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Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Türkiye
Phone: +90 (530) 177 30 97
E-mail: info@galenos.com.tr
yayin@galenos.com.tr
Web: www.galenos.com.tr
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The Journal of Pediatric Academy is the official publication of the Kayseri Child Health Association.

The Journal of Pediatric Academy which was established in 2020 is an international, unbiased double blinded peer-reviewed, open-access electronic and only-online published journal in the English language. The Journal of Pediatric Academy is published 4 times a year (March, June, September, December) and accepts original research articles, invited review articles, case reports and clinical images in all areas of pediatric research, which summarize recent developments about a particular subject based on standards of excellence and expertise.

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Kayseri Chamber of Medicine,
Seyitgazi Mah. Nuh Naci Yazgan Cad. Geriatri Merkezi Binası K:1 N:4, Melikgazi, Kayseri - Türkiye
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Journal of Pediatric Academy (JPA) reports on major advances in the diagnosis and treatment of diseases in children. Each issue presents informative original research articles, review articles, case reports, image corners, and letters to the editor from leading clinicians and investigators worldwide.

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Manuscript Types

JPA publishes the types of articles briefly described below.

Editorial Comment:

Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with a high reputation on the topic of the research article published in the journal. The authors are selected and invited by the journal to provide such comments. The text should contain 1500 words or fewer. it includes 5 figures and/or tables or fewer and 15 references or fewer.

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Invited reviews prepared by authors who have extensive knowledge of a particular field and whose scientific background has been translated into a large volume of publications with a high citation potential are welcomed. Submissions from such authors may also be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies.

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Letters To The Editor:

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Table 1.
Limitations for each manuscript type

Manuscript Type	Word Limit	Abstract Word	Limit Reference	Limit Table Limit	Figure Limit
Editorial comment	1500	No abstract	15	2	5
Original Article	3500	300	50	6	6
Invited Review	5000	350	100	6	10
Case Report	1500	200	15	2	5
Image corner	500	No abstract	5	-	3
Letter to the Editor	100	No abstract	5	1	1

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Journal Article:

1. Ang KK, Price RE, Stephens LC, et al. The tolerance of primate spinal cord to re-irradiation. *Int J Radiat Oncol Biol Phys*. 1993;25:459–464.

Journal Article published in non-English Languages:

2. Altuntaş N, Çelebi DT, Koçak M, Andıran N. Yenidoğan bebeklerde direkt coombs testi taraması ve pozitifliğinin morbidite üzerine, etkisi; tek merkezd eneyimi. *Pam Tip Derg* 2015;8:39-44. (in Turkish)

Book Chapter:

3. Dimery IW. Chemotherapy in head and neck cancer. In: Myerhoff WI, Rice DH, eds. Otolaryngology: head and neck surgery, 2nd ed. Philadelphia: WB Saunders, 1992:1027–1045.

Entire Book:

4. Virchow R. Cellular Pathology. Philadelphia: JB Lippincott, 1863.

Software:

5. Epi Info [computer program]. Version 6. Atlanta, GA: Centers for Disease Control and Prevention; 1994.

Online Journals:

6. Friedman SA. Preeclampsia: a review of the role of prostaglandins. Obstet Gynecol [serial online]. January 1988;71:22–37. Available from: BRS Information Technologies, McLean, VA. Accessed December 15, 1990.

Database:

7. CANCERNET-PDQ [database online]. Bethesda, MD: National Cancer Institute; 1996. Updated March 29, 1996.

World Wide Web:

8. Gostin LO. Drug use and HIV/AIDS [JAMA HIV/AIDS Web site]. June 1, 1996. Available at: http://www.ama-assn.org/special/hiv/ethics. Accessed June 26, 1997.

URL (Uniform Resource Locator)

9. (J. M. Kramer, K. Kramer [jmkramer@umich.edu], e-mail, March 6, 1996).

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Contents

Original Articles

Case Reports

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Parental Knowledge and Attitudes Toward Pediatric Fever: A Comparative Study Between Healthcare and Non-healthcare Parents

Author(s)

Gülcan Özomay Baykal, İlhan Asya Tanju

Affiliation(s)

Maltepe University Faculty of Medicine, Department of Pediatrics, İstanbul, Türkiye

