clinical, and laboratory data were collected using a standardized case record form.

Nasotracheal Aspiration (NTA) and Microbiological Analysis: Shortly after admission and before starting

antibiotics, NTA was performed under sterile conditions using a mucus extractor device (Global Medikit Limited, New Delhi, India) to collect lower respiratory tract secretions. Samples were sealed, placed in an icebox at 2–8 °C, and promptly transported to the International Research of Gene and Immunology Institute at Nam Khoa Biotek Laboratory (Ho Chi Minh City, Vietnam), which is certified under ISO 9001:2008 standards for real-time polymerase chain reaction (RT-PCR) testing. This procedure was carried out following the standardized protocol used at our institution to ensure specimen integrity and diagnostic accuracy.

Sample Quality Assessment: To ensure sample origin from the lower respiratory tract, all NTA specimens underwent Gram staining and microscopic evaluation. Specimens were considered high-quality if they contained fewer than 10 squamous epithelial cells (SECs) and more than 25 polymorphonuclear cells (PMNs) per low-power field (×100 magnification), indicating minimal upper airway contamination and active inflammation (3).

Microbial Identification: The RT-PCR process included three main steps: i) sample homogenization in phosphate-buffered saline with N-Acetyl L-Cysteine; ii) nucleic acid extraction using the BIO-RAD CFX96 system and NKRNADNAprep-MAGBEAD reagents; and iii) amplification using specific primers and TaqMan probes (Thermo Fisher Scientific). The RT-PCR panel included 46 respiratory pathogens (29 bacterial and 17 viral agents). A full list of targeted pathogens is provided in Appendix 1.

A sample was considered positive for bacterial infection if RT-PCR detected one or more pathogenic bacterial species at a concentration exceeding 10^5 copies/mL, consistent with thresholds used for lower respiratory tract specimens. For viral pathogens, a result was considered positive when at least one respiratory virus was detected with a viral load of $\geq 10^5$ copies/mL or a cycle threshold (Ct) value below 30, indicating active infection rather than asymptomatic carriage (3). Participants were categorized into either the bacterial severe CAP (BSCAP) group or the viral severe CAP (VSCAP) group. Assignment to the VSCAP required fulfillment of the following criteria: i) detection of at least one respiratory virus in NTA specimens (e.g., respiratory syncytial virus, rhinovirus); ii) absence of detectable bacterial DNA; iii) absence of clinical signs, symptoms, or radiographic evidence suggestive of empyema; iv) negative sputum culture results. Assignment to the BSCAP group required the following criteria: i) detection of one or more pathogenic bacteria in respiratory specimens by RT-PCR or culture (e.g., Streptococcus pneumoniae, Haemophilus influenzae); ii) absence of detectable respiratory viruses in the same specimen. Mixed infections, in which both bacterial and viral pathogens were concurrently identified in the same sample by RT-PCR or culture, were excluded from the final analysis to ensure clear etiological differentiation.

These classifications were used as the reference standard for subsequent comparisons of clinical and inflammatory marker profiles. The detailed process of patient screening, eligibility assessment, exclusion, and final inclusion in the study cohort is illustrated in the flowchart provided in Appendix 2.

Statistical Analysis

Statistical data were processed using standard medical statistical methods. Data analysis was conducted using Stata version 16.0. Qualitative variables were presented as frequencies and percentages, while quantitative variables were reported as mean ± standard deviation or median (interquartile range), as appropriate. Group comparisons were performed with a 95% confidence interval. A p-value of < 0.05 was considered statistically significant. The area under the receiver operating characteristic curve (AUROC) was used to evaluate the predictive ability of the basic inflammatory markers. Sensitivity, specificity, positive likelihood ratio (LR^+) and negative likelihood ratio (LR^-) were also calculated.

Ethics committee approval

The authors affirm that all procedures and experiments conducted in this study complied with the ethical standards outlined in the Declaration of Helsinki (1975), as revised in 2008, as well as relevant national regulations. The study protocol was reviewed and approved by the Ethics Committee in Biomedical Research at Hội đồng Đạo Đức trong Nghiên cứu Y sinh học Bệnh viện Nhi Đồng 1 (approval number: 425/GCN-BVND1, date: 17.11.2022). Written informed consent was obtained from the parents or legal guardians of all participants. They were fully informed of the study's objectives, procedures, potential risks, and their right to withdraw from the study at any time without consequences.

Results

Microbial Profile and Infection Complexity

61 children with severe CAP were included. RT-PCR identified 51 cases (83.6%) as bacterial and 10 cases (16.4%) as viral pneumonia. The distribution of cases by microbial etiology and infection complexity is shown in Figure 1. In the

BSCAP group (Figure 1A), 18 cases were classified as bacterial monoinfections and 33 as coinfections. Streptococcus pneumoniae (SP) and Haemophilus influenzae (HI) were the most common pathogens in monoinfections. The complexity of microbial etiology in severe CAP was particularly evident in bacterial coinfections involving SP, most notably SP–HI coinfection (10 cases). Notably, 8 patients presented with coinfections involving three distinct bacterial pathogens. A wide range of other bacterial species were also detected in coinfection profiles, including Moraxella catarrhalis (MC), Klebsiella pneumoniae (KP), and Staphylococcus aureus (both MRSA and MSSA). In contrast, the VSCAP group showed a simpler pathogen profile, with 7 monoinfection cases – mostly respiratory syncytial virus (RSV), and only 3 cases involving viral coinfections (see Figure 1B).

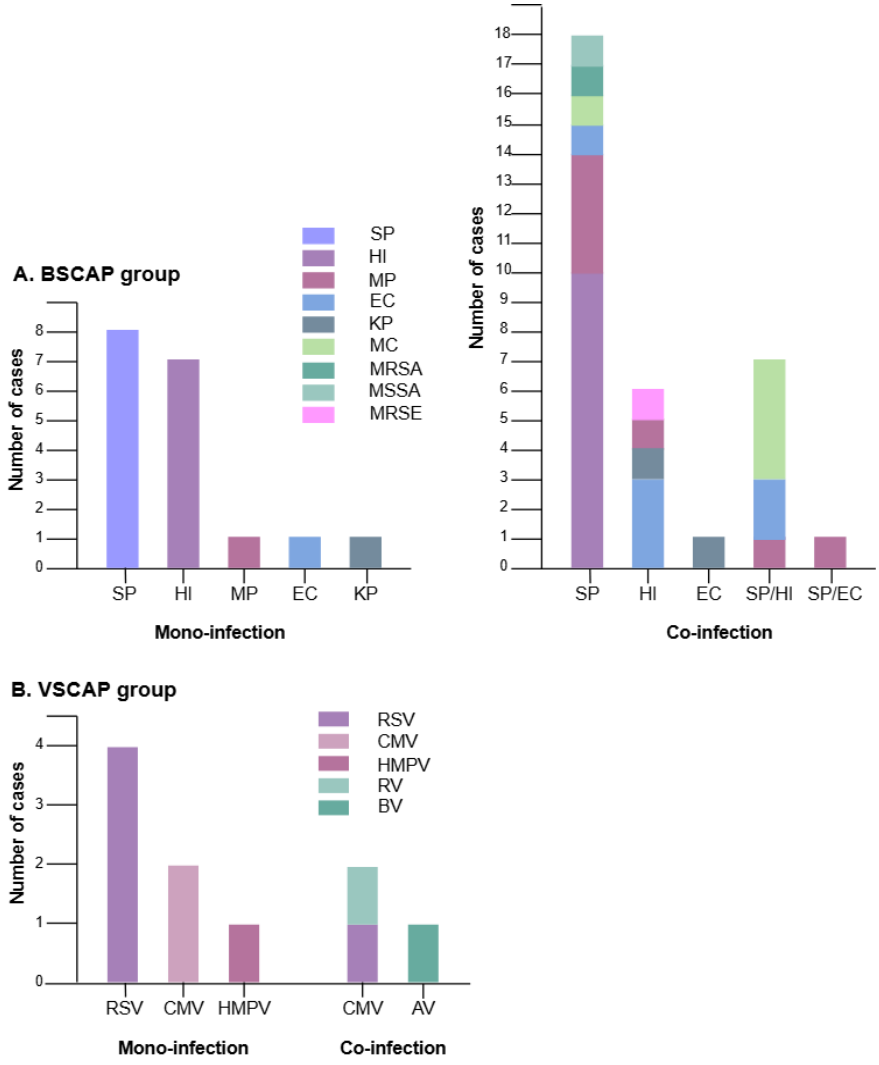

Figure 1. Distribution of pneumonia cases by etiology and infection complexity
(A) Bacterial severe community-acquired pneumonia (BSCAP) group: the bar graphs display the number of mono-infections and co-infections identified. *Streptococcus pneumoniae* (SP) and *Haemophilus influenzae* (HI) were the most common mono-infecting pathogens. Co-infections commonly involved combinations such as SP-HI, and SP/HI-MC (*Moraxella catarrhalis*), along with other pathogens including *Mycoplasma pneumoniae* (MP), *Klebsiella pneumoniae* (KP), *Methicillin-sensitive Staphylococcus aureus* (MSSA), Methicillin-resistant Staphylococcus aureus (MRSA), and *Staphylococcus epidermidis* (MRSE). (B) Viral severe community-acquired pneumonia (VSCAP) group: the figure shows the distribution of mono-viral and multi-viral infections. *Respiratory syncytial virus* (RSV), *Cytomegalovirus* (CMV), and *Human metapneumovirus* (HMPV) were frequently identified. Co-infections included CMV in combination with RSV and Rhinovirus (RV), as well as Adenovirus (AV) and Bocavirus (BV)

Clinical Characteristics and Laboratory Markers associated with Microbial Etiology

In Table 1, children with BSCAP were more likely to have a history of recurrent pneumonia (70.6% versus 20.0%, $p < 0.005$), incomplete vaccination (58.9% versus 20.0%, $p < 0.05$), and high fever (41.2% versus 10.0%, $p < 0.05$). Wheezing was significantly more common in VSCAP (100% versus 64.7%, $p < 0.05$). Other variables such as age, sex, prematurity, and nutritional status did not differ significantly between groups. In addition, children with BSCAP exhibited significantly higher levels of inflammatory markers compared to those with VSCAP. Median absolute neutrophil count (ANC) was 6.3 K/µL versus 3.2 K/µL ($p < 0.005$), neutrophil-to-Lymphocyte Ratio (NLR) was 1.4 versus 0.5 ($p = 0.0002$), and CRP was 10.2 mg/L versus 1.5 mg/L ($p = 0.01$).

Diagnostic Accuracy of Inflammatory Biomarkers and Impact of Combined Clinical Parameters

AUROC analysis was performed to evaluate the diagnostic utility of ANC, NLR, and CRP in predicting bacterial etiology (Table 2 and Figure 2). NLR demonstrated the highest discriminatory capacity with an AUROC of 0.87 (95% CI: 0.78–0.97, $p < 0.0001$). ANC also performed well with an AUROC of 0.79 (95% CI: 0.65–0.93, $p = 0.0015$), while CRP showed a moderate predictive value with an AUROC of 0.74 (95% CI: 0.58–0.90, $p = 0.01$). However, the differences between the AUROCs were not statistically significant ($p = 0.1427$).

Cut-off values were calculated using Youden's Index to optimize sensitivity and specificity (Table 3). An NLR ≥ 0.8 yielded a sensitivity of 78.4% and specificity of 90%, corresponding to an LR^+ of 7.9 and an LR^- of 0.2. In contrast, CRP ≥ 7 mg/L and ANC ≥ 5.8 K/µL showed lower sensitivity (56.9% and 60.5%, respectively) but similarly high specificity (both at 90%). When clinical features were incorporated into the diagnostic algorithm, the overall performance shifted. Combining NLR ≥ 0.8 and CRP ≥ 7 mg/L with the presence of high fever or a history of recurrent pneumonia slightly increased specificity to 93.3% and 94.4% respectively, while further reducing sensitivity. On the other hand, the correlation analysis between NLR and CRP revealed a Spearman's rho of 0.514 ($p < 0.0001$), suggesting a moderate positive correlation.

Table 1. Clinical and laboratory comparision between severe bacterial and viral CAP

Characteristics	Bacterial (n=51)	Virus (n=10)	p-value
Age <24 months, n (%)	44 (86.3)	8 (80.0)	>0.05†
Underlying conditions, n (%)	18 (35.3)	4 (40.0)	>0.05†
Incomplete vaccination, n (%)	30 (58.9)	2 (20.0)	<0.05†
History of pneumonia, n (%)	36 (70.6)	2 (20.0)	<0.005†
High fever, n (%)	21 (41.2)	1 (10.0)	<0.05†
Wheezing, n (%)	33 (64.7)	10 (100.0)	<0.05†
WBC (K/µL), median (min, max)	11.3 (8.3, 17.1)	11.9 (9.2, 16.4)	>0.05‡
ANC (K/µL), median (min, max)	6.3 (3.6, 10.8)	3.2 (1.5, 4.9)	<0.005‡
ALC (K/µL), median (min, max)	4.2 (2.8, 6.4)	6.4 (4.1, 8.8)	>0.05‡
NLR, median (min, max)	1.4 (0.9, 2.3)	0.5 (0.4, 0.7)	0.0002‡
CRP (mg/L), median (min, max)	10.2 (3.4, 31.4)	1.5 (1.0, 4.6)	0.01‡

CAP: Community-acquired pneumonia, WBC: White blood cell count, ANC: Absolute neutrophil count, ALC: Absolute lymphocyte count, NLR: Neutrophil-to-lymphocyte ratio, CRP: C-reactive protein, µL: Microliter, mg: Milligram, L: Liter, †Fisher's exact test, ‡Mann-Whitney U test

Table 2. AUROCs of basic inflammatory markers

Inflammatory markers	AUROC	95% confidence interval	p-value
CRP	0.74	0.58-0.9	0.01
ANC	0.79	0.65-0.93	0.0015
NLR	0.87	0.78-0.97	<0.0001

AUROC: Area under the receiver operating characteristic curve, ANC: Absolute neutrophil count, NLR: Neutrophil-to-lymphocyte ratio, CRP: C-reactive protein

Table 3. Optimal cut-offs and diagnostic metrics of inflammatory markers				
Inflammatory marker	**Sensitivity (%)**	**Specificity (%)**	**LR^+**	**LR^-**
CRP ≥ 7 (mg/L)	56.9	90	5.7	0.4
NLR ≥ 0.8	78.4	90	7.9	0.2
ANC ≥ 5.8 (K/µL)	60.5	90	6.1	0.4
CRP ≥ 7 (mg/L) + NLR ≥ 0.8 + high fever	55.5	93.3	8.8	0.2
CRP ≥ 7 (mg/L) + NLR ≥ 0.8 + history of pneumonia	57.3	94.4	8.5	0.3

LR^+: Positive likelihood ratio, LR^-: Negative likelihood ratio, CRP: C-reactive protein, NLR: Neutrophil-to-Lymphocyte ratio, ANC: Absolute neutrophil count, mg: Milligram, L: Liter, µL: Microliter

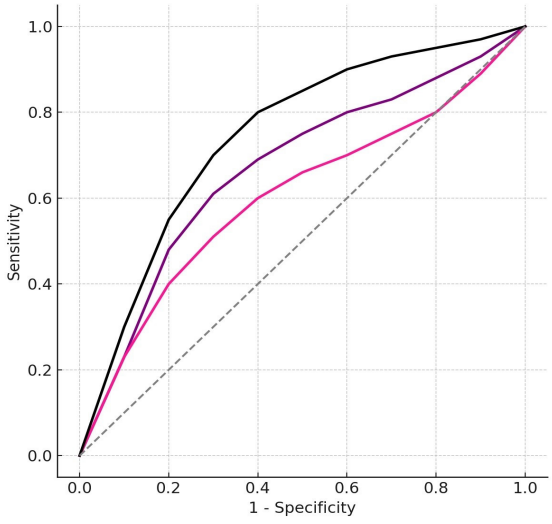

Figure 2. Receiver operating characteristic (ROC) curve of basic inflammatory
The neutrophil-to-lymphocyte ratio (NLR) (black) showed the highest discriminative performance (AUC = 0.8725), followed by neutrophils (purple; AUC = 0.7922) and C-reactive protein (CRP) (pink; AUC = 0.7412). The dashed diagonal line indicates no discrimination.

Discussion

This study highlights the microbial complexity in pediatric severe CAP, with a predominance of bacterial etiology confirmed by RT-PCR. Among the 61 children enrolled, 83.6% had bacterial pneumonia, reinforcing the high burden of bacterial pathogens. SP and HI were the most frequent organisms, consistent with global epidemiological data on pediatric CAP. (3,7). The frequent occurrence of SP–HI coinfections and the presence of triple-pathogen infections in 8 cases underscore the polymicrobial nature of BSCAP in children.

These findings align with previous reports suggesting that mono-infection is relatively uncommon in hospitalized pneumonia and that co-pathogen interactions may contribute to increased disease severity (3,8,9). The identification of multiple pathogens in the BSCAP emphasizes the need for diagnostic approaches capable of detecting co-infections, as treatment regimens may need to be adjusted accordingly, particularly in resource-limited settings where microbiological diagnostics are not routinely available. Moreover, the study highlights the value of molecular diagnostics such as RT-PCR in informing targeted treatment strategies.

A history of recurrent pneumonia is a notable risk factor for BSCAP in children. Although multiple microbial causes have been described, data on specific pathogens in recurrent cases remain limited. A 13-year study of 1,395 hospitalized children with severe CAP found bacterial pathogens in 70% of cases, suggesting that recurrent episodes may impair mucosal defenses and mucociliary clearance, facilitating chronic bacterial colonization and secondary infections (9). Clinically, high fever is more indicative of BSCAP, while wheezing is more typical of VSCAP. Studies have shown that bacterial pneumonia is often suspected in the absence of wheezing, whereas wheezing is a hallmark of viral infections. Moreover, high fever was significantly more common in bacterial cases, supporting the use of these symptoms to guide early etiological suspicion in severe pediatric CAP (9).

In many developing countries, accurately identifying the microbial etiology of pediatric pneumonia remains a significant challenge due to limited access to specific diagnostic tests (7). This often results in empirical antibiotic use, leading to inappropriate prescriptions and excessive use, thereby contributing to the growing problem of antimicrobial resistance. In this study, all children (100%) received antibiotic treatment prior to microbiological confirmation. The primary aim of our research was to evaluate the utility of accessible inflammatory biomarkers, namely CRP, ANC, and NLR, to differentiate between viral and bacterial severe CAP. These markers are readily available in primary care settings and resource-limited areas. Our findings indicate that children with BSCAP had significantly higher ANC, NLR, and CRP levels compared to those with viral pneumonia.

Neutrophils play a critical role in the early immune response to infection, particularly against bacterial pathogens (10,11). In our study, ANC was significantly higher in children with BSCAP (AUROC = 0.79; 95% CI: 0.65–0.93; p = 0.0015). This aligns with findings by Elemraid et al. (12), who reported higher neutrophil counts in bacterial compared to viral pneumonia, with an AUROC of 0.859 and a cut-off of 10,000 cells/mm³ yielding 88.1% specificity. Although our identified cut-off (5,800 cells/μL) was lower, it achieved a comparable specificity of 90%. This difference may reflect immunological dynamics in severe infections, such as enhanced tissue recruitment, toxin-induced bone marrow suppression, or immune modulation (13). Thus, while ANC is a useful diagnostic marker, lower thresholds may be more appropriate in severe CAP.

CRP, a liver-derived acute-phase reactant, is commonly used to assess systemic inflammation. CRP has been reported as an independent predictor of bacterial pneumonia (14). In this study, CRP demonstrated moderate diagnostic utility for BSCAP with an AUROC of 0.74 (95% CI: 0.58–0.90). A CRP cut-off of ≥ 7 mg/L yielded 56.9% sensitivity and 90% specificity (LR^+ 5.7; LR^- 0.4). Esposito et al. (15,16) reported varying CRP performance across studies, with mean CRP values ranging from 21.3–32.2 mg/L in bacterial cases and AUROCs between 0.58 and 0.63. While these studies confirm CRP's diagnostic relevance, an optimal threshold remains context-dependent. The lower cut-off observed in our cohort may reflect early-phase infections or immune dysregulation in severe cases, where pro-inflammatory signaling and hepatic CRP synthesis are suppressed (17). This suggests that lower CRP thresholds should be considered when evaluating children with severe pneumonia.

In recent years, the neutrophil-to-lymphocyte ratio (NLR), calculated from the absolute neutrophil and lymphocyte counts, has emerged as a promising biomarker for diagnosing bacterial infections such as sepsis and pneumonia. Previous studies reported AUROC values between 0.70 and 0.78, indicating moderate diagnostic accuracy, comparable to CRP and procalcitonin in emergency settings (18,19). In our study, NLR demonstrated the highest AUROC of 0.87 (95% CI: 0.78–0.97), with a cut-off value of ≥ 0.8 yielding a sensitivity of 78.4% and specificity of 90%. However, the difference between markers was not statistically significant ($p > 0.05$). In the early stages of severe pneumonia, particularly in rapidly progressing cases, NLR rises much earlier and is more sensitive than ANC and CRP levels (20). Lymphopenia and neutrophilia represent a physiological response to systemic inflammation, especially bacterial infections. Lymphopenia results from increased apoptosis, redistribution of lymphocytes into the reticuloendothelial system, and migration into lymphoid tissues. In contrast, neutrophilia occurs due to bone marrow stimulation by inflammatory cytokines. Therefore, NLR effectively integrates two opposing immune responses to systemic inflammation. Recent studies indicate that NLR has a stronger prognostic value than traditional inflammatory markers, including total leukocyte count, ANC, and CRP in CAP (9,21). However, a study published in Scientific Reports concluded that NLR alone is not a reliable marker for distinguishing bacterial from viral CAP (22). Thus, integrating clinical features and additional markers remains essential for improving diagnostic accuracy. A more accurate diagnostic approach involves combining NLR, lymphocyte-monocyte ratio (LMR), CRP levels, and clinical characteristics (23). According to Elemraid et al. (12), combining CRP, NLR, and ANC achieved an AUROC of 0.894, with 75.7% sensitivity and 89.4% specificity. Similarly, another study reported that adding clinical symptoms to CRP and NLR increased the AUROC to 0.897 (24). Research also shows that integrating serum amyloid A and CRP with clinical signs, such as wheezing or absence of fever, improves specificity but lowers sensitivity (14). These findings align with our study, where combining NLR and CRP with clinical features slightly increased specificity (93.3%–94.4%) at the cost of reduced sensitivity.

Study Limitations

This study has several limitations. First, the sample size was relatively small and limited to a single tertiary pediatric hospital, which may restrict the generalizability of the findings to other settings, particularly in rural or primary care contexts. Second, although RT-PCR was employed as the gold standard for etiological diagnosis, it may not fully distinguish between active infection and colonization, especially in cases of co-infection. Third, the exclusion of mixed bacterial-viral infections may limit insights into the full clinical spectrum of severe CAP in children. Fourth, inflammatory markers such as CRP, ANC, and NLR may be influenced by factors beyond infection, including underlying conditions or host immune responses, which were not fully accounted for in this study. Future studies should include larger, multicenter cohorts to enhance external validity. Incorporating quantitative viral and bacterial load data and additional biomarkers such as procalcitonin, serum amyloid A (SAA), and cytokine profiles may provide a more comprehensive understanding of host-pathogen interactions. Furthermore, machine learning models integrating clinical, laboratory, and imaging data

may improve diagnostic accuracy and support antibiotic stewardship, particularly in low-resource settings.