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Abstract

Fever is a leading cause of pediatric emergency visits and, despite often being self-limiting, remains a source of anxiety and frequent mismanagement. Parents' knowledge and attitudes significantly influence fever management and healthcare-seeking behaviors. This study aimed to evaluate and compare fever-related knowledge and attitudes between healthcare-professional parents and non-professional parents to inform targeted educational interventions. A cross-sectional study was conducted at the Departments of Pediatric Outpatient and Emergency, Maltepe University Faculty of Medicine and enrolled 400 parents (200 healthcare-professionals, 200 non-professionals). A 52-item structured questionnaire, administered through face-to-face interviews, assessed socio-demographic characteristics, fever management knowledge, and attitudes toward febrile seizures (FS). Among the survey participants, 23% were nurses, 18% were physicians, 5% were technicians, 3% were other healthcare staff, and 1% were emergency medical technicians. Information sources differed significantly between groups, with groups varying in their reliance on medical personnel, the internet, books, relatives, and personal experience. Both groups most commonly used axillary temperature measurements. Thermometer ownership was similar, but definitions of normal temperature and fever thresholds differed significantly. Knowledge gaps and fever-related anxiety were evident in both healthcare and non-healthcare parents, contributing to inappropriate management practices. Tailored educational strategies addressing misconceptions about fever and FS are essential to promote evidence-based pediatric care and improve child health outcomes.

Keywords: Fever, febrile seizures, parents' attitudes

Introduction

Fever is among the most frequent causes of pediatric emergency visits, accounting for 20-30% of presentations worldwide and up to 71% in Türkiye[1-5]. Although fever represents a physiological immune response rather than a disease itself, misconceptions regarding normal body temperature, fever thresholds and appropriate management remain widespread[1,2,6]. These misconceptions often provoke excessive parental anxiety and lead to unnecessary or inappropriate interventions[6-9].

While most febrile illnesses in children are self-limiting viral infections, persistent fears of serious bacterial disease and potential complications continue to influence

Correspondence: Gülcan Özomay Baykal MD, Maltepe University Faculty of Medicine, Department of Pediatrics, İstanbul, Türkiye
E-mail: gulcanozomaybaykal@gmail.com **ORCID:** 0000-0003-3427-1418

parental behavior[10-13]. The phenomenon known as "fever phobia," first described by Schmitt[14], reflects exaggerated concerns among caregivers and even healthcare providers, particularly regarding seizures, the most common seizure type in early childhood. Despite their generally benign prognosis, febrile seizures (FS) are frequently misinterpreted as indicators of brain damage or subsequent epilepsy, thereby prompting anxiety-driven management practices[15-19].

Highlights

- This study compared the fever knowledge of healthcare and non-healthcare parents.
- Healthcare professionals had greater knowledge of fever but nonetheless held important misconceptions.
- Non-healthcare parents relied more on touch to detect fever and reported greater anxiety.
- Fear of febrile convulsions was widespread in both groups, contributing to the phenomenon of "fever phobia".
- Education is urgently needed to promote safe, evidence-based fever management in children.

Previous studies conducted both internationally and in Türkiye have demonstrated persistent gaps in parental knowledge and attitudes toward childhood fever[10,20]. However, most existing research has focused on the general parent population, with limited attention to parents who are healthcare professionals. This distinction is clinically important, as healthcare-professional parents may be assumed to possess superior knowledge, yet simultaneously rely on outdated training, experiential practices, or heightened risk perception. Direct comparative data between parents who are healthcare professionals and those who are not remain limited.

Accordingly, the present study was designed to compare fever-related knowledge, attitudes, and management practices between healthcare-professional parents and non-healthcare-professional parents presenting to the pediatric outpatient and emergency services at Maltepe University Faculty of Medicine. By explicitly examining this underexplored comparison, the study aims to identify persistent misconceptions across both groups and to inform the development of targeted, evidence-based educational interventions for families and healthcare providers.

Materials and Methods

Study Design and Setting

This cross-sectional study was conducted between January and June 2017 at the Pediatric Outpatient and Emergency Departments of Maltepe University Faculty of Medicine, a tertiary care facility in İstanbul, Türkiye. The study recruited parents who were visiting the hospital with children aged 0-16 years. Parents accompanying children older than 16 years were excluded.

Participants

A total of 400 parents were enrolled, comprising 200 non-healthcare professionals (Group 1) and 200 healthcare professionals (Group 2). Healthcare professionals include physicians, nurses, technicians, and other medical staff. Eligibility criteria required that participants be the primary caregiver of the child and be able to provide informed consent. Recruitment occurred during routine clinical visits, and participation was voluntary. The category "other healthcare staff" included allied health professionals such as laboratory staff.

Variables and Data Collection

The primary outcomes were fever-related knowledge, attitudes, and practices, including temperature measurement methods, definitions of normal and febrile temperatures, management behaviors, and responses to FSs. Potential confounders, including socio-demographic characteristics and professional background, were recorded.