Conclusion

Basic inflammatory markers such as NLR, ANC, and CRP may offer valuable preliminary indications of severe bacterial pneumonia, particularly in resource-limited settings. However, due to their inherently modest sensitivity when used in isolation, relying solely on these markers may lead to diagnostic inaccuracies. Therefore, to enhance diagnostic precision, especially in distinguishing bacterial from viral etiologies, it is essential to incorporate a combination of clinical features, such as fever patterns or a history of recurrent infections, along with other complementary inflammatory biomarkers.

Ethics

Ethics Committee Approval: The study protocol was reviewed and approved by the Ethics Committee in Biomedical Research at Children's Hospital 1 (approval number: 425/GCN-BVND1, date: 17.11.2022).

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Footnotes

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

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Appendix 1-2 Link: https://d2v96fxpocvxx.cloudfront.net/37eae217-e8b5-4f55-976f-35df98003e83/content-images/e001bccd-38de-4200-83ba-8fa443cc6cd3.pdf

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Frequency of Vaccine Hesitancy and Its Determinants in Northeastern Türkiye: A Hospital-based Cross-sectional Study

Kuzeydoğu Türkiye'de Aşı Tereddütünün Sıklığı ve Belirleyicileri: Hastane Tabanlı Kesitsel Bir Araştırma

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Abstract

Introduction: The World Health Organization has recognized vaccine hesitancy as one of the top ten threats to global health. Consequently, it is imperative to investigate vaccine hesitancy both between and within countries. The aim of this study was to determine the prevalence of vaccine hesitancy among mothers of children aged five years and under in northeastern Turkey and to identify the factors associated with vaccine hesitancy.

Materials and Methods: This cross-sectional study was conducted with mothers presenting to the pediatric outpatient clinic of a public hospital. Maternal reluctance toward vaccination was evaluated using the Parents' Attitudes about Childhood Vaccines (PACV) scale. Data were analyzed by chi-square and logistic regression analysis.

Results: Of the participating mothers, 27.4% exhibited vaccine hesitancy. Independent predictors of vaccine hesitancy were having a male child, active use of social media, and the father's attainment of a university degree.

Conclusion: In this study, vaccine hesitancy was found to be considerably higher compared to other studies conducted in Turkey. Therefore, further research on vaccine hesitancy should be conducted at the national level, considering different communities and cultures, and local health policies should be developed to address the identified risk factors.

Keywords
Vaccine hesitancy, vaccine refusal, parents' attitudes about childhood vaccines scale, PACV, children under 5 years of age, Türkiye

Öz

Giriş: Dünya Sağlık Örgütü, aşı tereddütünü küresel sağlık için en büyük on tehditten biri olarak kabul etmiştir. Dolayısıyla, ülkeler arasında ve ülkeler içinde aşı tereddütünün araştırılması zorunludur. Bu çalışmanın amacı, Türkiye'nin kuzeydoğusunda beş yaş ve altı çocukların anneleri arasında aşı tereddütünün yaygınlığını belirlemek ve aşı tereddütüyle ilişkili faktörleri belirlemektir.

Gereç ve Yöntem: Bu kesitsel çalışma, bir kamu hastanesinin çocuk polikliniğine başvuran annelerle gerçekleştirildi. Annelerin aşıya karşı isteksizliği, Ebeveynlerin Çocukluk Çağı Aşılarına İlişkin Tutumları (PACV) ölçeği kullanılarak değerlendirildi. Veriler ki-kare ve lojistik regresyon analizi ile analiz edildi.

Bulgular: Katılımcı annelerin %27,4'ünde aşı tereddütü saptanmıştır. Aşı tereddütü ile anlamlı biçimde ilişkili bağımsız değişkenler; erkek çocuğa sahip olma, sosyal medyayı aktif kullanma ve babanın üniversite mezunu olması olarak belirlenmiştir.

Sonuç: Bu çalışmada, aşı tereddütünün Türkiye'de yapılan diğer çalışmalara kıyasla önemli ölçüde yüksek olduğu bulunmuştur. Bu nedenle, farklı toplumlar ve kültürler göz önünde bulundurularak ulusal düzeyde aşı tereddütü üzerine daha fazla araştırma yapılmalı ve belirlenen risk faktörlerini ele almak için yerel sağlık politikaları geliştirilmelidir.

Anahtar kelimeler
Aşı tereddütü, aşı reddi, ebeveynlerin çocukluk çağı aşılarına ilişkin tutumları ölçeği, 5 yaş altı çocuklar, Türkiye

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Introduction

Vaccines currently prevent more than 30 life-threatening diseases and infections, saving millions of lives annually and constituting a hallmark achievement in global public health (1). Childhood immunization programs, in particular, have driven substantial reductions in morbidity and mortality among children under five years of age (2). Nevertheless, the rising phenomenon of vaccine hesitancy—globally and regionally—now threatens to undermine these gains (3). Accordingly, the World Health Organization (WHO) has designated vaccine hesitancy as one of the ten greatest threats to global health.

WHO defines vaccine hesitancy as the reluctance or refusal to vaccinate despite the availability of vaccination services (4). As incidences of vaccine-preventable diseases decline, public confidence in the necessity and safety of vaccines has been increasingly questioned, leading some individuals to delay or completely forego recommended immunizations.

Vaccine hesitancy cannot be explained by a single cause; it stems from a multifaceted interplay of social, psychological, cultural, political, and personal factors. Vaccine hesitancy and related behaviors are further exacerbated by social media platforms (5). Social media platforms facilitate the rapid spread of misinformation, particularly among those with limited health literacy, leading to negative attitudes.

Given the significant contribution of vaccine hesitancy to declining vaccination rates, a comprehensive understanding of vaccine hesitancy is vital for developing strategies aimed at increasing childhood immunization rates (6). Therefore, the aim of this study was to determine the frequency of vaccine hesitancy among mothers of children aged 0–59 months old in Northeast Turkey and to identify causal factors related to vaccine hesitancy.

Materials and Methods

Study Setting: This study was conducted at the largest public hospital in northeastern Turkey, a region bordering Georgia, Armenia, the Nakhchivan Autonomous Republic (Azerbaijan), and Iran (7).

Economically, this area falls below the national average, and its health indicators rank lowest in Turkey. The number of healthcare personnel per 1,000 people is below the Turkish average. Both the infant mortality rate (11.2 per 1,000 live births) and maternal mortality rate (24.5 per 100,000 live births) are above the Turkish average. Additionally, the region has the lowest vaccination rates in Turkey (7).

Study Design: This research was designed as a cross-sectional observational study.

Study Population: The study population consisted of mothers of children aged 0–59 months who presented to the pediatric outpatient clinics of a public hospital in Northeastern Turkey. During the planning phase of the study, it was anticipated that data would be collected during the months of April, May, and June 2024. Therefore, the number of children aged 0–59 months who presented to the pediatric outpatient clinic in April, May, and June of the previous year (2023) was accepted as the study population. Accordingly, the population was determined as 1,813 eligible mother–child dyads.

Study Sample: The required sample size was calculated using the formula: $n = Nt^2\ p\ q/d^2\ (N - 1) + t^2\ p\ q$. Here, N is the number of individuals in the population, n is the number of individuals to be sampled, p is the prevalence (probability) of the event under investigation, q is the prevalence (probability) of the event not occurring; t is the theoretical value from the table at a specific degree of freedom and the determined margin of error, and d is the desired ± deviation relative to the prevalence of the event (8). Accordingly, with p = 0.50, q = 0.50, t = 1.96, and d = 0.05, the sample size was determined to be 317 individuals.

Dependent Variable: Vaccine hesitancy.

Independent Variables: Social and demographic characteristics related to the family, mother, and child.

Preparation of the Data Collection Form: The data collection form consisted of two main parts. The first part comprised questions regarding the sociodemographic characteristics of the child and family, and the second part consisted of the Parents' Attitudes Towards Childhood Vaccines Scale (PACV) questions. The PACV scale is a valid and reliable scale adapted for the Turkish population. Responses that indicate vaccine hesitancy are scored 2 points, responses that indicate non-hesitancy are scored 0 points, and responses indicating indecision are scored 1 point. The total scale score ranges from 0 to 30. For items with missing data, the total raw scores are recalculated using a simple linear calculation method to fit a scale ranging from 0 to 100 thus obtaining a transformed score. A transformed PACV score of <50 indicates no vaccine hesitancy, whereas a score ≥50 indicates vaccine hesitancy (9).

Pilot Study: Prior to data collection, the data collection form was tested on 6 mothers, and necessary corrections were made.

Ethical Considerations: Prior to the commencement of the study, ethical approval was obtained from the Clinical Research Ethics Committee of Kafkas University Faculty of Medicine with the (approval number: 80576354-050-99/556, date: 30.10.2024). All parents participating in the study were given detailed information about the purpose, scope, and confidentiality principles of the study, and written informed consent was obtained from those who agreed to participate voluntarily. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data Collection: Data were collected by a pediatrician during face-to-face interviews with mothers who brought their children to the pediatric outpatient clinic for examination and volunteered to participate in the study.

Exclusion Criteria: Mothers of children with contraindications to vaccination, and parents or caregivers other than the child's mother who brought the child to the hospital were not included in the study.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 20.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as frequencies and percentages. Chi-square tests were used for pairwise comparisons, and Backward Likelihood Ratio (LR) logistic regression analysis was performed to determine causal relationships. A p-value of <0.05 was considered statistically significant.

Results

In this study, the prevalence of maternal vaccine hesitancy was 27.4%.

In pairwise analyses, significant associations were observed between vaccine hesitancy and the following factors: child's gender (p = 0.007), following vaccine-related content on social media (p = 0.022), mother's education level (p = 0.036), father's education level (p = 0.007), mother's health insurance status (p = 0.035), and family income (p = 0.024) (Table 1).

Logistic regression analysis was performed to identify independent risk factors. Mothers of male children had 1.95-times higher odds (95% CI: 1.165–3.274), mothers who followed vaccine information on social media had 1.93-times higher odds (95% CI: 1.020–3.650), and those whose partners held a university degree had 1.75-times higher odds (95% CI: 1.034–2.956) of exhibiting vaccine hesitancy (Table 2).

Table 1. Effects of independent variables on the dependent variable (Northeastern Türkiye. 2024)

Independent variables		Vaccine hesitancy		Total	χ^2	P
		Yes	No			
		Number (%)*	Number (%)*	Number (%)**		
Place of residence	Urban	73 (29.8)	172 (70.2)	245 (77.3)	2.994	0.084
	Rural	14 (19.4)	58 (80.6)	72 (22.7)		
Number of children	Only child	57 (28.9)	140 (71.1)	197 (62.1)	0.580	0.446
	≥2 children	30 (25.0)	90 (75.0)	120 (37.9)		
Pregnancy order	First pregnancy	29 (32.2)	61 (67.8)	90 (28.4)	1.441	0.230
	Subsequent pregnancy	58 (25.6)	169 (74.4)	227 (71.6)		
Sex of the child	Male	54 (34.2)	104 (65.8)	158 (49.8)	7.170	0.007
	Female	33 (20.8)	126 (79.2)	159 (50.2)		
Social media use on vaccine content	Yes	21 (40.4)	31 (59.6)	52 (16.4)	5.231	0.022
	No	66 (24.9)	199 (75.1)	265 (83.6)		
Mother's parity	1	29 (31.9)	62 (68.1)	91 (28.7)	2.107	0.349
	2	29 (28.7)	72 (71.3)	101 (31.9)		
	3 and above	29 (23.2)	96 (76.8)	125 (39.4)		
Median age of mother	≤34 years	55 (28.5)	138 (71.5)	193 (60.9)	0.275	0.600
	≥35 years	32 (25.8)	92 (74.2)	124 (39.1)		
Mother's education	University graduate	41 (34.2)	79 (65.8)	120 (37.9)	4.382	0.036
	High school or lower	46 (23.4)	151 (76.6)	197 (62.1)		

Table 1. Continued						
Independent variables		Vaccine hesitancy		Total	χ^2	P
		Yes	No			
		Number (%)*	Number (%)*	Number (%)**		
Father's education	University graduate	43 (36.1)	76 (63.9)	119 (37.5)	7.225	0.007
	High school or lower	44 (22.2)	154 (77.8)	198 (62.5)		
Mother's employment status	Income generating	24 (28.2)	61 (71.8)	85 (26.8)	0.036	0.849
	Housewife	63 (27.2)	169 (72.8)	232 (73.2)		
Mother's health insurance status	SSI	82 (29.4)	197 (70.6)	279 (88.0)	4.426	0.035
	Green Card	5 (13.2)	33 (86.8)	38 (12.0)		
Father's employment status	Employed	80 (28.3)	203 (71.7)	283 (89.3)	0.899	0.343
	Unemployed	7 (20.6)	27 (79.4)	34 (10.7)		
Consanguineous marriage	Yes	16 (28.6)	40 (71.4)	56 (17.7)	0.043	0.835
	No	71 (27.2)	190 (72.8)	261 (82.3)		
Family type	Extended	26 (28.0)	67 (72.0)	93 (29.3)	0.017	0.895
	Nuclear	61 (27.2)	163 (72.8)	224 (70.7)		
Family income status	Income higher than expenses	26 (38.2)	42 (61.8)	68 (21.5)	5.062	0.024
	Income lower than expenses	61 (24.5)	188 (75.5)	249 (78.5)		
Primary decision-maker	Both parents	51 (28.7)	127 (71.3)	178 (56.2)	0.303	0.859
	Father	16 (26.2)	45 (73.8)	61 (19.2)		
	Mother	20 (25.6)	58 (74.4)	78 (24.6)		
Total		87 (27.4)	230 (72.6)	317 (100.0)		

*Row percentage, **Column percentage, SSI: Social Security Institution

Table 2. Results of logistic regression analysis (Northeastern Türkiye, 2024)							
Dependent variable: Vaccine hesitancy							
Independent variables		B	SE	Wald	P	Odds ratio	95% CI (min-max)
Sex of the child	Male	0.669	0.264	6.448	0.011	1.95	1.165-3.274
	Female					1	
Social media use on vaccines	Yes	0.657	0.325	4.079	0.043	1.93	1.020-3.650
	No					1	
Father's education	University graduate	0.559	0.268	4.344	0.037	1.75	1.034-2.956
	High school or lower					1	

Discussion

Numerous studies have quantitatively assessed parental attitudes and beliefs toward childhood vaccination in various countries. However, most studies did not employ a validated questionnaire. Furthermore, there were substantial differences in how questionnaires were developed and which items were included; creating challenges in comparing the findings (10).

In the present study, the frequency of vaccine hesitancy was 27.4%. Prevalence rates for pediatric vaccine hesitancy using the PACV scale are reported to range between 5.0% and 30.0% (10). For example, prevalence of vaccine hesitancy was 24.6% among mothers of preschoolers in Italy (11), 27.9% among mothers of 0–59-month-old children in Pakistan (12), 25.9% among a similar cohort in Cameroon (13), and 15.0% among mothers of neonates in Canada (14). In Turkey, the prevalence of vaccine hesitancy was reported as 9.4% and 13.0% in two studies conducted with mothers of preschool children (5,15), 13.8% in a study conducted with pregnant women (16), and 22.5% in a study conducted with mothers

of children aged 2–6 years (17). These findings underscore substantial heterogeneity in vaccine hesitancy both between and within countries, likely driven by local cultural norms, regional socioeconomic development, and social factors.

In our multivariable model, mothers of male children had 1.95-times greater odds of exhibiting vaccine hesitancy compared to mothers of females (95% CI: 1.16–3.27). Patriarchal family structure is dominant in the region where the present study was conducted. In the patriarchal family, a woman can only consolidate her position if she gives birth to a son. Therefore, in patriarchal families, different meanings are attached to boys and girls. A male child is seen as the continuation of the lineage and the family's security in old age. In such families, the woman's status is strengthened by bearing a male child, and by giving birth to a son, the woman gains prestige in society (18). In the literature, the misconception that vaccines "cause infertility in males" is prevalent both in Turkey (19,20) and in other countries (21,22). Consequently, it can be argued that parents hesitate to vaccinate their male children to shield them from the perceived risk of infertility.

Mothers who followed anti-vaccine content on social media had 1.93-times higher odds of exhibiting vaccine hesitancy compared with those who did not (95% CI: 1.02–3.65). Social media refers to interactive communication platforms where users search, utilize, and produce content online; in other words, it enables media communication transitioning from one-way content sharing to bidirectional content exchange (e.g., applications such as Weibo, Twitter, Facebook, Instagram, LinkedIn, and Pinterest) (23-25). An "infodemic" occurs when an overabundance of information—including false or misleading content—spreads across digital and physical environments during an outbreak, leading to public confusion and risky health behaviors (26). One study estimated that the proportion of health-related misinformation on social media ranged from 0.2 % to 28.8 % (27). In a study conducted during the COVID-19 pandemic, parents who used social media as a source of vaccine information reported 5.3-times greater hesitancy toward childhood immunizations than those who did not (28). In a study conducted in Turkey, vaccine hesitancy was three times more prevalent among parents following anti-vaccine groups on social media compared with non-followers (16). Another Turkish study likewise found a significant association between social media use and vaccine hesitancy in a bivariate analysis (15). Overall, studies consistently link social media-driven disinformation campaigns with declines in average vaccination coverage (29).

When mothers whose spouses had lower educational attainment were used as the reference group, those whose partners held a university degree demonstrated 1.75-times higher odds of exhibiting vaccine hesitancy (95% CI: 1.03–2.96). A previous study on COVID-19 vaccine acceptance has reported higher hesitancy among men than women (30). However, the relationship between education level and vaccine acceptance in the literature remains ambiguous. Multiple studies indicate that parents with less formal education tend to have lower trust in the medical community, express greater concerns about vaccine safety, and exhibit lower belief in the necessity and efficacy of vaccines (31). In contrast, other literature has determined that higher education fosters a more critical perspective leading to comprehensive questioning of vaccines, noting that individuals with higher education levels are approximately four-times more likely to worry about vaccine safety compared to those with lower education (32). Thus, it can be concluded that only education level may be acting as a confounder in the overall decision-making process regarding immunization.

Study Limitations

A key strength of this study is the use of the validated PACV scale. Furthermore, this is the first study conducted in this region using the PACV scale.

However, there are certain limitations of the study. Because of the hospital-centered design, caution is warranted when generalizing findings to the broader community. Another limitation is the cross-sectional nature of the data, representing only a specific time interval.

Conclusion

In this study, vaccine hesitancy was considerably higher compared to other research conducted in Turkey. Independent risk factors included having a male child, following vaccine-related content on social media, and having a spouse with university-level education.

Recommendations

Efforts to combat negative vaccine-related information on social media should be intensified both globally and nationally. Additionally, research on vaccine hesitancy targeting diverse populations and cultures should be conducted at the national level, and local health policies addressing identified risk factors should be developed. Crucially, these policies should include enhancing healthcare workers' awareness of vaccine hesitancy issues and expanding their capacity to provide personalized counseling to parents.

Ethics

Ethical Approval: Ethical approval was obtained from the Clinical Research Ethics Committee of Kafkas University Faculty of Medicine with the (approval number: 80576354-050-99/556, date: 30.10.2024).

Footnotes

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

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Multisegmental Tissue Doppler Imaging and Biochemical Indicators in Thalassemia Major

Talasemi Majorda Çok Segmentli Doku Doppler ve Biyokimyasal Göstergeler

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Abstract

Introduction: Since heart failure is among the most important mortality reasons among Thalassemia Major patients, these patients must be regularly checked for heart problems.
Our study was planned to compare pulse wave doppler images and segmental tissue doppler images from 8 different areas and their copeptin, NT-pro ANP, NT-proBNP, CK-MB, and ultra-sensitive troponin I value with those of healthy individuals.
Materials and Methods: Fifty-nine Thalassemia Major patients over the age of 10, who were asymptomatic concerning cardiac symptoms, were divided into two groups (Group 1T2*<20 msn and Group 2: >20 msn). Echocardiography data and biochemical parameters of patient groups were compared with the control group.
Results: In both patient groups, NT-proBNP values were found to be significantly higher compared to the control group ($p<0.001$), and no correlation was found between NT-proBNP and cardiac MRI. In tissue doppler imaging of lateral and medial sections of the mitral annulus, it was seen that IVCT and IVRT measurements of both patient groups were extended and Myocardial Performance Index (MPI) measurements were increased. E´, A´, and S measurements of Group 1 were found to be lower compared to the control group. There were no significant differences between the groups in terms of copeptin, NT-proANP, CK-MB, and US-Troponin I values.
Conclusion: Investigated biochemical indicators could not be strongly correlated with iron accumulation. By calculating MPI values with tissue doppler echocardiography, global cardiac dysfunction may be identified earlier and chelation therapy may be revised.

Keywords
Thalassemia, tissue Doppler imaging, T2* MRI

Anahtar kelimeler
Talasemi, doku doppler görüntüleme, T2* MRI

Öz

Giriş: Talasemi Majör hastalarında kalp yetmezliği en önemli ölüm nedenlerinden biri olduğundan, bu hastaların düzenli olarak kalp sorunları açısından kontrol edilmesi gerekmektedir.
Çalışmamızda, Talasemi Majör hastalarında 8 farklı bölgeden alınan nabız dalga doppler görüntüleri ve segmental doku doppler görüntülerinin yanı sıra copeptin, NT-pro ANP, NT-proBNP, CK-MB ve ultra-duyarlı troponin I değerlerinin sağlıklı bireylerle karşılaştırılması planlandı.
Gereç ve Yöntem: Kalp ile ilgili semptomları bulunmayan, 10 yaş üzeri 59 Talasemi Majör hastası iki gruba ayrıldı (Grup 1: T2*<20 msn ve Grup 2: T2*>20 msn). Hasta gruplarının ekokardiyografi verileri ve biyokimyasal parametreleri kontrol grubu ile karşılaştırıldı.

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Bulgular: Her iki hasta grubunda NT-proBNP değerleri kontrol grubuna göre anlamlı derecede yüksek bulundu (p<0,001) ve NT-proBNP ile kardiyak MRG arasında ilişki bulunmadı. Mitral anülüsün lateral ve medial kesimlerine ait doku doppler görüntülerinde her iki hasta grubunda da IVCT ve IVRT ölçümlerinin uzadığı ve Miyokardiyal performans indeksi (MPI) ölçümlerinin arttığı görüldü. Grup 1'in E´, A´ ve S ölçümleri kontrol grubuna göre daha düşük bulundu. Copeptin, NT-proANP, CK-MB ve ultra-duyarlı Troponin I değerleri açısından gruplar arasında anlamlı bir fark saptanmadı.
Sonuç: İncelenen biyokimyasal göstergeler demir birikimi ile güçlü bir şekilde ilişkilendirilemedi. Ancak doku doppler ekokardiyografi ile MPI değerleri hesaplanarak, bütünsel kardiyak fonksiyon bozukluğu daha erken tespit edilebilir ve şelasyon tedavisi yeniden düzenlenebilir.

Introduction

Beta-thalassemia major is a hereditary blood disorder, resulting in severe anemia as a result of anomalies in the beta chain of hemoglobin. In β-thalassemia patients, severe anemia develops progressively, starting from the first few months of extrauterine life. These patients require regular blood transfusions to treat severe anemia, which develops as a result of ineffective erythropoiesis, and to improve survival (1-4). Regular blood transfusions impose a significant iron burden on the organism, in particular on the heart and endocrine organs (5-9). Although iron chelators are used today to prevent iron burden, and to shape the treatment, regular monitoring of the body iron burden is necessary. Body iron burden alone is not sufficient in the determination of treatment, and monitorization of cardiac iron burden, which is directly related to long-term survival (10,11). The technique, considered the gold standard for monitoring cardiac iron burden, is cardiac T_2* Magnetic Resonance Imaging (T_2* MRI) (2). However, the unavailability of the T_2* MRI application in all healthcare institutions and its restricted use when available, the requirement of an appointment for MRI scans, potential problems, caused by the software program, and the patients' fear of MRI scans, suggest that it would be appropriate to use novel and reliable methods, which are easy to implement in clinical monitorization of patients.

Ferritin has been used for long years as a marker for monitoring iron accumulation in thalassemia patients and adjustment of iron chelation treatment doses. However, ferritin levels may be elevated in many conditions, such as inflammation, liver, and kidney disorders (12,13). In addition, there are studies, showing that ferritin levels are not associated with cardiac iron accumulation (14). Many studies have been conducted to determine whether various cardiac biomarkers were correlated with ferritin and whether they could be considered as an indicator in the demonstration of cardiac iron accumulation (15,16). Cardiac biomarkers include troponin, Creatinine Kinase MB (CK-MB), natriuretic peptides (N-terminal atrial natriuretic peptide (NT-ANP) and N-terminal brain natriuretic peptide (NT-BNP) and recently, copeptin. Copeptin molecule, a precursor peptide to arginine vasopressin (AVP), whose excretion is thought to be triggered by endogenous stress mechanisms, has been studied in non-thalassemia populations for various indications, in particular acute myocardial infarct and heart failure (17-19).

The objective of this study is to compare pulse wave (PW) Doppler images and segmental tissue Doppler (TD) images from 8 different areas and their NT-proANP, NT-proBNP, CK-MB, ultra-sensitive troponin I, and copeptin value of beta-thalassemia (ß-Thal) patients, who were grouped according to cardiac iron accumulation, with those of healthy individuals.

Materials and Methods

Before the study, approval was obtained from Akdeniz University Faculty of Medicine, Clinical Studies Ethics Committee. Informed consent was obtained from the persons in patient and control groups, who were over the age of 18, and from parents of persons, who were under the age of 18.

Patient and Control Group

63 ß-Thal patients, over the age of 10, who had been regularly monitored by Akdeniz University, Faculty of Medicine, Department of Pediatric Hematology, and as the control group, 29 healthy individuals with matching ages and genders, were included in the study. 4 patients in the ß-Thal group were excluded due to the absence of recent (within the last 6 months) T_2* MRI results. 5 persons in the control group were excluded from the study due to anemia, discovered during the study (hemoglobin <12 g/dL).

Cardiac MRI results of patients within the last six months were accessed via hospital electronic system records and MRI scans of all patients were made using a 1.5-Tesla (Siemens Magnetom Avanto) device. Patients were divided into two groups based on their T_2* MRI results:

Group 1: T_2* MRI < 20 msn n=26

Group 2: T_2* MRI ≥ 20 msn n=33

Age, gender, height, weight measurements, and last exercise dates of 59 ß-Thal patients and 24 control group individuals were recorded. After at least 10 minutes of rest and after confirmation that they had not consumed tobacco, alcohol, tea, and coffee within the last 2 hours and they had not made intensive exercise for the last 6 hours, blood pressure measurements were taken. Then, the blood samples of participants were taken to three separate tubes (with EDTA, heparin, and plain serum tube). After the acquisition of blood samples, while complete blood counts were studied on the same day, serum (for CK-MB, us-TrI, and NT-proBNP) and plasma (for NT-proANP, copeptin) were separated and stored at -80°C.

Measurement of Biochemical Parameters

Hemograms were studied using Advia 120 device and US-Troponin I, CK-MB, and NT-proBNP were measured using Siemens Centaur XP and Immulite 2000 devices. Copeptin and NT-proANP concentrations were determined via Sandwich enzyme-linked immunosorbent assay (20) method, using commercial kits (Copeptin: Cat. No: MBS2600645 and NT-proANP: Cat. No: MBS2023123) in line with kit protocols.

Echocardiographic Evaluation

Conventional and Tissue Doppler ECHO images of participants were obtained using 3 MHz probes of Vivid 7 Pro, Horten, Norway, device, with the patient lying on the left side. In conventional ECHO, regional contractile anomalies, systolic and diastolic diameters, volumes, ejection fraction, fractional shortening, and diameters of cardiac cavities were evaluated. Left ventricle (LV) diastolic functions were measured via transmitral pulse wave (PW) Doppler velocity records at the apical four-chamber position. Systolic and diastolic functions were recorded three consecutive times and the mean values for the same were recorded.

In TD ECHO, measurements of periods, required for MPI of both ventricles, were made using Pulse Wave Tissue Doppler (PWTD) mode. For this, recordings were obtained from a total of eight regions, with prompt on lateral and medial segments at the mitral valve level, lateral and medial at the tricuspid valve level, medial and basal at the intraventricular septum level, and LV and right ventricle (RV) lateral wall segment. In the records, measurements for wave and time intervals were taken separately. MPIs were calculated according to guidelines (20).

Statistical Analysis

Analyses were made using SPSS 22.0 package program. Descriptive statistics were presented using frequency, percentage, mean, standard deviation, and median, minimum, and maximum values. p values, less than 0.05 were deemed as statistically significant. In the analysis of relationships between categorical variables, Fisher's Exact Test or Pearson chi-Square test was used. In the normality test, when the number of samples in the group was less than 50, the Shapiro-Wilks test and when the number of samples was greater than 50, the Kolmogorov-Smirnov test was used. In the analysis of the difference between the measured values of the two groups, the Mann-Whitney U test was used when the normal distribution assumption could not be satisfied. In non-parametric comparison of the three groups Kruskal-Wallis test and for significant cases, Bonferroni-Dunn test was used as a post-hoc test. When the normal distribution assumption is satisfied, the ANOVA test was used in the comparison of three groups and the Tukey test was used in dual comparisons. The relationships between continuous variables, which are inconsistent with ordinal or normal distribution, were studied with the Spearman correlation test, and the Pearson correlation test was applied for those, which are consistent with normal distribution.

Results

In this study, while no significant difference was seen between the mean age of the control group and the patient group, it was determined that the mean age of Group 1 was higher compared to Group 2. No difference was seen between the groups in terms of gender, body mass index (BMI), height, and weight. Hemoglobin values were found to be higher in the control group, compared to the patient group ($p<0.001$). NT-proBNP values were found to be higher in both patient groups, compared to the control group ($p<0.001$). No significant differences were seen between the groups concerning CK-MB, NT-proANP, and copeptin values (Table 1). Concerning US-Troponin, I value, only two patients had above-normal values. T_2* MRI result of one of these patients was 41.47 and the other patient's value was 10.23 and they had no active cardiac complaints. US-Troponin I values of the control group were measured in the normal range. Therefore, they were not included in the comparison.

No significant differences were found between the groups in terms of mean values for all conventional ECHO parameters (Table 2). As a result of the evaluation of TD measurements from the medial and lateral sides of the mitral valve, it was

Table 1. Clinical and biochemical parameters of the cases						
Variables	**Group 1 n=26**	**Group 2 n=33**	**Control n=24**	**P1**	**P2**	**P3**
Gender	17F/9M	15F/18M	9F/15M	NS	NS	NS
Age median (min-max) year	24.6 (13.5-41.9)	18 (10.5-36.9)	22.2 (15.6-33)	0.009	NS	NS
Height (cm) mean ± SD	156.9±8.8	160.1±12.8	-	NS	-	-
Body Weight (kg) mean ± SD	49.6±8.8	54.8±14.2	-	NS	-	-
BMI (kg/m²) mean ± SD	20.1±2.5	21±3.3	-	NS	-	-
Hemoglobin g/dL mean ± SD	10.2±1.5	9.6±0.6	14.1±1.2	NS	<0.001	<0.001
Nt-ProBNP pg/mL mean ± SD	136.6±140.3	163.5±213.2	36.1±33.5	NS	<0.001	<0.001
CK-MB ng/mL mean ± SD	1.7±3.8	0.9±0.5	0.9±1.7	NS	NS	NS
Nt-ProANP pg/mL mean ± SD	211.3±162.9	167.8±122.9	110.1±48.4	NS	NS	NS
Copeptin pg/mL mean ± SD	23.9±17.3	30.9±25.9	33.3±14.7	NS	NS	NS
P1.Group 1 versus Group 2; P2. Grup 1 versus Control; P3. Grup 2 versus Control; NS. Non-significiant						

Table 2. Conventional echocardiographic parameters				
Variables mean ± SD	**Group 1 n=26**	**Group 2 n=33**	**Control n=24**	**P1,P2, P3**
AO (mm)	23.8±4.3	21.5±4.8	26.9±2	NS
LA (mm)	33.6±5.2	31±6.5	33.1±3.3	NS
AO/LA	0.7±0.1	0.7±0.2	0.8±0.1	NS
IVSD (mm)	9.4±2.2	9.8±2.3	8.8±1.4	NS
LVEDD (mm)	46.1±8.7	48.1±5.4	46.4±4.2	NS
LVPWD (mm)	9.1±1.5	8.2±2.2	8.8±1.6	NS
IVSS (mm)	13.4±3.0	13.1±2.2	12.1±2.0	NS
LVS (mm)	30.1±5.4	29.0±4.4	29.8±4.2	NS
LVPWS (mm)	12.9±2.8	11.8±2.6	12.3±2.2	NS
EF (%)	64.9±10.3	70±6.2	66.3±6.0	NS
FS (%)	36.4±8.1	39.9±5.3	36.6±4.7	NS
PVMAX (m/s)	1.1±0.1	1.1±0.2	1.1±0.1	NS
ME (m/s)	1±0.2	1±0.2	0.9±0.1	NS
MA (m/s)	0.5±0.2	0.6±0.1	0.6±0.1	NS
ME/MA	1.9±0.5	1.7±0.5	1.6±0.5	NS
TE (m/s)	0.6±0.2	0.7±0.1	0.6±0.1	NS
TA (m/s)	0.5±0.1	0.5±0.1	0.4±0.1	NS
TE/TA	1.2±0.4	1.3±0.5	1.2±0.4	NS

found that E, A, and S wave values in Group 1 were lower compared to those in the control group for both medial and lateral measurements of the mitral valve (p<0.05). In both patient groups, prolongations were seen in Interventricular Contraction Time (IVCT) and Interventricular Relaxation Time (IVRT) values in both medial and lateral measurements and an increase in MPI (p<0.05). E/E´ value, calculated with a measurement of the lateral annulus, was found to be higher in Group 1, compared to both Group 2 and the control group (p=0.001 and p<0.001); there were no significant differences in medial mitral annulus measurements (Table 3).

In Table 4, TD samples, obtained from the medial and lateral sides of the tricuspid valve, are evaluated. IVCT values, measured in both areas, were found to be prolonged in patient groups, compared to the control group (p=0.001 and p<0.001). Similarly, an increase was seen in MPI (p<0.01).

In TD ECHO scans, the E value, included in interventricular septum median (IVSM) parameters, was found to be lower in Group 1 compared to the other two groups (p=0.001). IVSM A value was found to be lower in both patient groups compared to the control group (p<0.001 with Group 1; p=0.001 with Group 2). IVSM S value of Group 1 was found to be lower compared to those of the other two groups (p=0.001 with Group 2; p<0.001 with Group 1). IVSM E/A rates of the patient groups were found to be higher compared to those of the control group (p<0.05). IVSM IVCT values of the patient groups were found to be higher compared to those of the control group (p<0.05). Concerning IVSM IVRT values, a prolongation was observed only in Group 1 compared to the control group (p=0.001). IVSM MPI values of patient groups were found to be significantly higher compared to those of the control group (p<0.05). Interventricular septum basal (IVSB) A value was found to be lower in patient groups compared to the control group (p<0.05). IVSB IVCT times of patient groups were found to be longer compared to those of the control group (p<0.001). IVSB IVRT times of patient groups were found to be longer compared to those of the control group (p<0.05). IVSB MPI values of patient groups

Table 3. Tissue Doppler measurements taken from the medial and lateral area of the mitral valve						
MM mean± SD	**Group 1 n=26**	**Group 2 n=33**	**Control n=24**	**P1**	**P2**	**P3**
E	9.9±2.3	13.8±4	12.2±2.1	<0.001	0.004	NS
A	6.8±2.7	8.9±2.1	9.3±1.6	0.009	0.001	NS
S	7.1±1.7	8.7±1.4	8.9±1.0	0.001	<0.001	NS
E/A	1.6±0.6	1.7±0.7	1.4±0.3	NS	NS	NS
IVCT	66.8±13.0	70.9±15.1	53.9±8.2	NS	0.002	<0.001
IVRT	72.7±14.3	74.6±10.8	61.2±6.2	NS	0.005	<0.001
ET	270.1±23.4	274.3±26.1	279.0±29.1	NS	NS	NS
MPI	0.5±0.5	0.6±0.5	0.4±0.2	NS	0.004	<0.001
E/E'	1.1±0.2	1±0.4	1±0.2	NS	NS	NS
ML mean ± SD	Group 1 n=26	Group 2 n=33	Control n=24	P1	P2	P3
E	12.6±4.7	17.9±4.4	16.6±3.0	<0.001	0.003	NS
A	7.1±3.8	7.7±2.3	10±1.7	NS	<0.001	0.007
S	8.8±2.9	10.6±2.2	10.7±1.9	0.044	0.046	NS
E/A	2.3±1.0	2.5±0.9	1.7±0.4	NS	NS	<0.001
IVCT	67.0±12.7	65.5±14.7	54.5±7.5	NS	0.001	0.007
IVRT	68.7±11.1	69.2±12.6	60.9±9.8	NS	0.047	0.028
ET	271.8±27.5	276.5±26.3	282.1±30.7	NS	NS	NS
MPI	0.5±0.1	0.5±0.1	0.4±0.1	NS	<0.001	0.001
E/E'	0.9±0.3	0.6±0.3	0.6±0.1	0.001	<0.001	NS

P1: Group 1 vs. Group 2; P2: Grup 1 vs. Control; P3: Grup 2 vs. Control; NS: Non-significant. Units of time-related parameters (IVCT, IVRT, ET) were measured in milliseconds; waves (E, A, S) were measured in meters/second

were found to be significantly higher compared to those of the control group ($p<0.001$). In ET values, no significant differences were seen between the groups both in IVSM and IVSB measurements (Table 5).

In the measurement, conducted on the left ventricle lateral (LVL) wall, A and S wave averages in Group 1 were found to be lower compared to those in the control group ($p<0.05$). No significant difference was found between the groups concerning LVL ET mean values. Right ventricular lateral (RVL) IVCT mean values were found to be prolonged in the patient group, compared to in the control group ($p<0.05$). In records, obtained from RVL, Group 1 IVRT value was found to be prolonged compared to the control group ($p<0.05$). No differences were found between groups concerning mean RVL E, RVL A, RVL S, RVL E/A, and RVL ET values (Table 6).

No significant correlation was found between cardiac T_2* MRI results of the patient group and TD echo results with biochemical indicators. A correlation, albeit weak, was determined only between NT-proBNP, among biochemical indicators of patients in Group 1, with MRI results ($p=0.027$, $r=-0.442$).

Discussion

The toxic effects of iron accumulation in the heart are one of the most significant causes of mortality and morbidity in thalassemia. Therefore, direct and indirect monitoring of the effects of cardiac iron is required at regular intervals. While cardiac iron may be directly imaged using MRI, whether this iron has caused a loss of function in the heart may only be understood (indirectly) using ECHO, electrocardiogram, etc., methods (21). However, no biochemical markers, showing the cardiac-specific iron burden have been discovered until today.

Evaluation of Biochemical Parameters

When NT-proANP, NT-proBNP, CK-MB, and copeptin are considered in patient and control groups, only NT-proBNP was found to be higher in the patient group, compared to the control. In line with the literature, in recent studies, it has been shown that NT-proBNP was elevated compared to controls, in ß-Thal patients, who had no clinical symptoms of heart failure (22-26). Among these studies, in the study by Kremastinos et al. (22,23) latent cardiac diastolic dysfunction

Table 4. Tissue Doppler measurements taken from the medial and lateral area of the tricuspid valve						
TM mean± SD	**Group 1 n=26**	**Group 2 n=33**	**Control n=24**	**P1**	**P2**	**P3**
E	12.2±2.8	13.6±3.2	12.3±2.1	NS	NS	NS
A	7.6±3.1	9.8±4.0	9.4±1.6	NS	NS	NS
S	9.3±1.8	10.2±1.9	9±1.1	NS	NS	NS
E/A	1.8±0.6	1.6±0.7	1.3±0.3	NS	NS	NS
IVCT	74.4±11.8	69.8±12.6	54.2±8.6	NS	<0.001	0.001
IVRT	69.8±13.7	73.3±13.2	61.2±6.2	NS	NS	0.003
ET	268.3±28.6	277.4±28.6	280.5±28.2	NS	NS	NS
MPI	0.5±0.1	0.5±0.1	0.4±0.1	NS	0.002	0.001
E/E'	0.5±0.1	0.6±0.3	0.5±0.1	NS	NS	0.031
TL mean ± SD	**Group 1 n=26**	**Group 2 n=33**	**Control n=24**	**P1**	**P2**	**P3**
E	13±3.7	15.6±3.1	14±2.0	0.001	NS	NS
A	13.3±4.3	14.3±4.6	12.0±2.7	NS	NS	NS
S	13.5±3.3	15.0±2.5	13.3±1.9	NS	NS	0.022
E/A	1±0.3	1.2±0.4	1.2±0.3	NS	NS	NS
IVCT	68.2±13.3	68.1±11.3	54.7±10.2	NS	<0.001	<0.001
IVRT	73.2±11.0	69.3±14.8	63.4±7.5	NS	0.002	NS
ET	282.7±31.2	269.1±27.5	277.3±23.4	NS	NS	NS
MPI	0.5±0.1	0.5±0.1	0.4±0.1	NS	<0.001	0.001
E/E'	0.5±0.1	0.5±0.2	0.4±0.1	NS	NS	NS

P1: Group 1 vs. Group 2; P2: Grup 1 vs. Control; P3: Grup 2 vs. Control; NS: Non-significant. Units of time-related parameters (IVCT, IVRT, ET) were measured in milliseconds, waves (E, A, S) were measured in meters/second.

Table 5. Tissue doppler measurements, taken from basal and median interventricular septum						
IVSb mean± SD	**Group 1 n=26**	**Group 2 n=33**	**Control n=24**	**P1**	**P2**	**P3**
E	10.3±2.8	13.2±2.8	12.2±2.1	0.003	NS	NS
A	6.8±2.2	8±2.4	9.3±1.6	NS	0.003	0.037
S	7.7±1.3	9.6±1.4	8.9±1.0	0.001	0.053	NS
E/A	1.7±0.6	1.8±0.6	1.4±0.3	NS	NS	0.017
IVCT	72.7±12.9	67.3±10.0	53.9±8.2	NS	<0.001	<0.001
IVRT	74±10.4	71.9±11.5	61.2±6.2	NS	0.002	0.002
ET	263.9±26.8	272.1±24.1	279.0±29.1	NS	NS	NS
MPI	0.6±0.1	0.5±0.1	0.4±0.1	NS	NS	NS
IVSm mean ± SD	**Group 1 n=26**	**Group 2 n=33**	**Control n=24**	**P1**	**P2**	**P3**
E	9.5±1.9	11.9±2.6	12.2±2.4	0.001	0.001	NS
A	5.2±1.8	6.5±1.6	8.2±1.2	NS	<0.001	0.001
S	5.8±1.1	7.3±1.1	7.9±0.9	0.001	<0.001	NS
E/A	2±0.7	2±0.8	1.5±0.4	NS	0.009	0.014
IVCT	67.9±11.2	70±11.5	57.0±9.9	NS	0.002	<0.001
IVRT	79±11.2	73.5±13.5	66.7±10.2	NS	0.001	NS
ET	272.2±27.3	274.5±27.1	274.2±26.1	NS	NS	NS
MPI	0.55±0.10	0.53±0.09	0.45±0.07	NS	0.001	0.011

P1: Group 1 vs. Group 2; P2: Grup 1 vs. Control; P3: Grup 2 vs. Control; NS: Non-significant. Units of time-related parameters (IVCT, IVRT, ET) were measured in milliseconds; waves (E, A, S) were measured in meters/second.

Table 6. Tissue Doppler measurements taken from the right and left lateral ventricle wall						
LVL Mean ± SD	**Group 1 n=26**	**Group 2 n=33**	**Control n=24**	**P1**	**P2**	**P3**
E	11.6±4.0	16.8±4.8	14±3.2	<0.001	NS	0.044
A	6.5±3.1	7.6±2.3	8.3±1.7	NS	0.015	NS
S	7.4±2.7	9.5±2.9	9.3±2.3	0.022	0.038	NS
E/A	2.3±1.3	2.5±1.1	1.8±0.5	NS	NS	0.015
IVCT	60.1±14	65.2±10.1	52.7±8.4	NS	NS	<0.001
IVRT	70.8±12.6	72.4±9.2	64.3±11.1	NS	NS	0.020
ET	274.1±33.6	277.2±23.7	276.4±29.9	NS	NS	NS
MPI	0.5±0.1	0.5±0.1	0.4±0.1	NS	NS	0.001
RVL mean ± SD	**Group 1 n=26**	**Group 2 n=33**	**Control n=24**	P1	P2	P3
E	13±3.0	14.4±3.7	14.6±2.5	NS	NS	NS
A	12.3±4.5	13.1±3.8	13.3±3.1	NS	NS	NS
S	12.0±2.5	13.2±2.7	12.9±2.1	NS	NS	NS
E/A	1.2±0.7	1.2±0.4	1.2±0.4	NS	NS	NS
IVCT	69.1±11.9	69.8±11.7	60.7±12.3	NS	0.042	0.022
IVRT	73.3±12.7	68.9±13.5	65.0±9.3	NS	0.022	NS
ET	282.8±31.3	267.0±25.1	279.4±27.4	NS	NS	NS
MPI	0.5±0.1	0.5±0.1	0.5±0.1	NS	NS	0.032

P1: Group 1 vs. Group 2; P2: Grup 1 vs. Control; P3: Grup 2 vs. Control; NS: Non-significant. Units of time-related parameters (IVCT, IVRT, ET) were measured in milliseconds; waves (E, A, S) were measured in meters/second

parameters and NT-proBNP are in correlation, and in the study by Tschöpe et al. (24), and Akpınar et al. (25), diastolic parameters were not correlated with NT-proBNP, yet an elevation in NT-proBNP without correlation, has been detected.

Delaporta et al. (27), divided 187 asymptomatic ß-Thal patients into MRI groups as in our study and calculated dry iron weights and consequently found a significant difference between groups in terms of NT-proBNP values. In our study, although this value was higher in patients compared to in the control group, no inter-group differences were seen in patient groups. Kostopoulou et al. (28), in a study, conducted on 90 asymptomatic ß-Thal patients, have divided the groups based on E/E´ values (diastolic dysfunction classification) and have evaluated proANP and NT-proBNP levels and shown that these parameters were early indicators of cardiac effects and it has been stated that the levels increased in case of presence of cardiac dysfunction. In our study, no significant inter-group difference was seen concerning NT-proANP. It was contemplated that the reason for the high measurement of natriuretic peptide NT-proBNP in the patient group and failure of NT-proANP to obtain a significant increase in patient groups, was the possibility of an influence on secretion by secondary reasons (such as volume burden, chronic anemia, asymptomatic patient distribution), rather than effects of cardiac iron accumulation on NT-proANP.

The lack of an inter-group significant difference concerning copeptin, suggests that this molecular structure could be elevated more in acute cases, rather than chronic cardiac failure (17). The reason for asymptomatic patient distribution suggests that copeptin release was not sufficient because asymptomatic patients constituted the majority of the study population.