Data was collected via structured, face-to-face interviews using a 52-item questionnaire developed based on literature review and expert input. The questionnaire included:

- Socio-demographics (13 items: age, education, number of children, occupation, professional role, and experience for healthcare professionals).
- Fever knowledge and attitudes (28 items: temperature sites, fever definition, antipyretic use, anxiety levels).
- FS (11 items: recognition, perceived causes, appropriate interventions).

The same instrument and method of administration were used for both groups to ensure comparability. Socio-demographic characteristics of the participants and sources of information regarding fever are summarized in **Tables 1, 2,** respectively. Knowledge-based items were evaluated for consistency with widely accepted pediatric clinical definitions: operational definitions of fever thresholds are presented in **Table 3**, and fever management practices are detailed in **Table 4**. Definitions and references regarding FS are provided in **Table 5**.

Definitions of thresholds for normal body temperature, fever, and high fever were aligned with standard pediatric clinical references and international practice guidelines and took into account commonly accepted temperature cutoffs used in routine pediatric care.

Items related to FS were classified based on established clinical characteristics, including age dependency, association with febrile illness, and recommended diagnostic and therapeutic approaches. Classifications reflected the accepted understanding that simple FS occur in children within a specific age range, are associated with fever, and do not routinely require neuroimaging, electroencephalography, or prophylactic antiepileptic treatment in the absence of atypical features.

Bias and Study Size

To minimize interviewer bias, all interviews were conducted by trained research staff using standardized instructions. A sample size of 400 participants (200

per group) was targeted to ensure sufficient statistical power to detect significant differences in knowledge and practice variables between the two groups. Convenience sampling was used to facilitate recruitment during routine clinical visits; however, this non-probability sampling method may introduce selection bias and limit generalizability compared to random sampling techniques.

Ethical Considerations

The study was approved by the Clinical Research Ethics Committee of Maltepe University Faculty of Medicine (approval number: 2016-900-57, date: 29.12.2016). Institutional permissions were obtained, and written informed consent was secured from all participants prior to enrollment.

Statistical Analysis

Analyses were performed using IBM Corp. (2013) IBM SPSS Statistics for Windows, version 22.0. IBM Corp., Armonk, NY. Descriptive statistics were presented as frequencies and percentages for categorical variables, and as means ± standard deviation or medians (range) for continuous variables. Normality was assessed using the Shapiro-Wilk test.

Between-group comparisons were conducted using Pearson's chi-square test or Fisher's exact test for categorical variables. Independent Samples t-tests or Mann-Whitney U tests were applied to continuous variables, depending on the distribution. A two-tailed p-value <0.05 was considered statistically significant.

Results

Participants

During the study period, 400 parents were enrolled: 200 non-healthcare professionals (Group 1) and 200 healthcare professionals (Group 2). All approached participants who met the eligibility criteria consented to participate; therefore, no data on non-participation or attrition are available.

Demographic Characteristics

The mean age of mothers was 34.4±5.9 years and of fathers was 37.7±6.5 years. University-level education was reported by 54.5% of mothers (n=218) and 59.5% of fathers (n=235). Among participating healthcare professionals, the occupational distribution was as follows: nurses (n=94, 47%), physicians (n=73, 37%), technicians (n=18, 9%), other allied health workers (n=13, 6%), and emergency medical technicians (n=2, 1%). Detailed socio-demographic characteristics are presented in **Table 1**.

Fever Awareness and Measurement Practices

Tactile perception was used more frequently by Group 1 (n=136, 68%) than by Group 2 (n=102, 51%; p=0.001) to detect fever. Conversely, thermometer use was significantly higher among healthcare professionals (n=175, 87.5%) than among non-healthcare parents (n=131, 65.5%; p<0.001). Axillary temperature was the preferred site of measurement in both groups, with no significant differences between groups. Nearly all participants reported having a thermometer at home (Group 1: 96; Group 2: 98.5%), with digital axillary thermometers the most common (**Tables 2, 3).** The frequency of fever monitoring was similar across groups, occurring most often at 15-30 -minute intervals (**Figure 1**).

Knowledge of Fever Thresholds

Correct identification of normal body temperature was higher in Group 2 (n=150, 75%) than in Group 1 (n=93, 46.5%; p<0.001). Knowledge of fever thresholds was also greater among healthcare professionals (n=104, 52%) than among non-healthcare parents (n=82, 41%) (p=0.027). Surprisingly, fewer healthcare professionals correctly identified high fever thresholds (n=60, 30%) compared with non-healthcare parents (n=90, 45%; p=0.002) (**Table 3**).

Table 1.
Socio-demographic characteristics of the study population

		n	%	Mean	SD
Gender	Male	124	31		
	Female	276	69		
Marital status	Married	371	92.8		
	Single	29	7.3		
Mothers' age groups	22-35	234	58.5		
	36-40	110	27.5	34.4	5.9
	41 and above	56	14		
Fathers' age groups	25-38	233	58.3		
	39-43	98	24.5	37.7	6.5
	44 and above	68	17		
Mothers' education levels	Primary school	15	3.8		
	High school	104	26		
	Vocational school	63	15.8		
	University	218	54.5		
Fathers' education levels	Primary school	13	3.3		
	High school	103	26.1		
	Vocational school	44	11.1		
	University	235	59.5		
Number of children	One	233	58.3		
	Two	150	37.5		
	Three	16	4		
	Four	1	0.3		
Number of children under age five	None	127	31.8		
	One	228	57		
	Two	45	11.3		
Place of residence	İstanbul and districts	390	97.5		
	Other	10	2.5		

SD: Standard deviation

Table 2.
Comparison of fever information sources and temperature measurement practices by healthcare background

			Group 1		Group 2		
			n	%	n	%	p
Where do you get information about fever?	Doctor/nurse	Yes	181	90.5	165	82.5	0.019
		No	19	9.5	35	17.50	
	Books	Yes	47	23.5	94	47	p<0.001
		No	153	76.5	106	53	
	Magazines/newspapers	Yes	12	6	6	3	0.148
		No	188	94	194	97	
	Television	Yes	22	11	9	4.5	0.015
		No	178	89	191	95.5	
	Internet	Yes	116	58	50	25.5	p<0.001
		No	84	42	150	75	
	Family/relatives	Yes	59	29.5	11	5.5	p<0.001
		No	141	70.5	189	94.5	
	Experience with a previous child	Yes	43	21.5	18	9	p<0.001
		No	157	78.5	182	91	
How do you recognize fever?	By touching skin (tactile perception)	Yes	136	68	102	51	p<0.001
		No	64	32	98	49	
	By general appearance (irritable, crying, etc.)	Yes	56	28	76	38	0.033
		No	144	72	124	62	
	Measuring with thermometer at home	Yes	131	65.5	175	87.5	p<0.001
		No	69	34.5	25	12.5	
	Measurement at healthcare facility	Yes	13	6.5	20	10	0.203
		No	187	93.5	180	90	
Where do you measure fever?	Axillary	Yes	128	64	146	73	0.053
		No	72	36	54	27	
	Rectum	Yes	5	2.5	6	3	0.76
		No	195	97.5	194	97	
	Forehead	Yes	52	26	39	19.5	0.121
		No	148	74	161	80.5	
	Ear	Yes	46	23	47	23.5	0.906
		No	154	77	153	76.5	
	Oral	Yes	38	19	5	2.5	p<0.001
		No	162	81	195	97.5	

Table 3.
Comparison of thermometer use and fever threshold knowledge between groups

		Group 1		Group 2			
		n	%	n	%	x^2	p
Do you have a thermometer at home?		192	96	197	98.5	2.337	0.126
What type of thermometer do you use?	Non-contact forehead	44	22	35	17.5	1.278	0.258
	Axillary digital thermometer	110	55	130	65	4.167	0.041
	Tympanic (ear) thermometer	59	29.5	53	26.50	0.446	0.504
	Mercury glass thermometer	22	11	19	9.50	0.245	0.621
What is the normal body temperature?	Correct answer*	93	46.5	150	75	34.065	p<0.001
What temperature is considered a fever?	Correct answer*	82	41	104	52	4.864	0.027
What temperature is considered a high fever?	Correct answer*	90	45	60	30	9.600	0.002

*: Responses regarding normal body temperature, fever, and high fever were evaluated based on widely accepted pediatric clinical definitions. Normal body temperature was considered to lie approximately between 36.5-37.5 °C, depending on measurement site. Fever was defined as a body temperature of ≥38.0 °C, in line with international pediatric consensus. High fever was operationally defined as ≥39.0 °C, consistent with pediatric clinical practice guidelines, with temperatures ≥40.0 °C considered very high fever in some clinical contexts[21]