Evaluation of Tissue Doppler ECHO Parameters

PWTD, among ECHO techniques, is a novel technique compared to ECHO and in particular in early detection of diastolic function, may provide more meaningful results compared to PW Doppler, regardless of preliminary burden. It may also provide information concerning regional cardiac dysfunction (10). Although sometimes the results of PWTD studies on thalassemia patients conflict, in publications, it has been stated that this technique was promising (10, 26, 29, 30).

Tissue doppler E´, A´, and S measurements, taken from medial (2) and lateral (ML) segments of the mitral valve, were decreasing in Group 1 compared to Group 2 and the control group and this suggested that increasing iron accumulation

caused a decrease in the relaxation ability of these regions of the myocardium. These results were interpreted to suggest that diastolic effects, which could not be detected on PW Doppler, could be detected with PWTD and these support the thesis that left ventricle dysfunction was between normal and prolonged relaxation patterns in Group 1.

When these results are evaluated without considering their significance, it was seen that Group 1 had the lowest LVL E´, A´, and S values and this was interpreted as diastolic involvement of the LVL segment. As a result of literature research, a study, conducted by Vogel et al. (10), was found concluding, in line with our study, that a decrease had been observed in E´ and S values in basal and lateral segments of 52 ß-Thal patients compared to the control group and no significant differences had been observed in A´ values. Similarly, in a study, conducted by Balkan et al. (31), on asymptomatic ß-Thal patients, it has been found that the patient group had decreased S and E´ values in PWTD images, obtained from the septal annulus and no significant difference has been found between the groups in terms of A´. In another study, conducted by Yavuz et al. (32), in contrast to our study, while an increase has been detected in the patient group for left ventricle basal E´, no difference has been observed for A´. As for interventricular septum basal results of the same study, while no significant difference has been detected neither for A´ nor E´, an increase has been detected in E´ in the interventricular septum median and LVL in the patient group. It has been concluded that the results could be explained with restrictive type diastolic dysfunction, yet an influence of preliminary burden was also possible. In a study, conducted by Agha et al. (33), no significant intergroup differences have been found in E´, A´, and S waves. In another study, conducted by Ragab et al. (34), 25 ß-Thal patients with a mean age of 12±5.7 have been included in the study, and images have been obtained from anterior, inferior, septal and lateral areas of the mitral annulus. In the study, it has been found that while S and A´ waves in patients were similar to those in the control group, E´ value was decreased in the patient group in lateral, anterior, and inferior measurements. Such discrepancies in the values, found in various studies, may be explained by the lack of a standard protocol in the studies, variations in measurements due to the dynamic structure of the heart, varying age distribution, racial characteristics of patients, and the location and extent of segmental iron retention.

In waves, measured at RVL, no significant inter-group differences were detected. While there are limited studies on this issue, in the study, conducted by Vogel et al. (10), RVL E´ values of 52 ß-Thal patients, are lower compared to the control group, and no significant inter-group differences have been seen concerning RVL S and RVL A´. In the same study, in the records, obtained from the right ventricular basal segment, it has been observed that S and E´ had increased and A´ had decreased in the patient group. In a study, conducted by Yavuz et al. (32), on younger 61 ß-Thal patients have been evaluated and RVL and E´ and A´ values in the right ventricular basal segment are higher in the patient group. These inter-study differences were caused by the segmental effects of iron on the heart and the variability of the age range of the selected patient profile between groups.

In a study, Pepe et al. (35), have shown that the quantity of iron retention in the interventricular septum in cardiac T_2^* MRI, reflected total cardiac iron burden. Therefore, records were taken and evaluated from the septums of patients using the TD method. In our study, IVSB E´ and S waves were lower in Group 1, compared to Group 2 and A´ value was lower in Groups 1 and 2, compared to the control group. IVSM E´ and S waves were lower in Group 1 and Group 2 compared to in control group and A´ value was lower in Groups 1 and 2 compared to in control group. In our patient group, it was seen that iron accumulation caused a deterioration of relaxation ability in the ventricular septum. In a study on a young patient group, conducted by Yavuz et al. (32), no differences have been observed compared to controls in terms of measurements in IVSB and E´ value in IVSM has been determined to be higher in the patient group and therefore, the results in the study have not been interpreted as significant and this has been attributed to the young age of selected patient profile and low level of iron accumulation, which had not yet caused any cardiac effects in septum (32).

When the E/E´ rates of the patient and control group are compared, it was seen that only the E/E´ rate, measured in the mitral lateral segment, was increased in Group 1, compared to Group 2 and the control group. This is consistent with the literature and in studies on asymptomatic ß-Thal patients, conducted by Kremastinos et al. (22), it is increased in the patient group compared to controls and increased more significantly with age (23). Similarly, in a study on 90 asymptomatic ß-Thal patients, conducted by Kostopoulou et al. (28), E/E´ rates have been found to have increased in the patient group (28). In our study, it was contemplated that the reason for the lack of an inter-group difference in terms of TM and TL E/E´ values, was the preservation of RV diastolic functions

In our study, IVRT, IVCT, and ET measurements were taken from eight different tissue doppler windows and MPI

was calculated. It was seen that in Mitral Medial (2), ML, and IVSB windows, IVRT, IVCT, and MPI values were prolonged in Group 1 and Group 2, compared to the control group. Similarly, in the IVSM window, while IVCT and MPI were found to have been prolonged in Group 1 and Group 2 compared to the control group, IVRT was found to have been prolonged only in Group 1 compared to the control group. When the parameters in MPI calculation are considered, it was seen that the reason for the increase in MPI was related to the prolongation of IVRT and IVCT, rather than the change in ET (no inter-group differences). We concluded that the presence of chronic anemia or the presence of additional aggravating factor, played a role at least in our patient group, in the increase of MPI in MM, ML, IVSB, and IVSM, along with iron accumulation.

Tissue doppler and correlation statistics, were analyzed for all patients, regardless of iron accumulation status, and in addition, for the group with iron accumulation (Group 1). Consequently, a strong correlation value could not be obtained in both group. Tissue doppler correlation values, which posed statistical significance, were detected weakly in E´, A´, and S waves, measured in the left side of the heart and interventricular septum. This situation could be explained with the conduction of a study on the asymptomatic patient group, the presence of segmental iron retention, and individual-specific hemodynamic entities at the moment of measurement.

Study Limitations

Two-dimensional speckle-tracking echocardiography is a new method, which has some limitations of the assessment of LV torsion. There is the crucial dependence on correct acquisition of a LV apical short-axis view (36). Monte et al. (37) showed no significant differences in longitudinal strain value between thalassemia and healthy individuals using the strain imaging by speckle tracking echocardiography. Tantawy et al. (38) and Parsaee et al. (39) the global LV longitudinal strain was significantly impaired in the patients compared with the controls, although radial and circumferential strain values were similar between the two groups. There were no significant correlations between cardiac T_2* MRI and speckle echocardiographic parameters in these studies. We perform TD echocardiography because of more usefull, quick and standart method in determine of diastolic dysfunction.

The difficulty of real-time iron burden imaging , deposition of iron in the heart in the form of a patch and inadequacy of MRI alone in the long-term monitoring, and instantaneous nature of functional evaluation (40), its insufficient contribution by itself in case of use of chelators, make only the use of the combination of these two monitorization techniques, meaningful (35).

Conclusion

In our study, investigated biochemical indicators could not be strongly correlated with iron accumulation. Detection of early cardiac dysfunction is very important since appropriate chelation therapy could allow recovery of heart function. We believe that in addition to T_2^* MRI, conventional ECHO, TD ECHO, ECG, and intermittent monitoring of ferritin and NT-pro BNP level have to use at least once a year. In particular, by calculating MPI values with TD echocardiography, global cardiac dysfunction may be identified earlier and chelation therapy may be revised.

We believe that future comparisons, made with MRI results of patients, by making standardized regional evaluations in the future (both for MRI and ECHO), would be more valuable for the demonstration of the relationship between iron accumulation and cardiac dysfunction.

Ethics

Ethical Approval: Ethical approval was obtained from the Clinical Research Ethics Committee of Akdeniz University Faculty of Medicine with the (approval number: 70904504/181, date: 24.04.2015).

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Footnotes

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ÖZGÜN ARAŞTIRMA ORIGINAL ARTICLE

Anoreksiya Nervozalı Ergenlerde Mortalite ve Nedenleri

Mortality and Its Causes in Adolescents with Anorexia Nervosa

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Öz

Giriş: Anoreksiya nervoza (AN) psikiyatrik hastalıklar içinde mortalitesi en yüksek olan hastalıktır. AN'li hastalarda en sık mortalite nedeni özkıyım olmakla birlikte ani kardiyak ölüm, ritim bozuklukları ve elektrolit bozuklukları diğer nedenleri arasındadır. Bu çalışma, AN ve atipik AN (AAN) nedeniyle takip ettiğimiz hastaların mortalite oranını ve nedenlerini belirlemeyi amaçlamaktadır.

Gereç ve Yöntem: Şubat 2014 ile Şubat 2025 tarihleri arasında hastanemiz Ergen Sağlığı bölümüne başvuran, AN veya AAN tanısı almış ve bölümümüzde takip edilmiş olan hastalar çalışmaya dahil edildi. Hastaların cinsiyetleri, başvuru anındaki yaş, vücut ağırlığı, boy, vücut kitle indeksi verileri tıbbi kayıtlar aracılığıyla elde edildi. Hastalara telefonla ulaşılarak hastaların son durumları, hasta kaybedildiyse ölüm nedeni öğrenildi.

Bulgular: AN ve AAN tanısıyla izlenen toplam 391 hastadan 322'si çalışmaya dahil edildi. Bu hastaların 110 tanesi AN (106 kız, 4 erkek), 212 tanesi AAN (188 kız, 24 erkek) tanılı idi. Hastaların başvuru yaşları AN grubunda 15,1±1,6 yıl, AAN grubunda 15,0±1,6 yıldı (p=0,545). Tüm hastalar için tanıdan itibaren geçen süre ortalaması 3,9 (2,7-6,3) yıldı. Medikal takibimiz sırasında kaybedilen hastamız yoktu, ancak AN tanısı alıp düzenli takibi olmayan bir hastanın özkıyım nedeniyle eksitus olduğu öğrenildi. Verilerine ulaşabildiğimiz AN ve AAN olan tüm hastalar için mortalite hızı 1000 kişi-yıl başına 0,7 iken; AN olan hastalar için 1000 kişi-yıl başına 1,9 olarak hesaplandı.

Sonuç: Literatürle uyumlu bir şekilde çalışmadaki en sık ölüm nedeni özkıyım olarak saptanmıştır ve medikal komplikasyonlara ikincil kaybettiğimiz hasta olmamıştır. Çalışmadaki mortalite oranı AN için bildirilen mortalite oranının altındadır. Bulgularımız, multidisipliner bir ekiple sık aralıklarla izlem yaklaşımının medikal komplikasyonlara bağlı mortaliteyi azaltabileceğini, ancak düzenli takip eksikliğinin mortalite riskini arttırdığını göstermektedir.

Anahtar kelimeler
Anoreksiya nervoza, atipik anoreksiya nervoza, mortalite hızı, özkıyım

Keywords
Anorexia nervosa, atypical anorexia nervosa, mortality rate, suicide

Abstract

Introduction: Anorexia nervosa (AN) is the psychiatric disorder with the highest mortality rate. Although suicide is the most common cause of death in patients with AN, sudden cardiac death, arrhythmias, and electrolyte imbalances are among the other causes. This study aimed to determine the mortality rate and causes of death in patients followed for AN and atypical AN (AAN).

Materials and Methods: Patients who presented to the Adolescent Health Department of our hospital between February 2014 and February 2025, were diagnosed with AN or AAN, and were followed in our department, were included in the study. Sex, age at presentation, body weight, height, and body mass index (BMI) data were obtained from medical records. Patients were contacted by phone to determine their current status, and for those who had died, the cause of death was recorded.

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Results: Of the 391 patients followed with AN or AAN, 322 were included in the study. Among them, 110 had AN (106 female, 4 male) and 212 had AAN (188 female, 24 male). The mean age at presentation was 15.1±1.6 years in the AN group and 15.0±1.6 years in the AAN group (p = 0.545). The median duration since diagnosis for all patients was 3.9 years (IQR 2.7–6.3). No deaths occurred during medical follow-up in our clinic; however, one patient with AN who was not under regular follow-up was reported to have died by suicide. For all patients with AN and AAN whose data were available, the mortality rate was 0.7 per 1000 person-years, whereas for patients with AN it was 1.9 per 1000 person-years.
Conclusion: Consistent with the literature, suicide was identified as the most common cause of death, and no patient was lost due to medical complications. The mortality rate in our study was lower than previously reported for AN. Our findings suggest that regular follow-up with a multidisciplinary team may reduce mortality due to medical complications, whereas lack of consistent follow-up increases the risk of death.

Giriş

Yeme bozuklukları, özellikle ergenlik ve genç erişkinlik döneminde ortaya çıkan, ciddi fiziksel ve psikososyal sonuçlara yol açabilen psikiyatrik bozukluklardır. Bu bozukluklar arasında en sık görülenlerden biri anoreksiya nervozadır (AN). AN, Ruhsal Bozuklukların Tanısal ve İstatistiksel El Kitabı-5'e ("Diagnostic and Statistical Manual of Mental Disorders-5", DSM-5) göre; enerji alımının bireysel ihtiyacın altında kalacak şekilde kısıtlandığı, buna bağlı olarak belirgin şekilde düşük vücut ağırlığının görüldüğü, kilo alma konusunda yoğun bir korkunun ya da mevcut düşük kiloya rağmen kilo alımını engelleyen davranışların (kısıtlama, çıkarma veya telafi edici yöntemler) görüldüğü, ayrıca kişinin beden algısında bozulma ve düşük kilonun oluşturduğu sağlık risklerini kavrayamama gibi belirtilerin varlığında tanı konulan psikiyatrik bir bozukluktur. Düşük vücut ağırlığı kriteri dışındaki tanı kriterlerinin karşılanması durumunda ise, atipik AN (AAN) tanısı konulmaktadır (1). AAN'nin, klinik seyir ve komplikasyonlar açısından AN kadar önemli olduğu, benzer morbidite ve mortalite oranlarına sahip olduğu gösterilmiştir (2,3).

AN'nin yaşam boyu prevalansı kadınlarda %1,4, erkeklerde %0,2 olarak bildirilmiştir (4). Başlangıç yaşı en sık 15–19 yaş arasında görülmektedir (5). Son yıllarda genel AN insidansı sabit kalmakla birlikte, 15 yaş altında görülme sıklığı artış göstermektedir (6). Bu artışın daha erken tanıya mı, yoksa başlangıç yaşının daha erken olmasına mı bağlı olduğu belirsizdir. Ancak bu durum, morbidite ve mortalitenin azaltılmasına yönelik önleme programları açısından önem taşımaktadır.

AN mortalitesi en yüksek psikiyatrik hastalık olarak bildirilmiştir (7). AN'ye bağlı mortalite hızı 1.000 kişi-yılı başına yaklaşık 5,1 olarak bulunmuştur (8). Bu hastalarda ölüm genellikle medikal komplikasyonlara veya özkıyıma bağlı olmaktadır. AN'de yeme bozukluğuna bağlı gerçekleşen ölümlerin yarısı çeşitli fiziksel komplikasyonlar nedeniyle olmaktadır (9). Bu komplikasyonlar malnutrisyon, tıkınırcasına yeme ve kompansatuvar davranışlar, alkol-madde kötüye kullanımı gibi durumların sonucunda ortaya çıkmaktadır. En sık mortalite nedeni ise %20 oranında özkıyım olarak bildirilmiştir (8).

AAN DSM-IV'te başka türde adlandırılamayan yeme bozuklukları ("eating disorders not otherwise specified", EDNOS) altında, DSM-5'te ise tanımlanmış diğer beslenme ve yeme bozuklukları ("other specified feeding or eating disorders", OSFED) başlığı altında yer almaktadır. AAN için literatürde mortalite ve özkıyım oranlarına ilişkin net veri olmamakla birlikte, EDNOS için yaşam boyu prevalans kadınlarda %4,3, erkeklerde %3,6 (4); mortalite hızı 1.000 kişi-yılı için 3,3 olarak bildirilmiştir (8). Kısıtlayıcı tipte AN ve AAN olan ergenlerde özkıyım eğilimi, kendine zarar verme, özkıyım düşüncesi ve özkıyım girişimlerini karşılaştıran bir çalışmada, AN ve AAN arasında fark saptanmamıştır (10). AN ve AAN olan ergenlerin karşılaştırıldığı başka bir çalışmada da, kendine zarar verme ve özkıyım düşüncelerinin iki grupta benzer düzeyde olduğu gösterilmiştir (11). Yani her iki hasta grubu da, hem fiziksel komplikasyonlar hem de özkıyım nedeniyle benzer şekilde yüksek mortalite riskine sahiptir ve yakın takip edilmelidir. Bu çalışma, AN ve AAN nedeniyle takip ettiğimiz hastaların mortalite oranını ve nedenlerini belirlemeyi amaçlamaktadır.

Gereç ve Yöntem

Çalışma Grubu

Çalışmaya, Şubat 2014–Şubat 2025 tarihleri arasında hastanemiz Ergen Sağlığı Polikliniği'ne başvuran; DSM-5 tanı ölçütlerine göre AN veya AAN tanısı almış, tanıdan itibaren en az bir yıl geçmiş olan ve hasta ve/veya ailesinden çalışmaya katılım için sözlü onam alınabilen bireyler dahil edilmiştir. Çalışmaya dahil edilen hastaların ilk başvuru anına ait klinik ve antropometrik verilerinin hasta dosyalarında eksiksiz olarak yer alması koşulu aranmıştır. Başvuru anına ait temel klinik veya antropometrik verileri eksik olanlar, hastane kayıtlarında geçerli iletişim bilgisi bulunmayan veya telefonla ulaşılamayanlar, hasta ve/veya ailesi çalışmaya

katılmayı reddedenler çalışmaya dahil edilmemiştir.

Çalışmamızda yeme bozukluğu tanısı, yapılandırılmış klinik görüşme yoluyla, DSM-5 tanı ölçütleri temel alınarak deneyimli klinisyenler tarafından konulmuştur. DSM-5 tanı kriterlerine göre belirgin biçimde düşük vücut ağırlığına neden olacak şekilde enerji alımını kısıtlayan, kilo almaktan korkan, belirgin şekilde düşük vücut ağırlığına rağmen kilo almayı güçleştiren davranışlarda bulunan ve beden algısı bozuk olan hastalar AN olarak kabul edilmiştir. Düşük vücut ağırlığına sahip olmak dışındaki AN tanı kriterlerini karşılayan, vücut ağırlığının en az üç ay içinde %10'unu kaybetmiş olup, vücut kitle indeksi (VKİ) yaş ve cinsiyete göre 50. persentildeki VKİ değerinin (medyan VKİ) %85'i veya üzerinde olan hastalar AAN olarak sınıflandırılmıştır. Her iki grupta da, son üç ay içinde düzenli olarak tıkınırcasına yeme ve çıkarma davranışı gösteren hastalar "tıkınırcasına yeme/çıkarma tipi" olarak, bu davranışları göstermeyen hastalar ise "kısıtlayıcı tip" olarak değerlendirilmiştir (1).

Başvuru Verileri

Hastaların cinsiyetleri, başvuru anındaki yaş (yıl), vücut ağırlığı (kg), boy (cm), VKİ (kg/m^2) verileri elektronik tıbbi kayıtlar ve hasta dosyaları aracılığıyla elde edilmiştir. VKİ, vücut ağırlığının (kg) boyun metre cinsinden karesine bölünmesiyle hesaplanmıştır. VKİ'nin yaş ve cinsiyete göre 50. persentildeki değeri medyan VKİ olarak kabul edilmiştir. VKİ, medyan VKİ'ye bölünüp 100 ile çarpıldığında medyan VKİ yüzdesi elde edilmiştir. Başvuru tarihinden son kontrol tarihine kadar geçen zaman, poliklinik takip süresi (ay) olarak belirlenmiştir. Başvuru tarihinden hastaların telefonla arandığı tarihe geçen süre tanıdan itibaren geçen süre (yıl) olarak kabul edilmiştir.

Güncel Veriler

Hastane kayıtlarından bulunan telefon numarasından hasta veya yakınlarına ulaşılmış, çalışma ile ilgili bilgi verilerek hastalar çalışmaya davet edilmiştir. Sözel olarak çalışmaya katılmayı kabul eden hastaların güncel yaş ve son durumları, eğer hasta eksitus olduysa nedeni öğrenilmiştir. Ölen hastaların, toplam hasta sayısına oranı yüzde olarak belirtilmiştir. Mortalite hızı ise, 1000 kişi-yıl başına düşen ölüm sayısı olarak ifade edilmiştir. Bu amaçla, ölen hasta sayısı toplam takip süresine (kişi-yıl) bölünmüş ve sonuç 1000 ile çarpılmıştır.

İstatistiksel Analiz

Verilerin değerlendirilmesinde, istatistiksel analizler için IBM SPSS Statistics for Windows, Version 27.0 (Armonk, NY: IBM Corp.) programı kullanılmıştır. Kategorik değişkenler sayı ve % ile tanımlanmıştır. Sürekli değişkenler için normal dağılım gösterenler ortalama±standart sapma ile, normal dağılım göstermeyenler ise ortanca (çeyrekler arası aralık, Q1–Q3) şeklinde gösterilmiştir. Parametrelerin normal dağılıma uygunluğu "Kolmogorov-Smirnov" ve "Shapiro-Wilk" testi ile değerlendirilmiştir. Sürekli değişkenler parametrik test varsayımları sağlanıyorsa Student t testi, sağlanmıyorsa Mann-Whitney U testi ile karşılaştırılmıştır. Gruplar arasındaki kategorik değişkenlerin dağılımı Ki-kare testi ile değerlendirilmiştir. P değerinin 0,05'in altında olduğu durumlar istatistiksel olarak anlamlı olarak kabul edilmiştir.

Etik Kurul Onayı

Bu çalışma GO 19/837 proje numarası ile 03.09.2019 tarihinde Hacettepe Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu tarafından onaylanmıştır.

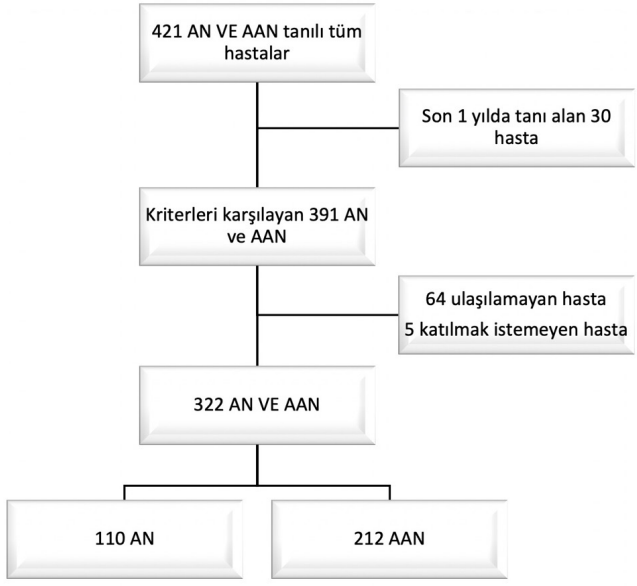
Bulgular

Toplam 391 ergen çalışmaya dahil edilme kriterlerini karşılamıştır. Bu hastalardan, telefonla ulaşılabilen 327 hastadan 5 tanesi çalışmaya katılmayı kabul etmemiş, 322 hasta (110 AN, 212 AAN) çalışmaya dahil edilmiştir. Hasta seçim kriterlerine göre çalışmaya dahil edilme ve dışlanma nedenleri ile hasta sayılarını gösteren akış şeması Şekil 1'de verilmiştir.

Hastaların başvuru anındaki yaşları AN grubunda 15,1±1,6 yıl, AAN grubunda 15,0±1,6 yıldı ve aralarında istatistiksel olarak anlamlı fark yoktu (p=0,545). AN olan 110 hastanın 106 (%96,4) tanesi kız, 4 (%3,6) tanesi erkek; AAN olan 212 hastanın ise 188 (%88,7) tanesi kız, 24 (%11,3) tanesi erkekti (p=0,020). AN grubunda 97 (%88,2) hasta kısıtlayıcı tip, 13 (%11,8) hasta tıkınırcasına yeme/çıkarma tipi iken, AAN grubunda bu sayılar 159 (%75) ve 53 (%25) idi (p=0,005). Hastaların başvurudaki antropometrik bilgileri tablo 1'de verilmiştir.

Hastaların güncel yaşları ortalaması AN grubunda 19,9±3,0 yıl, AAN grubunda ise 19,4±2,5 yıl idi (p=0,112). Tüm hastalar için ortalama poliklinik takip süresi 10,1 (3,1-22,6) ay iken, AN grubunda bu süre 11,0 (3,4-23,3) ay, AAN grubunda ise 10,1 (2,9-22,0) ay idi (p=0,542). Tanıdan itibaren geçen süre ortalaması ise tüm hastalar için 3,9 (2,7-6,3) yıl, AN grubu için 4,2 (2,7-6,3) yıl ve AAN grubu için de 3,7 (2,6-6,2) yıldı (p=0,219). Medikal takip sırasında kaybedilen hasta yoktu, ancak izlemde olmayan ve telefonla ulaşılan hastalardan bir tanesinin özkıyım nedeniyle eksitus olduğu öğrenildi. Poliklinik takibine 1 ay arayla 2 kez gelen, kısıtlayıcı tipte AN tanısıyla takipli bir kız hastaydı. Başvuru yaşı 13,25 yıl olan hastanın, başvuru anında VKİ 15,89 kg/m^2 (medyan VKİ'nin %84,07'sinde) idi. Bunun dışında eksitus

Tablo 1. Hastaların başvuru anındaki antropometrik verileri			
	AN	**AAN**	
	Ortalama±SD	**Ortalama±SD**	**p**
Başvuru yaşı (yıl)	15,1±1,6	15,0±1,6	0,545
	Median (IQR)	Median (IQR)	p
Başvurudaki kilosu (kg)	39,9 (35,7-43,8)	50,2 (46,3-56,5)	<0,001
Başvurudaki boyu (cm)	160,6 (155,5-165,0)	162,0 (157,5-166,2)	0,028
Başvurudaki VKİ (kg/m^2)	15,6 (14,3-16,5)	19,4 (18,0-21,0)	<0,001
Medyan VKİ	20,16 (19,38-20,63)	20,00 (19,21-20,57)	0,312
Medyan VKİ yüzdesi	78,50 (71,11-81,46)	96,98 (90,49-105,20)	<0,001
AAN: Atipik anoreksiya nervoza, AN: Anoreksiya nervoza, VKİ: Vücut kitle indeksi			



Şekil 1. Hasta seçim kriterlerini gösteren akış şeması

olan hasta yoktu. Buna göre takip ettiğimiz ve güncel verilerine ulaşabildiğimiz, AN ve AAN olan tüm hastaların %0,3'ü, sadece AN hastalarının ise %0,9'u exitus olmuştu. Mortalite hızı ise tüm hastalar için 1000 kişi-yıl başına 0,7; AN grubu içinse 1000 kişi-yıl başına 1,9 olarak bulundu.

Tartışma

Bu çalışma ergenlikte tanı alan AN ve AAN hastalarının mortalite oranını ve nedenlerini belirlemeyi amaçlamaktadır. Çalışmamızda kısıtlayıcı tipte AN tanılı bir hasta, özkıyım nedeniyle kaybedilmiştir, AAN grubunda ise kaybedilen hasta olmamıştır. Literatürle uyumlu bir şekilde çalışmadaki en sık ölüm nedeni özkıyım olarak saptanmıştır ve medikal komplikasyonlara ikincil kaybettiğimiz hasta olmamıştır. Çalışmadaki mortalite hızı yeme bozuklukları için bildirilen mortalite hızının altında kalmıştır.

Çalışmamızda mortalite hızı AN hastalarında 1000 kişi-yıl başına 1,9 idi. Toplum genelinde yaş ve cinsiyet açısından eşleştirilmiş bireylerle karşılaştırıldığında, ayaktan tedavi edilen AN hastalarında mortalite riskinin 2 kat, yatarak tedavi edilenlerde ise 5 kattan fazla arttığı gösterilmiştir (12). Arcelus ve ark. (8) tarafından yeme bozukluklarına bağlı mortalite oranlarını inceleyen, az sayıda ergen çalışmasını içeren geniş çaplı meta-analizde,

AN hastalarının mortalite hızı 1000 kişi-yıl başına 5,1 ölüm olarak bildirilmiştir. Standardize edilmiş mortalite oranı (SMR) ise 5,9 olup, yaklaşık 6 kat artmış mortalite riskine karşılık gelmektedir. Daha güncel bir çalışmada ise tanı anında 15 yaşından büyük AN'li geniş bir hasta grubunda, çok ağır malnütrisyon ve/veya somatik komplikasyonlar nedeniyle klinik beslenme ünitesine ilk yatıştan ortalama 5 yıl sonra, kaba mortalite hızı %11,5 olarak bulunmuştur. Mortalite riski, aynı toplumdaki genel popülasyona kıyasla 15 kat daha yüksek saptanmıştır (SMR = 15,9) (13). Yine hastane yatışı olan AN hastalarının değerlendirildiği bir çalışmada, yatıştan ortalama 10 yıl sonraki kaba mortalite hızı % 7,5, SMR 10,6 olarak bulunmuştur (14). Buna karşın, referans merkezlerdeki gibi seçilmiş hastaların değil, nispeten hafif AN olgularının değerlendirildiği, yaşlarının ortancası 19 yaş olan 208 hastanın medyan 22 yıllık takip süresince incelendiği bir çalışmada, tüm nedenlere bağlı mortalite oranları AN hastaları ile genel popülasyon arasında benzer bulunmuştur (15). AN ile ilgili mortalite çalışmalarının çoğu, genellikle hastaneye yatırılan, akut komplikasyonlar gelişmiş hastaların takip edildiği referans merkezlerinde yapılmıştır. Bu nedenle mortalite oranları bu merkezlerin dışında daha düşük olabilir (16). Ayrıca ergenlik döneminde yoğun tedavi alan hastalarda ölüm riskinin daha düşük olduğu gösterilmiştir (17). Hatta ergenlikte tanı alıp, yoğun tıbbi destek ve nutrisyonel tedavi alan AN hastalarında, 10-15 yıllık takip süresinde mortalite saptanmayan çalışmalar vardır (18-20). Diğer taraftan çocukluk döneminde başlangıç olarak kabul edilen, hastalığın 14 yaş altında başladığı AN hastalarının ortalama 7,5 yıl takip edildiği bir çalışmada, hastaların %1,5'inin kaşeksi nedeniyle kaybedildiği bildirilmiştir (21). Bizim çalışmamızda da çocukluk döneminde başlangıç olan ve takipsiz olan bir hasta kaybedilmiş, bunun dışında ölen hastamız olmamıştır. Bizim hastanemiz ağır ve hastane yatışı gereken hastalar kadar, ayaktan tedavi edilen hastaların da çok fazla olduğu 3. basamak referans bir merkezdir. Mortalite oranının erişkin hastalar için bildirilenden düşük, ergen çalışmaları ile benzer olmasında hastaların yaşı, multidisipliner, yoğun ve etkin bir tedavi almış olmaları etkili olmuş olabilir.

Çalışmamızda eksitus olan tek hasta özkıyım nedeniyle kaybedilmişti. AN'li hastalarda en sık mortalite nedeni özkıyım olarak bildirilmiştir. Bunun dışında ani kardiak ölüm, ritim bozuklukları ve elektrolit bozuklukları gibi medikal komplikasyonlar mortalitenin diğer nedenleridir (22). Bizim çalışmamızda medikal komplikasyon nedeniyle kaybedilen hastamız yoktu.

Hastalığa ilişkin içgörünün olması, sosyal ilişkilerin iyi olması iyi prognozla ilişkili iken; yeme bozukluğunun daha ileri yaşta başlaması, hastalık süresinin uzun olması, vücut ağırlığının ve VKİ'nin düşük olması, kilo restorasyonu sonrasında düşük vücut yağı yüzdesi, psikiyatrik komorbiditelerin varlığı ve hastane yatışı gerekliliği kötü prognozla ilişkilidir (6,8,17,23-25). Ergenlikte başlayan AN için daha geç yaşta başlangıç ve premorbid mükemmeliyetçilik, iyi prognostik faktörler olarak tanımlanmaktadır (26). Çocukluk döneminde başlayan AN hastalarında, prognozun daha kötü olduğu saptanmıştır (27). Ayrıca yine hastalığın 14 yaş altında başladığı vakalarda, ruhsal bozuklukların daha sık eşlik ettiği de gösterilmiştir (21). Kaybedilen hastanın hastanede yatış öyküsü ve çok düşük kilo ve VKİ gibi risk faktörleri olmamasına rağmen; AN'nin 14 yaşından önce başlaması ve hastanın takipsiz olması risk oluşturmaktadır. Hastanın özkıyım nedeniyle kaybedilmiş olması; bu hastaların medikal komplikasyonlar kadar psikiyatrik komorbiditeler ve özkıyım düşünceleri açısından da yakın izlenmesinin önemli olduğunu göstermektedir. Yeme bozukluğu nedeniyle takip edilen ergenlerin özkıyım düşüncelerinin ve girişimlerinin değerlendirildiği bir çalışmada, AAN grubunda özkıyım düşüncelerinin daha fazla olduğu, kendine zarar verme ve özkıyım girişimlerinin ise AAN ve AN gruplarında benzer olduğu bulunmuştur (28). Bu nedenle özkıyım riskinin AN ile benzer hatta daha yüksek olduğu AAN hastaları da benzer şekilde dikkatle değerlendirilmelidir.

Takibe uyumsuzluk, mortalite açısından en önemli risk faktörlerinden biri olarak öne çıkmaktadır (29). Bizim çalışmamızda kaybedilen hastanın, düzenli takibe gelmediği görülmüştür. Ergenlerde yeme bozukluğu tedavisinin sürekliliği, hem medikal komplikasyonların erken saptanması hem de psikiyatrik semptomların yakın takibi için kritik önemdedir. Literatürde de tedaviye uyumsuzluk, daha kötü prognoz, artmış relaps riski ve mortalite ile ilişkili bulunmuştur (29). Bu nedenle, hastaların ve ailelerin düzenli izlemin önemi konusunda bilgilendirilmesi, randevu uyumunu artıracak yaklaşımların geliştirilmesi ve takibi aksayan hastalar için aktif hatırlatma sistemlerinin oluşturulması mortalite riskini azaltabilir.

Çalışmanın Kısıtlılıkları

Bu çalışmanın en önemli kısıtlılığı, izlem süresinin literatürde yer alan diğer mortalite çalışmalarından kısa olmasıdır. Bu nedenle mortalite oranı düşük saptanmış olabilir. Ayrıca geçerli telefon numarası olan ve katılmayı kabul eden hastalar çalışmaya dahil edilmiştir. Ancak retrospektif tasarım nedeniyle uzun zaman önce takipten çıkan hastalara

erişim zorlaşmıştır. İletişim kurulamayan hastalar daha ağır vakalar olabilir ya da iletişim kurulamamasının nedeni hastanın kaybedilmiş olması olabilir. Takip edilen hastaların hepsine ulaşamamış olmak mortalitenin olduğundan düşük tahmin edilmesine yol açmış olabilir. Ayrıca eşlik eden psikiyatrik ve tıbbi komorbiditelerin sistematik olarak değerlendirilmemiş olması başka önemli bir kısıtlılıktır. Aynı zamanda çalışmamız tek merkez verisi sunduğundan, sınırlı bir örneklem için mortalite verisi sunulmuştur. Ancak hastanemiz uzun yıllardır yeme bozukluğu hastalarının izlendiği ve toplamda en fazla hastanın takip edildiği merkez olduğundan, ülkemiz verilerini büyük ölçüde yansıttığını düşünmekteyiz.

Sonuç

Sonuç olarak, bulgularımız ergenlik döneminde yoğun ve multidisipliner tedavi uygulamalarının medikal komplikasyonlara bağlı mortaliteyi azaltabileceğini; buna karşılık, hastaların takipsiz kalmasının mortalite açısından önemli bir risk oluşturduğunu göstermektedir. Özellikle tanı anında belirgin kilo kaybı, düşük vücut kitle indeksi, uzun hastalık süresi ve tıbbi komplikasyonların varlığı, daha olumsuz klinik seyirle ilişkili olabilecek göstergeler olarak öne çıkmaktadır. Yeme bozukluğu olan ergenlerin multidisipliner ve çok yönlü olarak yakın izleminin öncelikli olarak ele alınması kritik önem taşımaktadır.

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Ten Years of Experience in The Diagnosis and Treatment of Neonatal Arrhythmias

On Yıllık Neonatal Aritmi Tanı ve Tedavi Deneyimimiz

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Abstract

Introduction: Neonatal arrhythmias (NA) are rare in the neonatal period but cause mortality and morbidity. NA often occurs as a continuation of arrhythmias in the fetal period. The aim of this study is to retrospectively evaluate the incidence, prenatal diagnosis rate, clinical features and treatment outcome of NA in our neonatal intensive care unit.

Materials and Methods: The data of neonates with atrial or ventricular extrasystole, conduction system abnormality, hereditary arrhythmia, bradyarrhythmia and tachyarrhythmia treated in the Neonatal Intensive Care Unit of Uludag University Faculty of Medicine for ten years were retrospectively reviewed and included in the study. Patients with sinus tachycardia and sinus bradycardia were excluded from the study.

Results: NA was detected in a total of 39 of 3703 patients. The most common arrhythmia was supraventricular tachycardia (n=15, 38.5%). Fourteen patients were diagnosed in the prenatal period, while seven patients had multiple arrhythmias. The most common etiologic cause (n=20, 51.2%) was congenital heart disease, while two patients had a history of maternal systemic lupus erythematosus. Antiarrhythmic treatment was required in 25 (64.1 %) patients. Cardioversion or defibrillation was performed in three patients. In 16 patients, the arrhythmia was under control at follow-up, and 5 patients continued antiarrhythmic therapy.

Conclusion: Cardiac arrhythmias can already begin in the prenatal period and be accompanied by various underlying cardiac or systemic diseases. These patients usually do not respond to first-line drug therapy and are controlled by second-line or multi-medication therapy. Cardioversion, on the other hand, is rarely necessary. Appropriate treatment initiated in a timely manner is of great importance for neonates.

Keywords
Neonatal arrhythmia, prenatal diagnosis, antiarrhythmic treatment

Öz

Giriş: Yenidoğan aritmileri (NA) yenidoğan döneminde nadirdir olup mortalite ve morbidite ile sonuçlanabilir. NA genellikle fetal aritmilerin devamı olarak ortaya çıkar. Bu çalışmanın amacı; yenidoğan yoğun bakım ünitemizde NA'nın insidansının, prenatal tanı oranının, klinik özelliklerinin ve tedavi sonuçlarının retrospektif olarak değerlendirilmesidir.

Gereç ve Yöntem: Uludağ Üniversitesi Tıp Fakültesi Yenidoğan Yoğun Bakım Ünitesi'nde on yıl boyunca tedavi gören atriyal veya ventriküler ekstrasistol, iletim sistemi anormalliği, kalıtsal aritmi, bradiaritmi ve taşiaritmisi olan yenidoğanların verileri retrospektif olarak incelenerek çalışmaya dahil edildi. Sinüs taşikardisi ve sinüs bradikardisi olan hastalar çalışma dışı bırakıldı.

Anahtar kelimeler
Neonatal aritmi, prenatal tanı, antiaritmik tedavi

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Bulgular: Toplam 3703 hastanın 39'unda NA tespit edildi. En sık görülen aritmi supraventriküler taşikardiydi idi (n=15, %38,5). On dört hastaya prenatal dönemde tanı aldı, yedi hastada ise multipl aritmi saptandı. En sık etyolojik neden (n=20, %51,2) konjenital kalp hastalığı iken, iki hastada maternal sistemik lupus eritematozus öyküsü mevcuttu. Hastaların 25'ine (%64,1) antiaritmik tedavi başlandı. Üç hastaya kardiyoversiyon veya defibrilasyon uygulandı. Takipte 16 hastada aritmi kontrol altına alınabildi, 5 hastada ise antiaritmik tedaviye devam edildi.
Sonuç: NA prenatal dönemde başlayabilir. Altta yatan çeşitli kalp hastalığı veya sistemik hastalıklarla birlikte olabilir. Hastalar tek ilaç tedavisine yanıt vermediğinde aritmi çoklu ilaç tedavisi ile kontrol altına alınmaya çalışılmaktadır. Nadiren kardiyoversiyon tedavisi gerekmektedir. Yenidoğanlar için uygun tedavinin zamanında başlatılması büyük önem taşımaktadır.

Introduction

Although neonatal arrhythmias (NA) are rare in the neonatal period, they are accompanied by various clinical conditions and cause mortality and morbidity (1). In neonates, cardiac arrhythmias occur in 1-5% of cases (2). NA often occurs as a continuation of arrhythmias in the fetal period. Therefore, prenatal diagnosis is important for the early diagnosis and treatment of NA (1). Although life-threatening arrhythmias are rare, their diagnosis is important (3). Many benign arrhythmias are detected during routine monitoring in neonatal intensive care units without prenatal diagnosis (4). The type of treatment depends on many factors, e.g. the type, duration and frequency of the arrhythmia, the patient's clinical condition, tolerance and cardiac function. For all types of arrhythmias, the first step is to determine whether the patient is hemodynamically stable; aggressive treatment strategies should be used for arrhythmias that present with hemodynamic instability (5). The intrauterine treatment of fetal arrhythmias is an interesting topic on which research is ongoing. Studies on the development of modified technologies for the diagnosis and treatment of fetal arrhythmias are currently being conducted in the literature (6). The aim of this study is to retrospectively evaluate the incidence, prenatal diagnosis rate, clinical characteristics and response to treatment of NA in our neonatal intensive care unit.

Materials and Methods

The study included newborns diagnosed with arrhythmia by routine electrocardiography (ECG) between January 2011 and July 2021 in the neonatal intensive care unit of Uludag University Faculty of Medicine and followed up with a diagnosis of NA by 24-hour rhythm Holter monitoring. Patients were divided into four groups according to their arrhythmia types: premature complex and extrasystoles (premature atrial or ventricular contraction and extrasystoles), tachyarrhythmias [supraventricular tachycardia (SVT), ectopic atrial tachycardia (EAT), atrial flutter, ventricular tachycardia], bradyarrhythmias [second-degree and complete atrioventricular (AV) block], hereditary arrhythmias (long QT syndrome, short QT syndrome). The diagnosis was confirmed by genetic testing in patients with hereditary cardiac arrhythmias. Patients with isolated sinus tachycardia, sinus bradycardia and arrhythmias due to secondary causes such as electrolyte disturbances and sepsis were excluded from the study. The demographic characteristics of the patients (sex, gestational age, birth weight, APGAR score, maternal and gestational diseases) and clinical characteristics (prenatal diagnosis, prenatal treatment, concomitant cardiac pathologies, type of arrhythmia, condition of presence of multiple arrhythmias, treatment methods) were retrospectively collected and approved by the Ethics Committee of Uludag University Faculty of Medicine for Clinical Research.

Statistical Analysis

For statistical analysis, SPSS software, version 19 was utilized. $P<0.05$ were regarded as significant for all analyses.

Results

NA was detected in 39 out of 3703 patients who were hospitalized and followed up during the study. Of the patients, 17 were girls and 22 were boys, the average gestational age was 38 weeks, 9 babies were preterm, and 30 were term babies (Table 1). A prenatal diagnosis was made in 14 (35.9%) patients, and 6 of these patients were treated during the prenatal period. Seven patients had multiple cardiac arrhythmias, and 13 patients had congenital cardiac pathology.

Two mothers had a history of systemic lupus erythematosus (SLE), and three mothers had a history of diabetes (Table 2).

Looking at the distribution of arrhythmias in order of frequency, SVT was the most common, ventricular extrasystole (VES) was the second most common, followed by atrial extrasystole (AES), EAT, complete AV block, supraventricular extrasystole, respectively (Table 3). The clinical characteristics of patients diagnosed with SVT, the most common type of arrhythmia, are given in Table 4.

The most common etiologic cause (n=20, 51.2%) was congenital heart disease, while the most common concomitant cardiac pathology (n=3, 7.6%) was dilated cardiomyopathy. Genetic testing was performed on three patients. Genetic testing revealed long QT syndrome type 2 in only one patient. Mutations in genes associated with 22q11 deletion were detected in one patient with Di George syndrome and another patient with dilated cardiomyopathy (BAG3, MYPN, FLNC, SYNE1).

Twenty-five (64.1%) patients required antiarrhythmic therapy in the postnatal period, 9 received a single drug and 16 responded to dual or multidrug treatment (Table 5). Adenosine was the most preferred drug as the first treatment option in 9 (23%) patients in the acute treatment. Propranolol was used second in the treatment of chronic periods in 9 patients (23%) (Table 6).

Cardioversion or defibrillation was performed in a total of 3 patients. While 1 of these patients had an SVT attack, 1 patient had ventricular tachycardia and ventricular fibrillation, and 1 patient had atrial flutter. Cardioversion was performed in 2 patients with SVT and atrial flutter, and 1 patient with ventricular fibrillation with ventricular tachycardia was defibrillated. When evaluating the prognosis of the patients, it was found that the arrhythmia was controlled in 16 patients during follow-up, while 5 patients continued antiarrhythmic therapy. The age of the 5 patients who continued treatment was determined to be 1 to 5 years. Complete AV block was observed in two patients in the control Holters, WPW was observed in three patients and long QT syndrome was continued in one patient.

Discussion

Neonatal arrhythmias are rare in neonatal intensive care units, but different rates of their incidence are reported in the literature. Jones et al. (7) reported an incidence of NA of 4.8% based on ECG results obtained in the first two days of life in 1028 healthy newborns. In another study, cardiac arrhythmias were detected in 33 cases using the standard ECG technique in 3383 healthy term infants and the incidence was 0.1% (8). In contrast, Turner and Wren (9) found a frequency of NA of 24.4 per 100,000 live births. In our study, the frequency of NA was reported as 1%. In a study conducted in our country, NA was shown to be more common in girls than in boys (10). However, in our study, 56.4% of the patients were male. In preterm infants, the incidence of NA has been reported to be 23.6-38.5% (1,10-12). The incidence of NA in preterm infants in our neonatal intensive care unit was 23%, similar to that reported in the literature.

NA usually occurs as a continuation of cardiac arrhythmias in the fetal period (1). Therefore, prenatal diagnosis is important for early diagnosis and treatment of NA. Fetal arrhythmias can be observed in 2% of pregnancies, and pregnant women referred to pediatric cardiologists for fetal echocardiography with a provisional diagnosis of NA account for 10-20% of referrals (6). In studies conducted in our country, the prenatal diagnosis rate of NA was reported to be 34-52.9% (1,12,13). In our study, the prenatal diagnosis rate was 35.9%. In 6 patients with a prenatal diagnosis, treatment began in the prenatal period. In the intrauterine period, sotalol was administered to one patient with fetal

Table 1. Demographic and clinical characteristics of patients with neonatal arrhythmia

Birth weight (g) (mean±standard deviation)	3310±679
Gestational age, med (min - max)	38 (26-42)
Prematurity, n (%)	9 (23)
Male gender, n (%)	22 (56.4)
Caserean rate, n (%)	36 (92.3)
APGAR (1st minute), med	8
APGAR (5th minute), med	9
Prenatal diagnosis, n (%)	14 (35.9)
Gestational age in prenatal diagnosis, med (min - max)	36.5 (25-39)
Prenatal treatment, n (%)	6 (15.4)
Fetal echocardiography, n (%)	23 (59)
Congenital cardiac pathology, n (%)	13 (33.3)
Multiple arrhythmias, n (%)	7 (17.9)
Mortality, n (%)	1 (2.6)

The parameters showing normal distribution were given as mean ± SD, and the parameters not showing normal distribution were given as median (25%-75%)

SVT and two patients with fetal tachycardia, salbutamol was administered to two patients with fetal complete AV block and digoxin was administered to another patient with fetal tachycardia. Especially in cases of congenital heart disease, heart failure, hydrops fetalis and persistent cardiac arrhythmias, intrauterine administration of pharmacologic agents or insertion of pacemakers should be considered in cases with heart block (6). One of the patients treated pharmacologically during the intrauterine period who was included in our study had non-immune hydrops fetalis, none of them had structural congenital heart disease on fetal echocardiography, and antiarrhythmic medication was started because of persistent arrhythmias.

Table 2. Distribution of maternal gestational or chronic diseases

Maternal gestational or chronic diseases	n (%)
Maternal diabetes	3 (7.6)
Chronic hypertension	1 (2.6)
Hypothyroidism	1 (2.6)
Epilepsy	1 (2.6)
Sinus vein thrombosis	1 (2.6)
Maternal SLE, n (%)	2 (5.1)
Tetralogy of Fallot	1 (2.6)

SLE: Systemic lupus erythematosus

Table 3. Distribution of arrhythmia types

Arrhythmia	n (%)
SVT	15 (38.5)
VES	4 (10.3)
WPW	1 (2.6)
Complete AV block	2 (5.1)
AES	3 (7.7)
EAT	3 (7.7)
Supraventricular extrasystole	2 (5.1)
Short QT sydrome	1 (2.5)
Atriyal flutter	1 (2.5)
SVT + WPW	2 (5.1)
EAT+ VES	1 (2.5)
SVT + VES	1 (2.5)
VES + AES	1 (2.5)
AES + ventricular tachycardia + ventricular fibrillation	1 (2.5)
AES with block + long QT syndrome	1 (2.5)

SVT: Supraventricular tachycardia, VES: Ventricular extrasystole, WPW: Wolff Parkinson White sydrome, AV: Atrioventricular, AES: Atrial extrasystole, EAT: Ectopic atrial tachycardia

NA may be accompanied by congenital heart disease. The literature reports that 15-47% of newborns with cardiac arrhythmias have structural congenital heart disease (1,13,14). Similar to the literature, cardiac pathology was considered the etiologic cause in 50.2% of patients in our study, while structural complex cardiac pathology was found in 33.3% of patients. Maternal diseases may also be a predisposing factor for NA. Systemic diseases such as gestational diabetes and SLE in the mother are among the known risk factors for NA (13). In two of our patients, the mother had a history of SLE and a complete AV block was diagnosed in the prenatal period. Congenital AV block is a rare condition that presents clinically in the prenatal, natal or postnatal period and is characterized by transplacental passage of maternal anti-Ro/SSA and anti-La/SSB antibodies. In the literature, treatments with maternal sympathomimetics, digoxin and salbutamol have been tried in the prenatal period. There is a lifelong pacemaker requirement of more than 60% in the postnatal period (15,16). Our patients with a history of maternal SLE and AV block were treated with maternal salbutamol in the antenatal period and followed up in the postnatal period without the need for a pacemaker. All types of arrhythmias can be observed in the fetus and neonate. The most common are sinus tachycardia and bradycardia, SVT and, less commonly, atrial flutter, ventricular arrhythmias and complete heart block (1). In our study, patients with sinus tachycardia and bradycardia were excluded. SVT is the most common, followed by VES, AES, ectopic atrial tachycardia, complete AV block and other arrhythmias. The incidence of SVT, the most common type of arrhythmia in our study, ranged from 1/250 to 1/1000 in infancy (17). Twenty-three percent of SVT patients are diagnosed during the neonatal period. The literature reports that SVT accounts for 30-40% of NA (1,18). In our study, the frequency of SVT was 38.4%. Sotalol was started as fetal treatment in two patients and digoxin in one patient. Hinkle et al. (19) suggested a combination of digoxin as the first choice for fetal treatment, sotalol as the second choice and sotalol together with digoxin as the third choice. In the acute postnatal period, adenosine was the most common first choice.

Hereditary arrhythmias are rare. They arise as a result of the development of cardiac channelopathy, which is associated with mutations in genes that code for important ion channels of the heart. They arise due to the development of cardiac channelopathy, which is associated with gene mutations that code for important ion channels of the heart. Congenital long QT

Table 4. Clinical features of patients with supraventricular tachycardia

Arrhythmia Type	Fetal Echo	Prenatal Diagnosis	IU anti-arrhythmic	Postnatal Echo
SVT	-	-	-	VSD, TAPVR, left atrial izomerism, PFO
SVT	+ (TR, SVT)	+	+ (sotalol)	PFO
SVT	+ (normal)	+	-	Normal
SVT + WPW	+ (normal)	+	+ (sotalol)	Moderate MR, moderate TR, mild AR
SVT	Inlet VSD	-	-	Inlet VSD, large PDA, IAS aneurysm
SVT	-	-	-	PFO, mild MR
SVT	+ (normal)	+	-	PFO
SVT	+ (normal)	+	-	Dilated CMP
SVT	+ (normal)	+	+ (digoxin)	Small PDA, PFO, mild MR, mild TR
SVT	-	-	-	Small PDA, mild TR, PFO
SVT + VES	-	-	-	PFO
SVT	-	-	-	PFO
SVT	-	-	-	Mild systolic dysfunction
SVT	+ (normal)	-	-	Minimal AR
SVT	Tetralogy of Fallot	-	-	Tetralogy of Fallot
SVT	-	-	-	Pulmonary HT, HF, severe TR, minimal AR, ASD
SVT	Right atrial dilatation	-	-	Severe TR, VSD, large PDA, deformity of the tricuspid valve
SVT + WPW	-	-	-	PDA; PFO, physiological dilatation of right cavities

SVT: Supraventricular tachycardia, VES: Ventricular extrasystole, TAPVR: Total anomalous pulmonary venous return, PFO: Patent foramen ovale, TR: Tricuspid regurgitation, WPW: Wolff Parkinson White sydrome, MR: Mitral regurgitation, AR: Aort regurgitation, VSD: Ventricular septal defect, PDA: Patent ductus arteriosus, IAS: Interatrial septal, CMP: Cardiomyopathy, HT: Hypertension, HF: Heart failure, ASD: Atrial septal defect

Table 5. Types of arrhythmia according to the state of treatment

	Without Treatment n (%)	Single Drug Therapy n (%)	Multipl Drug Therapy n (%)	Cardioversion or Defibrilation n (%)
SVT	1 (2.5)	4 (10.2)	9 (23)	1 (2.5)
VES	2 (5.1)	1 (2.5)	1 (2.5)	0
WPW	1 (2.5)	0	0	0
Complete AV block	2 (5.1)	0	0	0
Atrial extrasystole	3 (7.6)	0	0	0
Ectopic atrial tachycardia	1 (2.5)	1 (2.5)	1 (2.5)	0
Supraventricular extrasystole	2 (5.1)	0	0	0
Short QT sydrome	1 (2.5)	0	0	0
Atrial flutter	0	0	0	1 (2.5)
SVT + WPW	0	1 (2.5)	1 (2.5)	0
EAT + VES	0	0	1 (2.5)	0
SVT + VES	0	0	1 (2.5)	0
VES + AES	1 (2.5)	0	0	0
AES + ventricular tachycardia + ventricular fibrillation	0	0	0	1 (2.5)
AES with block + long QT sydrome	0	1 (2.5)	0	0

SVT: Supraventricular tachycardia, VES: Ventricular extrasystole, WPW: Wolff Parkinson White sydrome, AV: Atrioventricular, EAT: Ectopic atrial tachycardia, AES: Atrial extrasystole

Table 6. The first choice antiarrhythmic drug according to the type of arrhythmia						
	Adenosine n (%)	**Propranolol n (%)**	**Digoxin n (%)**	**Sotalol n (%)**	**Amiodarone n (%)**	**Esmolol n (%)**
SVT	7 (17.9)	4 (10.2)	3 (7.6)	-	-	-
VES	-	2 (5.1)	-	-	-	-
EAT	1 (2.6)	-	-	1(2.6)	-	-
AF	-	-	-	-	1 (2.6)	-
SVT + WPW	1 (2.6)	1 (2.6)	-	-	-	-
EAT + VES	-	-	-	-	1 (2.6)	-
SVT + VES	-	1 (2.6)	-	-	-	-
AES + VT + VF	-	-	-	-	-	1 (2.6)
AES + long QT	-	1 (2.6)	-	-	-	-

SVT: Supraventricular tachycardia, VES: Ventricular extrasystole, EAT: Ectopic atrial tachycardia, AF: Atrial fibrillation, WPW: Wolff Parkinson White sydrome, AES: Atrial extrasystole

syndrome, short QT syndrome, catecholaminergic polymorphic VT and Brugada syndrome are examples of genetic cardiac arrhythmias (19). In our study, long QT syndrome was detected in a patient with blocked atrial extrasystole whose genetic study is currently underway, and the diagnosis of another patient with short QT syndrome was genetically confirmed.

While many benign arrhythmias do not require treatment in the neonatal period, some types of arrhythmias with clinical signs should be treated with antiarrhythmic therapy (20). In the study conducted by Naumburg et al. (21), 72.2% of patients with fetal arrhythmias received antiarrhythmic therapy in the postnatal period. In our study, 25 (64.1%) patients required antiarrhythmic therapy in the postnatal period; 9 patients received a single drug and 16 responded to dual or multidrug treatment. The choice of first-line or acute medication for treatment depends on the type of arrhythmia. In our study, adenosine was the most commonly used drug as a first-line acute treatment, as SVT was the most common in 9 (23%) patients. In life-threatening tachyarrhythmias, apart from drug treatment, cardioversion or defibrillation must be performed urgently and without delay. Synchronized cardioversion is performed for SVT and ventricular tachycardia, while defibrillation is used for ventricular fibrillation (22). In our study, cardioversion with AES was performed in 2 patients with SVT and atrial fibrillation, ventricular tachycardia and ventricular fibrillation, and defibrillation was performed in our hemodynamically unstable patient, and the arrhythmia was controlled.

Return to sinus rhythm was achieved in 75-96% of pediatric patients receiving adenosine with a diagnosis of SVT (19). In our study, 16 of the 25 patients treated with medication responded to treatment and their medication could be discontinued during follow-up. In five patients, a return to sinus rhythm was achieved by adenosine therapy in the acute phase, and in 10 patients who did not respond to adenosine therapy in the acute phase and required chronic antiarrhythmic treatment. Two of the 5 patients still being treated with SVT, one patient with SVT, one patient with WPW, one patient with VES and one patient with long QT syndrome are currently being followed up with antiarrhythmic medical treatment. A return to sinus rhythm was achieved in 83.3% of our drug-treated patients with SVT and their treatment was completed after an average of 19.5 $\pm$ 16.8 months.

Study Limitations

Major limitation of this study is that it is retrospective. This was a retrospective, descriptive study and the number of patients was not sufficient to clarify etiological issues. Secondly, although drug-induced arrhythmias were underestimated, prospective observations with a larger number of patients could have been performed to obtain a clearer picture of the drug of first choice in neonatal arrhythmias and the response to the drug. Despite these limitations, we believe that our current data will be useful in increasing awareness about NA.

Conclusion

In conclusion, arrhythmias are rare in the perinatal period but are among the most important cardiac problems. They can occur together with various underlying cardiac or systemic diseases. Prenatal diagnosis is very important for treatment in the postnatal period. It is important to start treating affected patients in the prenatal period. Patients who do not respond to single-drug therapy in acute treatment may require a high level of second-line treatment with chronic medication. Patients with hemodynamic instability

or resistant arrhythmias may require cardioversion or defibrillation. Careful examination and continuous cardiac monitoring in the postnatal period as well as good prenatal monitoring and fetal echocardiography are important for early diagnosis if required. Careful examination, continuous cardiac monitoring in the postnatal period, good prenatal monitoring and fetal echocardiography, if needed, are essential for early diagnosis.

Ethics

Ethics Committee Approval: The study received approval from the institution's ethics committee Bursa Uludağ University Faculty of Medicine Clinical Research Ethics Committee (decision no: 2011-KAEK-26, date: 08.11.2021).

Footnotes

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

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Systemic Inflammatory Indices (SII and SIRI) in Obese Pediatric Patients: A Retrospective Study

Obez Çocuk Hastalarda Sistemik Enflamasyon Göstergeleri: SII ve SIRI İndekslerinin Retrospektif Değerlendirmesi

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Abstract

Introduction: Childhood obesity is associated with systemic inflammation and metabolic disturbances. This study aimed to investigate the relationships between obesity, systemic immune-inflammation index (SII), and systemic inflammation response index (SIRI) in children and adolescents.

Materials and Methods: A total of 217 children (126 controls, 91 obese; mean age 12.2 ± 3.4 years) were included. Anthropometric measurements, laboratory parameters, and inflammatory indices (SII, SIRI) were assessed. Multiple linear regression analyses were performed to examine associations between BMI SD, age, gender, pubertal status, and inflammatory indices.

Results: Obese children had significantly higher weight SD, height SD, BMI SD, NEU, MPV, glucose, total cholesterol, LDL-C, TG, ALT, GGT, SII, and SIRI compared to controls ($p<0.05$), while HDL-C was lower ($p=0.041$). Regression analyses showed that BMI SD was a significant positive predictor of both SII and SIRI ($p<0.001$), whereas age, gender, and pubertal status were not significant. The models explained 8.6% and 7.2% of the variance in SII and SIRI, respectively.

Conclusion: Our findings indicate that childhood obesity is associated with elevated systemic inflammatory markers and that BMI SD is a strong predictor of systemic inflammation. These results highlight the importance of early weight management to reduce inflammatory risk in children and adolescents.

Keywords
Childhood obesity, NLR (Neutrophil-to-lymphocyte ratio), PLR (Platelet-to-lymphocyte ratio) MPV (min platelet volume), puberty SII (Systemic immune inflammatory index), SIRI (Systemic Inflammatory Response Index)

Öz

Giriş: Çocukluk çağında obezite, sistemik inflamasyon ve metabolik bozukluklarla ilişkilidir. Bu çalışmada, çocuk ve ergenlerde obezite ile sistemik immün-inflamasyon indeksi (SII) ve sistemik inflamasyon yanıt indeksi (SIRI) arasındaki ilişkiler araştırılmıştır.

Gereç ve Yöntem: Çalışmaya toplam 217 çocuk (126 kontrol, 91 obez) dahil edildi; yaş ortalaması 12,2 ± 3,4 yıl idi. Antropometrik ölçümler, laboratuvar parametreleri ve inflamasyon indeksleri (SII, SIRI) değerlendirildi. Çoklu doğrusal regresyon analizleri ile BMI SD, yaş, cinsiyet ve pubertal durum ile inflamasyon indeksleri arasındaki ilişkiler incelendi.

Bulgular: Obez çocuklarda, kontrol grubuna kıyasla ağırlık SD, boy SD, BMI SD, NEU, MPV, glukoz, total kolesterol, LDL-C, TG, ALT, GGT, SII ve SIRI seviyeleri anlamlı olarak yüksekti ($p<0,05$); HDL-C seviyeleri ise düşüktü ($p=0,041$). Regresyon analizleri, BMI SD'nin hem SII hem de SIRI için anlamlı pozitif bir belirleyici olduğunu gösterdi ($p<0,001$), yaş, cinsiyet ve pubertal durum ise anlamlı etkiler göstermedi. Modeller sırasıyla SII ve SIRI varyansının %8,6 ve %7,2'sini açıkladı.

Anahtar kelimeler
Çocukluk çağı obezitesi, NLR (Nötrofil-lenfosit oranı), PLR (Trombosit-lenfosit oranı), MPV (Ortalama trombosit hacmi), puberte, SII (Sistemik immun-inflamatuar indeks), SIRI (Sistemik inflamatuar yanıt indeksi)

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Sonuç: Çalışmamız, çocukluk çağında obezitenin sistemik inflamasyon ile ilişkili olduğunu ve BMI SD'nin inflamasyonun güçlü bir belirleyicisi olduğunu göstermektedir. Bulgular, erken dönemde kilo yönetimi ve inflamatuvar riskin azaltılmasının önemini vurgulamaktadır.

Introduction

Childhood obesity is one of the most common chronic health problems today. According to the 2013 Turkey Demographic and Health Survey (TNSA), the prevalence of overweight or obesity among children under the age of five is 10.9% (1). The results of the 2009 Study on Monitoring Growth in School-Age Children in Turkey (TOÇBİ) indicate that among children aged 6–10, 14.3% are overweight and 6.5% are obese. The obesity rate is 7.5% in boys and 5.4% in girls, while the rate of being overweight is 15.1% in boys and 13.5% in girls (2).

Furthermore, according to the 2009–2010 Health Behaviour in School-Aged Children (HBSC) survey, 7% of 11-year-old girls and 16% of boys are classified as overweight or obese. Among 13-year-olds, the rates are 10% for girls and 18% for boys, while in the 15-year age group, 6% of girls and 17% of boys are considered overweight or obese (3).

It has become clear that obesity is not only a condition related to energy imbalance, but is also associated with chronic low-grade systemic inflammation. Adipose tissue synthesizes and secretes a large number of hormones, cytokines, extracellular matrix proteins, growth factors and vasoactive factors that we call adipokines. These cytokines and adipokines induce leukocytosis in obese individuals by increasing neutrophils (NEU) in the intravascular space and accelerating bone marrow production (4).

Hematologic parameters such as white blood cell (WBC) count, NEU and lymphocyte counts (LYM), NEU to LYM ratio (NLR), platelet count (PLT), PLT to LYM ratio (PLR), and mean platelet volume (MPV) have been suggested to be associated with systemic inflammation and increased cardiometabolic risk (5).

WBC, NEU and LYM, along with NLR, may serve as markers of systemic inflammation. NLR has recently emerged as a potential prognostic indicator and may be associated with carotid intima-media thickness in children aged 7 to 9 years (6).

MPV is a marker of PLT function. MPV greater than normal (above 10 femtoliters) indicates that PLT WBC are more active and is associated with an increased risk of cardiovascular disease (7).

Systemic Immune-Inflammation Index (SII) and Systemic Inflammation Response Index (SIRI), which include four basic hematologic cell types (NEU, Monocyte (MON), LYM and PLT), are the next generation of objective inflammation indicators developed based on peripheral blood parameters, which can provide more clinical information and have practical use. They have been reported to be associated with the prognosis and development of diseases that are positively associated with coronary artery stenosis, cancer and obesity in adult studies (8-10). Although the prognostic and diagnostic value of these indices in various diseases in the adult population has been investigated, their role in childhood obesity is still unclear (8).

Therefore, the aim of this retrospective case-control study is to evaluate the utility of SII and SIRI indices as markers of systemic inflammation in obese pediatric patients.

Materials and Methods

Study Sample

This retrospective case-control study included data from 91 obese patients aged 5 to 18 years who were admitted to the Pediatric Endocrinology Outpatient Clinic of Kayseri City Training and Research Hospital between April and December 2023 due to excess weight. All patients had a body mass index (BMI)-for-age > +2 SD (Standart deviation score), were diagnosed with simple (primary) obesity, and had no chronic diseases.

As the control group, 126 non-obese subjects aged 5 to 18 years without chronic disease were randomly selected from patients attending the same clinic.

Exclusion criteria: Malignancies, infection, bone marrow suppressive disorder, malabsorptive disorder, medication use, history of lung, liver or kidney disease, including any inflammatory disorder; c-reactive protein more than 10 mg/L, WBC count less than $4x10^3$ µ/ml or more than $13.5x10^3$ µ/ml, PLT less than $150x10^3$ µ/ml or more than $450x10^3$ µ/ml and anemia.

Age, gender, anthropometric measurements, puberty, complete blood count and biochemical test results were analyzed.

Body weights and heights were measured with Seca digital scale and Harpenden Stadiometer during the initial examination. Height, weight and BMI SD were evaluated according to age and gender appropriate charts. A BMI of over 2 SD according to age and gender was considered obesity (11). Puberty status of the patients was determined

according to Tanner Marshall pubertal staging system. Stage 1 was considered prepubertal according to Tanner Marshall staging (12).

Complete blood count, blood glucose, Gamma Glutamyl Transferase (GGT, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), Total cholesterol, triglyceride (TG)), liver function tests (alanine aminotransferase (ALT), aspartate aminotransferase (AST)) were evaluated after at least 10 hours of fasting. Venous samples for complete blood count were collected in potassium EDTA tubes and analyzed within 2 hours. Blood cell count was performed with an automated cell counter (LH 780, Beckman Coulter, Krefeld, Germany) using the impedance method. LYM, NEU and PLT (expressed as $\times 10^3$ cells/µl) were measured using automated hematology analyzers. Index calculations:

Neutrophil-Lymphocyte Ratio (NLR): NEU/LYM

Platelet-Lymphocyte Ratio (PLR): PLT /LYM

Systemic Immune-inflammation Index (SII): (PLT × NEU) / LYM (9).

Systemic Inflammatory Response Index (SIRI): (NEU × MON) /LYM

Statistical Analysis

Mean, standard deviation, median, minimum-maximum values, ratio, frequency values were used in descriptive statistics of the data. Qualitative data were analyzed with chi-square test. The distribution of the data was analyzed by Kolmogorov Simirnov test. Mann-Whitney U test was used to compare groups for variables that did not show normal distribution; Student t test was used to compare groups for variables that showed normal distribution. Spearman correlation analysis was used to determine the relationship between variables that did not show normal distribution, and Pearson correlation analysis was used for variables with normal distribution. A value of $p<0.05$ was considered statistically significant.

In the study, multiple lineer regression analysis was performed to evaulate the effects of SII and SIRI indices on the other variables. Because SII and SIRI showed right-skewed distributions, $\log_{10}$-transformed values (log-SII, log-SIRI) were additionally used for regression analyse.

A priori power analysis was conducted assuming a moderate effect size (Cohen's d = 0.5), a significance level of 0.05, and desired power of 0.95. The calculated sample size per group to detect differences in SII and SIRI was approximately 88 participants. Given that the study included 126 controls and 91 obese participants, the sample size was sufficient to detect moderate effect sizes with high power.

Approval for this study was obtained from the Kayseri City Hospital Clinical Research Ethics Committee of decision number: 1009, date: 12.12.2023).

Results

General Characteristics of the Study Groups

A total of 217 children were included in the study, comprising 126 in the control group and 91 in the obese group. The mean age was 12.2 ± 3.4 years. There were no statistically significant differences between the groups in terms of age and gender distribution ($p>0.05$). Weight SD, height SD, and BMI SD were significantly higher in the obese group compared to the control group (all $p<0.001$) (Table 1).

Comparison of inflammatory and metabolic parameters between obese and control groups

Among laboratory parameters, NEU, MPV, glucose, total cholesterol, LDL-C, TG, ALT, GGT, SII, and SIRI levels were significantly higher in the obese group ($p<0.05$). HDL-C levels were significantly lower in the obese group compared to the control group ($p=0.041$). No significant differences were observed between the groups regarding LEU, MON, PLT, hemoglobin, AST, NLR, and PLR levels ($p>0.05$) (Table 1).

In terms of inflammatory indices, both SII and SIRI were significantly elevated in obese children. Mean SII was 528.5 ± 194.3 in the obese group versus 448.1 ± 209.6 in controls ($p=0.008$), and median SIRI was 1.00 (0.70–1.43) in obese subjects and 0.79 (0.49–1.10) in controls ($p<0.001$ (Table 1).

Comparision by Pubertal Status

In the pubertal group, obese children had significantly higher weight SD, height SD, BMI SD, NEU and erythrocyte counts, glucose, total cholesterol, HDL-C, LDL-C, TG, ALT, GGT, and SIRI levels compared to controls ($p<0.05$) . Pubertal sub-analysis results are summarized in Supplementary Table 1.

Association Between BMI-SD and Inflammatory Indices: Regression Analysis

Multiple linear regression analyses were conducted to examine the relationship between SIRI and SII as dependent variables and several predictors, including BMI SD, age, gender, and pubertal status. The models explained 8.6% of the variance in SII ($R^2 = 0.086$, Adjusted $R^2 = 0.066$) and 7.2% of the variance in SIRI ($R^2 = 0.072$, Adjusted $R^2 = 0.052$). Among the predictors, BMI SD was a significant positive predictor for both SII and SIRI ($p <0.001$), indicating that for each one-unit increase in BMI SD, SII increased by 38.16

units and SIRI increased by 0.103 units. Age, gender, and pubertal status showed no significant effects in either model. Regression assumptions, including multicollinearity and independence of residuals, were satisfied (VIF <2; Durbin–Watson ≈ 2) (Tables 2 and 3).

Table 1. General characteristics and laboratory findings of obese and control subjects

	Control group (n:126)	Obese group (n:91)	p value
Age years*	11.93 (8.64-15.44)	13 (10.12-15.24)	0.142
Gender male*	44 (34%)	41 (45%)	0.131
Weight SD	-0.05 ± 1.32	2.66 ±0.93	<0.001
Height SD	-0.27 ± 1.41	0.53 ± 1.39	<0.001
BMI SD kg/m^{2}*	0.26 (-0.67-1.21)	2.43 (2.14-2.85)	<0.001
NEU 10^{3}/µ/l*	3.83 (2.57-4.77)	4.57 (3.59- 5.86)	<0.001
LYM 10^{3}/µ/l*	2.88 (2.25-3.32)	2.85 (2.54-3.30)	0.349
Hb g/dl	13 (12-14)	13.7 (13-14)	0.060
Erythrocytes 10^{6}/L	4.96 ± 0.39	5.17 ± 0.42	<0.001
MON 10^{3}/L*	0.55 (0.45-0.67)	0.62(0.51-0.73)	0.066
PLT 10^{3}/µ/l*	315 (263-346)	327 (286-366.5)	0.064
MPV fl*	9.6 (9-10)	9.8 (9.2-10)	0.009
Glucose mg/dl*	84 (78.7-87)	87(82-92.75)	0.001
Total-C mg/dl	133.56 ±18.72	156.01 ±30.21	<0.001
HDL-C mg/dl	49.4 ± 9.68	44.86 ± 8.87	0.041
LDL-C mg/dl	80.12 ±15.59	96.23 ± 25.67	0.001
TG mg/dl*	76 (64.75-92.75)	102 (76-163)	0.001
AST U/L*	23 (18-26.5)	21 (17-27)	0.607
ALT U/L*	14 (11-17)	20 (14-27)	<0.001
GGT U/L*	12 (9-14)	17 (13-24)	<0.001
NLR*	1.36 (0.97-1.98)	1.56 (1.14-2.04)	0.063
PLR*	108 (90-144.5)	111.5 (93.25-128.75)	0.680
SII, 10^{3}/µ/l	448.07 ± 209.61	528.54 ± 194.26	0.008
Log SII	5.98 ±0.46	6.20 ± 0.37	0.002
SIRI, 10^{3}/µ/l*	0.79 (0.49-1.10)	1.00 (0.70-1.43)	<0.001
Log SIRI	-0.32 ± 0.58	-0.01 ± 0.56	<0.001

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BMI: Body mass index, GGT: Gamma glutamyl transferase, Hb: Hemoglobi, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, LYM: Lymphocyte, MON: Monocyte, MPV: Mean platelet volume, NEU: Neutrophil, NLR: Neutrophil/lymphocyte ratio, N: Number, PLT: Platelet, PLR: Platelet/lymphocyte ratio, SD: Standard deviation score, SII: Systemic immune-inflammatory index, SIRI: Systemic inflammatory response index, TG: Triglyceride, Total-C: Total-cholesterol, bold represents statistically significant values (p<0.05). Data are presented as mean ± standard deviation for normally distributed variables and median (interquartile range) for non-normally distributed variables. Student's t-test was used to compare groups for variables with normal distribution. *Mann-Whitney U test was applied. **Chi-square test was applied

Table 2. Multiple linear regression analysis predicting SII

Variable	B	Std. Error	Beta	t	VIF	95% CI for B	p
Constant	464.78	55.81	—	8.33	—	354.6-574.88	<0.001
BMI SD	38.16	10.30	0.272	3.71	1.08	17.84- 58.47	<0.001
Age	-1.98	5.09	-0.033	-0.39	1.49	-12.02- 8.07	0.698
Gender	-49.19	30.82	-0.116	-1.60	1.05	-110.00- 11.62	0.112
Puberty	19.38	45.71	0.037	0.42	1.56	-7 0.80- 109.56	0.672

CI: Confidence Interval. Note: Gender coded as 0 = Male, 1 = Female. Pubertal stage indicates whether puberty has started (1 = Yes, 0 = No). Model summary: R = 0.294, R^2 = 0.086, Adjusted R^2 = 0.066, Standard Error = 199.55, Durbin-Watson = 1.49. No multicollinearity detected (VIF<2)

Table 3. Multiple linear regression analysis predicting SIRI

Variable	B	Std. Error	Beta	t	VIF		95% CI for B	p
Constant	0.879	0.175	—	5.02	—		0.533-1.224	<0.001
BMI SD	0.103	0.032	0.235	3.25	1.08		0.041-0.166	0.001
Age	-0.014	0.016	-0.074	-0.87	1.50		-0.046-0.018	0.388
Gender	-0.017	0.095	-0.012	-0.17	1.05		-0.200-0.172	0.863
Puberty	0.198	0.141	0.122	1.40	1.56		-0.081-0.477	0.163

CI: Confidence Interval. Note: Gender coded as 0 = Male, 1 = Female. Pubertal stage indicates whether puberty has started (1 = Yes, 0 = No). Model summary: R = 0.268, R^2 = 0.072, Adjusted R^2 = 0.052, Standard Error = 0.639, Durbin-Watson = 1.79. No multicollinearity detected (VIF<2).

Discussion

In this study, obese children and adolescents were found to differ from their normal-weight peers in terms of hematological parameters and inflammation markers. Overall, the obese group showed significantly higher levels of NEU, MPV, glucose, total cholesterol, LDL-C, TG, ALT, GGT, SII, and SIRI. These findings support the association between obesity and systemic inflammation as well as metabolic disorders.

Adipose tissue functions as an inflammatory organ by continuously secreting various cytokines, adipokines, and immune cells into the systemic circulation. Studies have shown that these bioactive substances are valuable indicators for diagnosing and monitoring systemic inflammation. In chronic inflammation, increases in NEU and PLT and decreases in LYM are often observed. Especially, NLR and PLR are inexpensive and accessible markers that reflect the clinical manifestations of metabolic inflammation (13). In our study, obese children and adolescents were found to have significantly higher NEU, MPV, SII, and SIRI compared to their normal-weight peers. These findings support the close association between obesity and inflammatory processes, highlighting the systemic inflammation originating from adipose tissue and its clinical reflections. Interestingly, parameters such as LEU, MON, PLT, hemoglobin, AST, NLR, and PLR did not show significant differences between the groups. This may suggest that while some classic inflammatory markers remain within normal ranges in early or moderate stages of obesity, composite indices like SII and SIRI may offer greater sensitivity in detecting subclinical inflammation. Additionally, the elevated MPV values in the obese group could reflect enhanced platelet activation, which has been linked to endothelial dysfunction and cardiovascular risk in obese children (14).

Increased leptin in obesity may increase the number of circulating NEU by triggering NEU chemotaxis and activation. Furthermore, obesity-induced hypoxia is another factor that increases NEU infiltration in adipose tissue. Several studies in recent years have found a positive correlation between BMI and NEU. Increased NLR is used as an indicator of inflammatory status in obese individuals and is associated with cardiometabolic risk factors (15,16). On the other hand, there are studies reporting that no difference was found in obese and normal weight children and that it cannot be considered as a marker of metabolic syndrome compared to adults (4,17). In the study, NEU and NLR were higher in obese patients but no difference was found in NLR when patients were classified according to puberty. While erythrocytes increase with increased erythropoietin due to hypoxia in obese patients, anemia due to chronic inflammation is also observed (18). Increased erythrocyte in obese people has been associated with increased BMI, diabetes risk, and central obesity (19). Similarly, in our study, erythrocyte count was found to be high in obese pubertal subjects.

Obesity has been associated with thrombocytosis and thrombosis, while hyperinsulinemia, hypertriglyceridemia, and hypertension are independently associated with thrombosis, regardless of obesity. In addition, increased leptin levels in obesity may increase the risk of PLT aggregation and cardiovascular disease (20). In the prepubertal group, higher PLT counts were observed, highlighting the need for further studies on this topic. MPV is a common indicator of PLT activity. Increased MPV has been associated with increased waist circumference, increased risk of diabetes (21,22). In our study, MPV was found to be higher in obese subjects, both in the pubertal group and in the prepubertal group.

In pubertal children, the metabolic and inflammatory burden of obesity appears to intensify. Obese individuals in this group showed significantly higher levels of erythrocyte counts, glucose, total cholesterol, LDL-C, HDL-C, triglycerides, ALT, GGT, Log SII and Log SIRI than controls. These alterations reflect the compounded effects of hormonal changes during

puberty on obesity-related pathophysiology. The decrease in HDL-C and increase in triglycerides and liver enzymes are particularly concerning due to their association with future cardiovascular risk. Overall, the findings indicate that while obesity-related complications begin in the prepubertal period, they become more pronounced and widespread during puberty, emphasizing the critical importance of age- and stage-specific interventions for effective obesity management (23).

In our study, children with and without puberty were compared. Adolescence is a complex developmental stage in which sex steroids and metabolic processes change significantly in the transition from childhood to adulthood. Physiologic insulin resistance, fluctuations in growth hormone and increased sex steroids, coupled with obesity, can have a synergistic effect on inflammation. Increased growth rate and cellular renewal processes can also increase the sensitivity of the immune system (23).

SII quantifies the relationship between PLT, NEU and LYM. It is a relatively stable marker despite physiological conditions. SII has been found to be associated with other inflammatory diseases, including heart failure, rheumatoid arthritis, acute pulmonary embolism and chronic kidney disease (24). SII has a role as an additional measure of cardiometabolic instability in predicting metabolic syndrome in obese children (25). In the study by Zhang et al. (24), although SII was found to be high in obese children, there was no linear relationship between SII and obesity. Increased SII levels were positively correlated with obesity up to a certain threshold (threshold log SII: 6.410), but negatively correlated with obesity after crossing the threshold. Increased peripheral proinflammatory cytokines in systemic inflammation may lead to weight loss due to increased energy expenditure, lipolysis, weight loss and decreased appetite due to the inflammatory environment around the vagus (24). In our study, Log SII was found to be higher in the both pubertal and prepubertal obese groups.

SIRI is a new index used to reflect systemic inflammation and immune response. SIRI has been used in past studies to predict and assess the prognosis of diseases such as pneumonia, rheumatoid arthritis and acute pancreatitis. Inflammation is directly associated with insulin resistance and chronic metabolic disorders as well as increased cardiovascular risk (26). In our study, it was observed to increase in obese children.

Multiple linear regression analyses in our study revealed significant positive associations between BMI SD and both the SII and SIRI. In contrast, age, sex, and pubertal status did not have significant effects in either model. These findings indicate that, as reported in the literature, increased body weight in children and adolescents is associated with a marked impact on systemic inflammation (27).

In contrast to several previous studies that have reported significant associations between SII and SIRI with metabolic parameters such as glucose levels, lipid profiles, and liver enzymes, our findings did not reveal such correlations in the pediatric population studied (8,24,28). This discrepancy may be attributed to differences in study populations, particularly age, pubertal status, and the pathophysiological progression of obesity-related complications in children versus adults.

Study Limitations

The limitations of my study include the limited number of patients. Confounding factors such as screen time, activity status, parental weight and socioeconomic status, which have a role in the development of obesity in children, were not included in the study. The volume of PLT distribution may vary, especially in samples taken in EDTA tubes (29). The strength of the study is that a wide age range was included and the cases were classified according to puberty.

Conclusion

In conclusion, NEU, erythrocytes and MPV were increased in obese children compared to their healthy peers. SIRI index was higher in adolescent obese children compared to their peers. Obesity in adolescence, in combination with hormonal and metabolic changes, triggers inflammatory processes and poses a significant threat in terms of long-term cardiometabolic risks. Indices such as SII and SIRI can be used as valuable biomarkers for monitoring this inflammatory response and early intervention. Therefore, monitoring the level of inflammation should be addressed with multidisciplinary approaches as well as early diagnosis and treatment of obesity in adolescence.

Ethics

Ethical Approval: Approval for this study was obtained from the Kayseri City Hospital Clinical Research Ethics Committee of decision number: 1009, date: 12.12.2023).

Footnotes

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

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Supplementary Link: https://d2v96fxpocvxx.cloudfront.net/cf9d60d6-523c-458a-a2e6-78728d3ffbb0/content-images/25709180-c2dc-483b-b0c5-e7c6c6979ac6.pdf

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CASE REPORT OLGU SUNUMU

A Girl with Imerslund Grasbeck Syndrome: Presentıng with Hypocalcemia

Hipokalsemi ile Prezente Olan İmmeslund Grasbeck Sendromu Tanısı Alan Kız Hasta

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Abstract

Although Imerslund-Gräsbeck syndrome (IGS) is a rare disease, it can also cause rare comorbid clinical conditions. IGS or selective vitamin B12 (cobalamin) malabsorption with proteinuria is a rare autosomal recessive disorder characterized by vitamin B12 deficiency. IGS is caused by mutations in the gene CUBN encoding cubilin or AMN encoding amnionless. Homozygous or compound heterozygous mutations in either CUBN or AMN lead to IGS. Vitamin D deficiency is considered a major public health concern. Inadequate sun exposure, limited oral intake, and impaired intestinal absorption are common risk factors for vitamin D deficiency. Moreover, vitamin D binding receptor protein and 25-OHD urinary extraction are associated with profound vitamin D deficiency, in IGS. Constitutional symptoms, such as weakness and fatigue, are the conditions that may occur in the deficiency of both vitamin B12 and vitamin D. For this reason, we would like to emphasize the importance of monitoring vitamin D levels periodically in patients diagnosed with IGS, as clinical findings may be similar.

Öz

Imerslund-Gräsbeck sendromu (IGS) nadir görülen bir hastalık olmakla birlikte nadir görülen komorbid klinik durumlara da neden olabilir. IGS veya proteinüri ile birlikte selektif B12 vitamini (kobalamin) malabsorpsiyonu, B12 vitamini eksikliği ile karakterize nadir bir otozomal resesif hastalıktır. Cubulini kodlayan CUBN veya amnionlessi kodlayan AMN genlerinde homozigot ya da kompaund heterozigot mutasyonlar sonucunda oluşur. D vitamini eksikliği majör bir halk sağlığı sorunu olarak sıklıkla karşımıza çıkmaktaıdr. Yetersiz güneş ışığına maruziyet, yetersiz oral alım, intestinal emilimde bozukluk D vitamini eksikliğinin yaygın sebepleridir. Ayrıca IGS'de D vitamini bağlayıcı reseptör proteini ve 25-OHD idrar ekstraksiyonu derin D vitamini eksikliği ile ilişkilidir.Halsizlik, yorgunluk gibi yapısal belirtiler hem B12 vitamin eksikliğinde hem de D vitamini eksikliğinde ortaya çıkabilmektedir. Bu sebeple IGS tanısı alan hastalarda klinik olarak bulgular benzer olabileceğinden aralıklı olarak D vitamini düzeylerinin takibinin yapılması önemini vurgulamak isteriz.

Keywords
Imerslund Grasbeck Syndrome, hypocalcemia, megaloblastic anemia

Anahtar kelimeler
İmerslund Grasbeck Sendromu, hipokalsemi, megaloblastik anemi

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Introduction

Imerslund-Gräsbeck syndrome (IGS) or selective vitamin B12 (cobalamin) malabsorption with proteinuria is a rare autosomal recessive disorder characterized by vitamin B12 deficiency (1). IGS is caused by mutations in the gene CUBN encoding cubilin or AMN encoding amnionless. Homozygous or compound heterozygous mutations in either CUBN or AMN lead to IGS (2,3). Vitamin D deficiency is considered a major public health concern. Inadequate sun exposure, limited oral intake, and impaired intestinal absorption are common risk factors for vitamin D deficiency (4). Moreover, vitamin D binding receptor protein and 25-OHD urinary extraction are associated with profound vitamin D deficiency, in IGS. Constitutional symptoms, such as weakness and fatigue, are the conditions that may occur in the deficiency of both vitamin B12 and vitamin D. For this reason, we would like to emphasize the importance of monitoring vitamin D levels periodically in patients diagnosed with IGS, as clinical findings may be similar.

Case Report

An 11-year-old Syrian girl patient who complained of weakness, easy fatigue, numbness in hands and feet, loss of appetite, and hypocalcemia was detected in laboratory parameters. She was referred to the pediatric endocrinology clinic of our hospital. Height: 141cm (-0.5 SDS), weight: 41kg (0.4 SDS) BMI: 20.5 (0.8 SDS). There was consanguinity between the parents. Muscle weakness, cramps, limb paresthesia, Chovestek sign, and Trousseau sign were not detected. The neurologic examination evaluated according to age was normal. Abdominal examination was normal and the liver and spleen were nonpalpable. There was no jaundice, but she was pale.

Laboratory findings showed WBC: 6800/mm3, Hb: 9.8 g/dl, MCV: 116 fl, PLT: 280000/mm3, Calcium (Ca): 5.8mg/dl, Phosphorus (P): 3.1mg/dl, Alkaline Phosphatase (ALP): 360U/L, Magnesium:1.8mg/dl, 25-OH D3: 1.4ng/ml, Lactate Dehydrogenase (LDH): 589U/L, Parathormone (PTH): 406.2pg/ml, ionized Ca:1.1. In a spot urine sample, Calcium/Creatinine ratio was 0.02 and there was proteinuria (+2). In peripheral blood smear; poikilocytosis, anisocytosis, macroovalocytosis, and hypersegmented neutrophils were observed (Figure 1, 2). Iron levels and erythrocyte folate levels were normal. Folic Acid level was 8 ng/ml but Vitamin B12 level was found to be immeasurably low (Table 1).

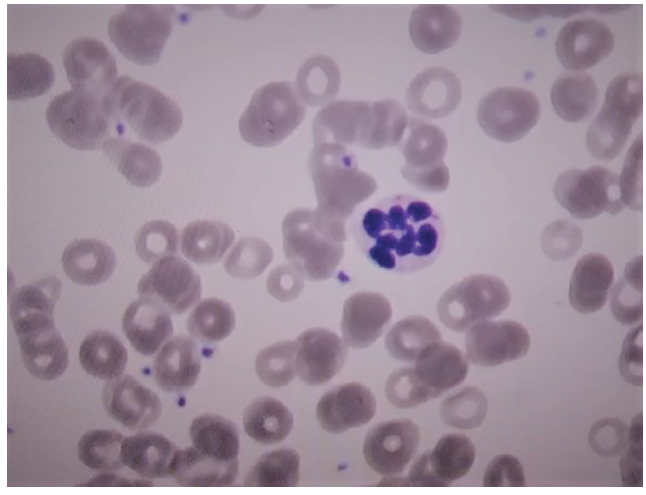

Figure 1. Peripheral Blood Smear - Hypersegmented neutrophil

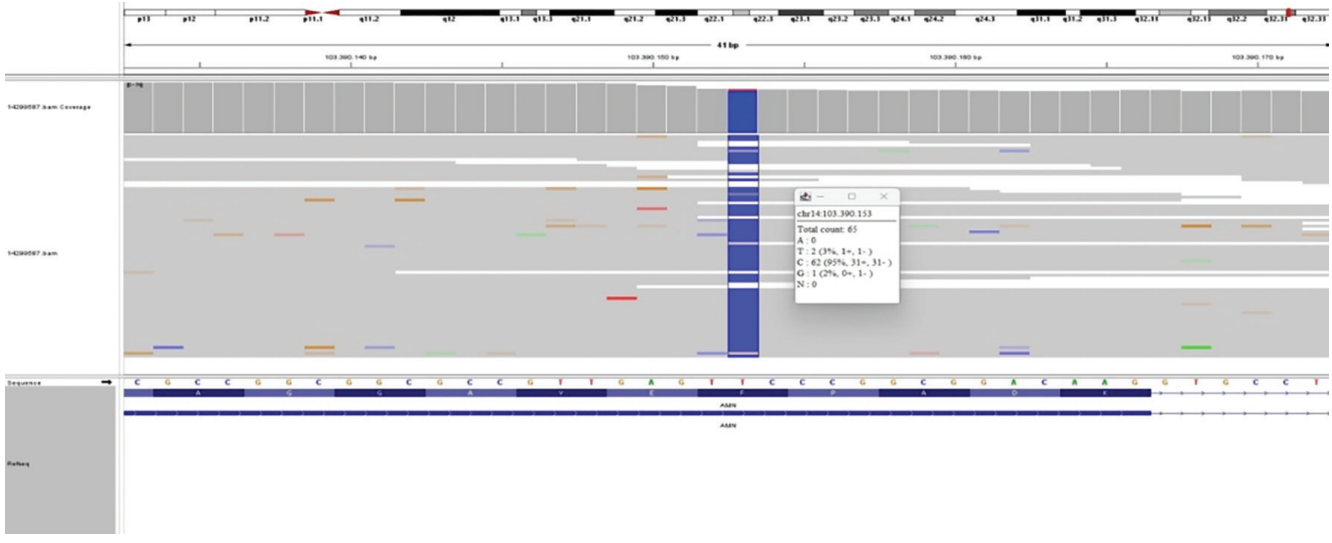

Figure 2. Genetic AMN variant

Tablo 1. The patient's laboratory findings before and after treatment (3 month later)			
Parametre	**Reference range**	**Before treatment**	**After treatment**
Hemoglobin (g/dL)	11.5 – 15.5	9.8	12.8
MCV (fL)	75 – 90	116	83
WBC (/mm³)	5,000 – 14,000	6800	7,200
Platelet (/mm³)	150,000 – 450,000	280,000	280,000
Vitamin B12 (pg/mL)	200 – 900	<83	640
Folat (ng/mL)	3 – 17	<3	9.2
25-OH D3 (ng/mL)	20 – 50	1.4	24
Ca (mg/dL)	8.5 – 10.5	5.8	9.4
Phosphorus (mg/dL)	2.5 – 5.5	3.1	4.3
Ürine protein	Negatif	++	Negatif
PTH (pg/ml)	15-65	406.2	90
ALP U/L	30-120	360	125

The initial differential diagnoses list included hypocalcemia, vitamin D deficiency, vitamin B12 deficiency, megaloblastic anemia and Imerslund-Gräsbeck syndrome (IGS). Megaloblastic anemia, proteinuria, and vitamin B12 deficiency were detected. She is the daughter of a family of Iraqi origin. Because the patient had a consanguineous marriage between the parents and described a diet rich in vitamin B12, IGS was primarily suspected and genetic testing was performed.

Intravenous Ca was given immediately as 1cc/kg and then oral Ca and vitamin D 6000 Ü/ day treatment was started. The first administration of cyanocobalamin (1000 mcg/day) IM for three consecutive days was given, and the maintenance dose consisted of 1000 mcg a week for one month (four doses overall), followed by 1000 mcg administered monthly.

Genomic DNA (gDNA) was extracted from peripheral venous blood samples taken from the patient following the manufacturer's protocol using High Pure PCR Template Preparation Kit (Roche Diagnostics, Mannheim, Germany). Clinical Exome Sequencing Libraries were prepared according to the manufacturer's using Human Comprehensive Exome Panel (Twist Bioscience, South San Francisco). Following the target process, libraries were sequenced on the DNBSEQ-G400 (MGI Tech, China) at 80-100X on-target depth with 150 bp paired-end. Alignment to GRCh38 was done using BWA-MEM 0.7.17 (5). GenomizeSeq (Version 6.13.1) software was used for analysis with the reference human genome (GRCh38). Variants of interest were visually checked on Integrative Genomics Viewer (IGV) (6). The Human Genome Mutation Database (HGMD, http://www.hgmd.cf.ac.uk/ac/index.php), VarSome (https://varsome.com/), and ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), novel variants in the databases were checked. Genetic analysis showed a homozygous variant c.149T>C (p.Phe50Ser) in the AMN (NM_030943.4) gene. This change, defined as uncertain significance in the ClinVar database, was not recorded in the public population databases of the Leiden Open Variation Database (LOVD, https://www.lovd.nl) and Genome Aggregation Database (gnomAD, https://gnomad.broadinstitute.org/).

Our case presented with symptoms of vitamin D deficiency and was diagnosed with autosomal recessive hereditary imerslund-gräsbeck syndrome, which is a rare form of vitamin B12 deficiency. The patient 's nutritional history should be taken carefully, and his personal and family history should be questioned in detail. Although our patient had both vitamin D and vitamin B12 deficiencies, there were no specific physical examination findings for these deficiencies.

Discussion

Inherited causes of vitamin B12 malabsorption in children include lack of intrinsic factor, abnormal intrinsic factor, and a deficiency of transcobalamin II (7). IGS is a relatively rare cause of megaloblastic anemia due to the malabsorption of vitamin B12. The clinical and laboratory abnormalities show a significant overlap in IGS and intrinsic factor deficiency (IFD) and are characterized by megaloblastic anemia and low vitamin B12. The presence of asymptomatic proteinuria is specific to IGS. In the past, the Schilling test was used to differentiate between conditions. Currently, genetic testing is

used as the first line of investigation (8). Proteinuria has been described in many IGS cases, although its absence does not exclude the diagnosis (9).

In our patient, the detection of asymptomatic proteinuria in repeated urine analyses was an important clue that led us to the diagnosis. As a result of the genetic test, AMN c.149T>C homozygous pathogenic variant was detected. The CUBN and AMN genes encode two subunits (cubilin and amnionless) of the cobalamin intrinsic factor of the ileal mucosa (10). The cubilin-amnionless complex is called cubam, and is considered to be essential for intestinal cobalamin uptake, renal protein reabsorption and early rodent embryogenesis (11). The Cubam receptor is expressed in the small intestine and proximal renal tubules of the kidney. Low-molecular-weight proteinüria had been previously reported in some IGS patients due to CUBN and AMN gene mutations previously (12). The common feature of these patients is the lack of cubilin cell surface expression, which is caused by both mutation. Also, our patient had vitamin D deficiency and hypocalcemia. But, we could not associate vitamin D deficiency at a level that would cause hypocalcemia with low intake alone. Fyfe et al. (11) demonstrated that the functional cobalamin–intrinsic factor receptor consists of a complex of cubilin and amnionless.

Several IGS cases have been reported from Türkiye, mostly in consanguineous families (3-13,14). Karagüzel et al. (13) described two Turkish children with homozygous CUBN mutations, both presenting with proteinuria and megaloblastic anemia. Similarly, Karagüzel et al. (13) and Aksu et al. (14) emphasized that unexplained megaloblastic anemia accompanied by mild proteinuria should raise suspicion for IGS in the Turkish pediatric population (13,14). Including these regional data underscores the need for awareness in areas where consanguineous marriage is prevalent.

In 2013, Storm reported four Imerslund gräsbeck patients with AMN gene mutation and showed ürinary extraction of albumin, transferrin, VDBP, apoa1, α1M, and RPB proteins. Our observation of vitamin D deficiency in our affected patient is thus consistent with the proposed hypothesis.

From a clinical perspective, hypocalcemia and vitamin D deficiency in our patient highlight the importance of a multidisciplinary approach, involving hematology, endocrinology, and genetics. Patients with IGS should be monitored for metabolic abnormalities beyond cobalamin deficiency. Periodic follow-up of calcium, phosphorus, and vitamin D status is recommended to ensure optimal long-term management.

Conclusion

Our patient demonstrates that Imerslund–Gräsbeck syndrome may coexist with profound vitamin D deficiency, leading to an unusual presentation with hypocalcemia. Clinicians should consider evaluating vitamin D status in patients with IGS to ensure comprehensive management. Reporting such cases is crucial to improve understanding of the phenotypic variability and optimize long-term follow-up strategies.

Footnotes

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DERLEME REVIEW

Haftalık Büyüme Hormonu Somatrogon ve Klinik Kullanım İlkeleri

Weekly Growth Hormone Somatrogon and Clinical Use Principles

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Öz

Rekombinant insan büyüme hormonu yaklaşık 40 yıldır kullanımda olup günlük tek doz şeklinde uygulanmaktadır. Uzun etkili büyüme hormonları tedavi uyumunu artırmak ve tedavi yükünü azaltmak için geliştirilmektedir. Ülkemizde ilk ve tek haftalık büyüme hormonu olan somatrogonun hastalar tarafından iyi tolere edildiği, ciddi advers olaya rastlanmadığı belirlenmiştir. Somatrogon, 9 Mart 2023'te ülkemizde ruhsat almış ve 17 Mayıs 2024'te geri ödeme kapsamına girmiştir. Önerilen dozlama haftada bir kez, haftanın aynı günü 0,66 mg/kg/hafta şeklinde olup 24 mg ve 60 mg şeklinde kullanıma hazır ve tek kullanımlık iki farklı kalemi vardır. Somatrogonun haftalık uygulama kolaylığı ve tedavi yükü açısından avantaj sağlaması ve tedavi uyumunu iyileştirmesi beklenmektedir. Ayrıca uzun dönem çalışmaları ile tedavi etkinliği, güvenliği ve uyumunun yakın takip edilmesi önemlidir.

Abstract

The recombinant human growth hormone has been used for about 40 years and is administered as a single daily dose. Long-acting growth hormones are developed to enhance therapy adherence and reduce therapy load. Somatrogone, the first and only weekly growth hormone in our country, has been well tolerated by patients, and no serious adverse events have occurred. Somatrogon obtained a license in our country on March 9, 2023, and was reimbursed on May 17, 2024. The recommended dosage is once a week, 0.66 mg/kg/dose on the same day of the week, available for use in the forms of 24 mg and 60 mg. Somatrogon is expected to provide an advantage in ease of weekly administration and treatment load and improve treatment compliance. It is also essential to closely monitor the long-term studies and the treatment's effectiveness, safety, and adherence.

Anahtar kelimeler
Büyüme hormonu, haftalık tedavi, somatragon, tedavi uyumu

Keywords
Growth hormone, weekly treatment, somatrogone, adherence

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Giriş

Uzun etkili Büyüme Hormonları: Kısa Geliştirilme Tarihi, Dünya Ve Türkiye'de Onay Durumu

Rekombinant insan büyüme hormonu (rhGH) 1985'teki FDA onayı ile kullanıma girmiştir (1). 35 yılı aşkın süredir klinik pratikte günlük büyüme hormonu kullanılmaktadır, 20 kayıt kütüğü ile somatropin tedavisinin gerçek yaşamdaki etkinliği ve güvenliliği gösterilmiştir (2,3). Günlük büyüme hormonu tedavisine uyumun tedavi sürecinde azaldığı ve düşük uyumun tedavi başarısızlığına neden olduğu çalışmalarda gösterilmiştir (4,5). Uyumu arttırarak tedavi başarısını yükseltmek ve tedavi yükünü azaltmak için uzun etkili büyüme hormonu preparatları uzun süredir geliştirilmeye çalışılmaktaydı (6). Haftalık büyüme hormonlarının farklı formları birçok ülkede faz çalışmalarını geçip piyasaya sürülmüştür. Güncel olarak Amerika Birleşik Devletler'i ve Avrupa Birliği Ülkeleri'nde haftalık büyüme hormonları; Somatrogon, Somapacitan ve Lonapegsomatropin ruhsatlı olarak kullanımdadır (7). Ülkemizde Somatrogon 9 Mart 2023 tarihinde ruhsat, 17 Mayıs 2024'ten itibaren ise geri ödeme alarak kullanıma ilk giren uzun etkili büyüme hormonu olmuştur.

Somatrogon Molekül Yapısı ve Etki Mekanizması

Somatrogon, insan koryonik gonadotropinin (hCG) beta zincirinden C-terminal peptidin (CTP) 3 kopyası ile rhGH füzyonu ile oluşturulmuş bir glikoproteindir (8). CTP füzyon proteini teknolojisi sayesinde somatrogonun klirensi azalmakta, dolaşımdaki yarı ömrü uzamaktadır ve haftalık olarak kullanılabilmesine olanak sağlamaktadır (9). Somatrogon, rhGH'ye benzer biçimde, büyüme hormonu reseptörüne bağlanarak ve karaciğerden salgılanan insulin like growth factor 1(IGF-1) aracılığı ile etkilerini göstermektedir (10).

Farmakokinetik profili belirlemeye yönelik yapılan bir çalışmada somatrogonun günlük rgGH'ye göre 5 ila 10 kat daha uzun yarı ömre sahip olduğu gösterilmiştir (11). Farmakodinamik modele göre somatrogon enjeksiyonunu takiben 48. saatte alınan IGF-1 ölçümünün maksimum değeri, 96. saatte alınan IGF-1 ölçümünün ise hafta boyu olan ortalama değeri yansıttığı gösterilmiştir (12).

Klinik Araştırma Programı

2009 yılında faz 1 klinik çalışmalar ile somatrogon klinik geliştirme programı başlamıştır (13). Faz 2 çalışmasında prepubertal büyüme hormonu eksikliğine sahip çocuklarda somatrogonun 0,66 mg/kg/hafta dozunun, somatropin 34 mcg/kg/gün dozu ile benzer etkinlikte olduğuna kanaat getirilmiştir. Bu çalışmada somatrogonun hastalar tarafından iyi tolere edilmiş, ciddi advers olaya rastlanmamış ve güvenliliği gösterilmiştir (11). Faz 2 çalışması (2012 yılında başlayan), açık etiketli bir uzatma formatında devam ettirilmiştir, 5 yıllık takip sonucu ortaya çıkan sonuçlarda; hastaların yıllık boy uzama hızları ve boy standart deviasyon skoru (SDS) kazançları faz 2 çalışmasına hem somatrogon ile başlayan hem somatropin ile başlayıp uzatma çalışmasında somatrogon ile devam eden hastalarda korunmuş, çalışmadaki hastalar tarafından uzun dönemde iyi tolere edilmeye devam etmiştir (14).

Faz 3 çalışmasında (2017 yılında başlayan) prepubertal büyüme hormonu eksikliğine sahip 3-12 yaş arasındaki çocuk hastalarda somatrogonun etkinliği ve güvenliği gösterilmiştir. İlk aşamada 109 hastalık somatrogon grubuna karşılık, 115 somatropin grubunda hasta 1:1 randomize edilmiştir. Somatrogon grubundaki hastalar 0,66 mg/kg/hafta, somatropin grubundaki hastalar ise 34 mcg/kg/gün tedavileri ile 1 yıl boyunda takip edilmiştir. Somatrogon grubundaki hastaların boy uzama hızı 10,1 cm/yıl, somatropin grubundaki hastaların boy uzama hızı 9,78 cm/yıl olarak kaydedilmiştir. Bu sonuçlara göre haftalık somatrogon tedavisinin yıllığa çevrilmiş boy uzama hızı açısından günlük somatropin tedavisi ile benzer etkinlikte olduğu gösterilmiştir. Somatrogon bu çalışmada günlük somatropin ile benzer güvenlik profili göstermiş, çoğunlukla hafif ve orta şiddette tedavi esnasında ortaya çıkan advers olaylar gözlenmiş ve hastalar tarafından iyi tolere edilmiştir (15).

Endikasyon, Pozoloji ve Klinik Pratiğe Yönelik Öneriler

Ülkemizde güncel olarak 3 yaş üzerindeki pediatrik hastalarda büyüme hormonu yetersizliğine bağlı büyüme bozukluğu tedavisinde endikasyonu bulunmaktadır. Somatrogon için önerilen dozlama; haftada bir kez, haftanın aynı günü, günün herhangi bir saatinde 0,66 mg/kg/hafta şeklindedir. Doz, hekimin her bir hastanın gereksinimleri konusundaki uzman bilgisine dayanarak yukarı veya aşağıya yuvarlanabilir. Somatrogon karın, uyluk, kalça veya üst kol bölgesine subkutan enjeksiyon ile uygulanır. Enjeksiyon bölgesi mutlaka haftada bir değiştirilmeli yani rotasyon uygulanmalıdır. Üst kola ve kalçaya uygulama bakım veren kişi tarafından uygulanmalıdır. Hastalar ve bakım veren kişiler uygulama konusunda eğitim almalıdırlar.

Somatrogon 24 mg/1,2 ml ve 60 mg/1,2 ml şeklinde 2 form halinde kullanıma hazır ve tek kullanımlık kalemler ile uygulanmaktadır. 24 mg içeren kalem formu 0,2 mg artışlarla

bir defada maksimum 12 mg uygulamaya izin vermektedir. 60 mg içeren kalem formu 0,5 mg artışlarla bir defada maksimum 30 mg uygulamaya izin vermektedir. 30 mg üzerinde haftalık doz ihtiyacı olan hastalarda (vücut ağırlığı >45 kg) 2 enjeksiyon 2 farklı ekstremiteye uygulanmaktadır. Aşırı kilolu veya şişman hastalarda maksimum dozla ilgili herhangi bir yönlendirme olmadığından, klinisyen dozu hesaplarken fiili vücut ağırlığı yerine ideal vücut ağırlığı veya vücut yüzey alanını kullanmak isteyebilir.

Somatrogon dozu gerekli durumlarda hastanın büyüme hızı, vücut ağırlığı IGF-1 serum konsantrasyonuna göre ayarlanabilir. İlk IGF-1 düzeyi tedavi başlandıktan en erken 6-8 hafta sonra, son dozdan 4 gün sonra bakılmalıdır. Ardından 4 ile 6 ayda bir IGF-1 bakılmalıdır. IGF-1 için hedeflenen standart sapma skoru (SDS), 2 SDS'yi geçmeyecek şekilde (-2 ve +2 arasında) üst normal aralıkta olmalıdır. Serum IGF-I konsantrasyonu cinsiyet ve yaşa göre ortalama referans değerini 2 SDS'den fazla aşan hastalarda somatrogon dozu %15 azaltılmalıdır.

Hastanın büyüme hızı ilk yıl içinde artmazsa, tedaviye uyum ve büyüme başarısızlığının diğer nedenleri (örn. hipotiroidizm, yetersiz beslenme, ileri kemik yaşı) değerlendirmelidir. 4-6 ayda bir oksoloji, 12 ayda bir pubertal durum/tiroid fonksiyonu yapılmasını önerilir. Ergenlik döneminde pubertal durumun daha sık değerlendirilmesi düşünülmelidir. Tıbbi endişelerin söz konusu olması durumunda veya nihai yetişkin boyuna yakın olduğu düşünülen genç birinde büyüme potansiyeli değerlendiriliyorsa tedavi sırasında 12-24 ayda bir kemik yaşını değerlendirmeyi göz önünde bulundurulmalıdır. Epifiz/büyüme plakları kapandığına dair kanıt olduğunda tedavi kesilmelidir.

Hastalar düzenli dozlama günlerini sürdürmelidir. Bir doz atlanırsa atlanan dozu takip eden 3 gün içinde mümkün olan en kısa sürede somatrogon uygulanmalı ve sonrasında her zamanki haftada bir dozlama düzenine devam edilmelidir. Eğer 3 günden uzun süre geçtiyse, unutulan doz atlanarak sonraki doz planlanan normal günde uygulanmalıdır. Her durumda, hastalar daha sonra haftada bir kez olarak düzenli normal doz programlarına devam edebilir. İki doz arasındaki süre en az 3 gün olacak şekilde gerekirse haftalık uygulama günü değiştirilebilir. Yeni bir uygulama günü belirlendikten sonra haftalık uygulamaya devam edilmelidir.

Somatrogon buzdolabında (2-8 °C) saklanmalı, dondurulmamalıdır. Direkt güneş ışığından korumak için kutusunda saklanmalıdır. Kalem doğrudan buzdolabından çıkarılıp uygulanabilir, ancak daha rahat bir enjeksiyon için kalemi 30 dk. oda sıcaklığında tutulup ardından uygulanması tavsiye edilmektedir. Kullanılmadan önce oda sıcaklığında en fazla 2 saat kalabilir. İlk kullanım tarihinden itibaren 4 haftadan fazla (28 gün) geçtiyse, içinde ilaç kalmış olsa bile kalemin atılması gerekir. Aynı kalem bu 28 günlük sürede en fazla 5 kez kullanılabilir. Kullanıma hazır kalem boşsa, dondurulmuşsa, 32°C'den yüksek bir sıcaklığa maruz kaldıysa, her bir kullanımda buzdolabından 2 saatten fazla süre için çıkarılmışsa, 5 defa kullanıldıysa veya ilk kullanımından sonra 28 günden fazla süre geçtiyse içinde kullanılmamış ilaç olsa dahi kalem atılmalıdır. Tüm dozlar doğru şekilde uygulandıktan sonra, az miktarda steril somatrogon çözeltisi kalemde kalabilir. Hastalara kalan çözeltiyi kullanmaya çalışmamaları ve kalemi doğru şekilde imha etmeleri yönünde talimat verilmelidir.

Güvenlik ve Gelecek

Haftalık büyüme hormonunda en büyük tartışma konusu uzun dönem etki ve yan etkilerdir. Günlük büyüme hormonunda şu ana kadar yaklaşık 200 binin üzerindeki çocuğun uzun dönem güvenlik verileri vardır. Ancak hem hekimlerin hem de ailelerin ülkemizde kısa süre önce kullanılmaya başlayan uzun etkili büyüme hormonunun etki ve yan etkileri konusunda endişeleri doğaldır. Çalışmalarda etkinlik ve güvenlik açısından günlük büyüme hormonu tedavisine göre benzer sonuçlar yer alsa da, uzun dönemli veriler için yeni çalışmalara ihtiyaç vardır. Şu ana kadar en fazla 5 yıllık veriler tam metin halinde ve 8 yıllık veriler poster halinde sunulmuş ve belirgin yan etki gözlenmemiştir (2,16,17). Yine 3 yaşın altındaki çocuklarda tedavi etkinliği ve pubertal dönemdeki doz ayarında çalışmalara ihtiyaç vardır.

Sonuç

Haftalık uygulamaya izin veren uzun etkili büyüme hormonu preparatları kullanım kolaylığı ve tedavi yükü açısından hastalara avantaj sağlamaktadır, bu nedenle tedavi uyumunu iyileştirmesi beklenmektedir. Somatrogon başlanan hastalarda tedavi etkinliği, güvenliği ve uyumunun yakın takip edilmesi önemlidir.

Dipnot

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EDİTÖRE MEKTUP LETTER TO THE EDITOR

Trombositopeni Etiyolojisinde Hatırlanması Gereken Bir Sebep: Portal Hipertansiyon

A Cause to be Remembered in the Etiology of Thrombocytopenia: Portal Hypertension

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Sayın Editör,

"Çocukluk Çağı Trombositopenisi: Retrospektif Bir İnceleme" başlıklı makaleniz (1) sistematik yaklaşımıyla ülkemizdeki pediatrik trombositopeni etiyolojilerine yönelik kapsamlı bir incelemedir.

Makalede siroz yalnızca "otoimmün hastalıklar" başlığı altında sınıflandırılmıştır. Oysa siroz; otoimmün hepatit dışında viral, metabolik, genetik, vasküler veya idiopatik birçok farklı etiyolojik sebeplere bağlı olarak gelişebilir. Bu nedenle sirozun tek bir grup altında sınıflandırılması, etiyolojik çeşitliliğin göz ardı edilmesine neden olabilir. Ayrıca, sirozun kendisi doğrudan trombositopeni nedeni olmaktan çok, siroza bağlı gelişen portal hipertansiyon ve hipersplenizmin sekonder etkisiyle trombositopeni geliştiği göz önünde bulundurulmalıdır (2).

Dahası, yalnızca sirotik hastalarda değil, non-sirotik portal hipertansiyon tablolarında da (örneğin portal ven trombozu, konjenital hepatik fibrozis, idiopatik portal hipertansiyon) hipersplenizme bağlı olarak da trombositopeni gelişebilir (3,4). Literatürde, portal hipertansiyonlu çocuk hastaların %60'ından daha fazlasında hipersplenizm bulunduğu ve bu hastaların %55-75'inde trombositopeni geliştiği bildirilmiştir. Bu oran, portal hipertansiyona sekonder gelişen hipersplenizmin çocukluk çağında trombositopeninin önemli fakat gözden kaçabilen bir nedeni olduğunu ortaya koymaktadır (4,5).

Makalede 440 hastadan oluşan bir trombositopeni kohortu sunulmasına rağmen, hipersplenizm kaynaklı sekonder trombositopeni nedenlerine dair doğrudan bir alt grup tanımlanmamıştır. Bu durum, pediatrik hasta yönetiminde özellikle izole trombositopeni ile başvuran portal hipertansiyon hastalarının gözden kaçmasına neden olabilir.

Bu bağlamda hem literatürle uyumlu hem de klinik pratiği destekleyici şekilde, makaleye aşağıdaki katkıların yapılmasının uygun olacağını düşünüyorum:

1. Sirotik olgularda trombositopeninin primer nedeni siroz değil, siroza sekonder gelişen portal hipertansiyon ve hipersplenizmdir.
2. Hipersplenizm yalnızca sirotik değil, non-sirotik olgularda da trombositopeniye sebep olabilir. Non-sirotik olgularda özellikle portal ven trombozu gibi prehepatik nedenler de unutulmamalıdır.

3. Gelecek çalışmalarda, hipersplenizm kaynaklı trombositopeninin, ayrıca sorgulanması gereken bir alt grup olarak tanımlanması, tanısal sınıflamaların daha eksiksiz yapılmasına katkı sağlayacaktır.

Dipnot

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