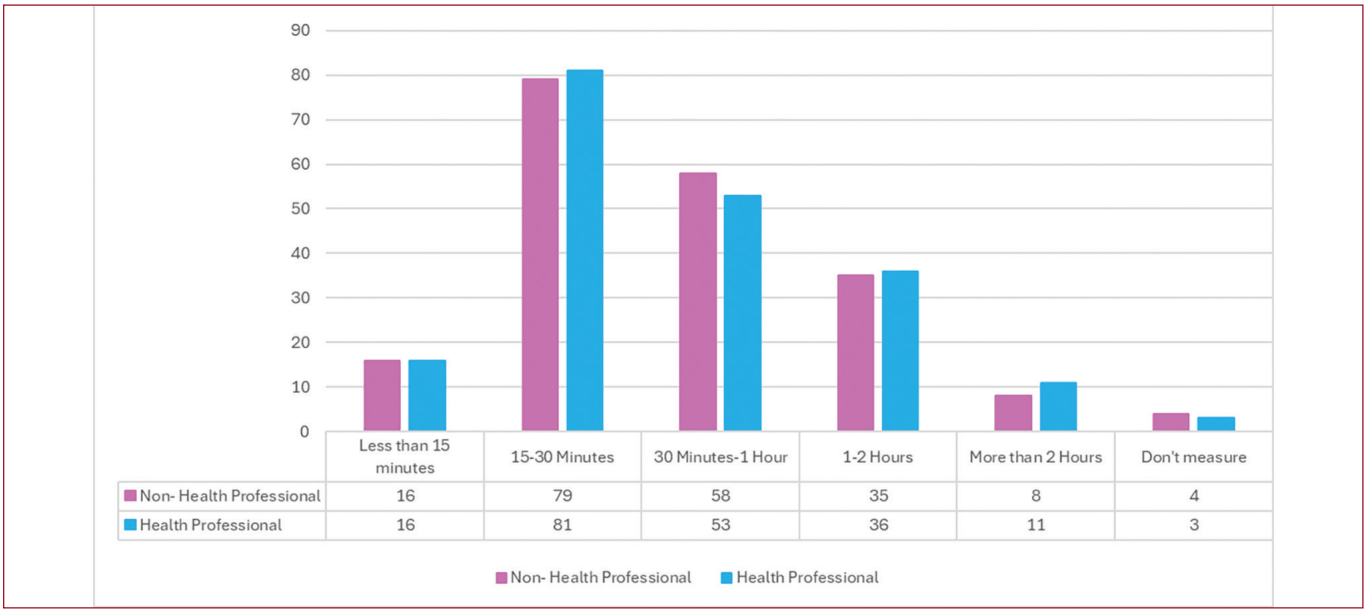

Figure 1. Comparison of the frequency of fever measurement between healthcare professionals and non-healthcare professionals

Table 4.
Comparison of fever management practices and antipyretic use among groups

		Group 1		Group 2		
		n	%	n	%	p
What do you do when your child has a high fever?	Cover them/dress in layers	2	1	5	2.5	0.253
	Apply cold compresses	98	49	168	84	p<0.001
	Give a shower	160	80	165	82.5	0.522
	Remove clothing	48	24	99	49.5	p<0.001
	Give antipyretic medication	158	79	159	79.5	0.902
	Give antibiotics	3	1.5	16	8	0.002
	Apply cloth with cologne	8	4	4	2	0.241
	Apply cloth with vinegar	28	14	21	10.5	0.286
	Make them drink water	74	37	77	38.5	0.757
Do you give a shower during high fever?	Yes	168	84	178	89	0.143
At what temperature do you give a shower?	37 °C	3	1.5	1	0.5	0.269
	38 °C	32	16	37	18.5	
	38.5 °C	57	28.5	75	37.5	
	39 °C	64	32	55	27.5	
	40 °C	12	6	9	4.5	
	Not high fever	32	16	23	11.50	
Do you give antipyretic medication during high fever?	Yes	174	87	180	90	0.347
When do you give antipyretic medication?	When they feel hot to touch	17	8.5	14	7	0.575
	If they have chills or shivering	37	18.5	26	13	0.131
	When measured high with thermometer	174	87	179	89.5	0.438
	If they look unwell	21	10.5	19	9.5	0.739
At what temperature do you give antipyretic medication?	37 °C	19	9.5	2	1	p<0.001
	38 °C	68	34	92	46.7	
	38.5 °C	67	33.5	73	37.1	
	39 °C	25	12.5	12	6.1	
	Do not give medication	21	10.5	18	9.1	
Do you always have antipyretic medication at home?		194	97	190	95	0.307

Fever Management Behaviors

Antipyretic use was the most common management strategy in both groups (Group 1: n=158, 79%; Group 2: n=159, 79.5%; p=0.902), followed by tepid sponging and showering (**Table 4**). Cold applications were significantly more frequent among healthcare professionals (n=168, 84%) than among non-healthcare parents (n=98, 49%; p<0.001). Antibiotic use was low overall but was higher in Group 2 (n=16, 8%) than in Group 1 (n=3, 1.5%; p=0.002).

Regarding the timing of antipyretic administration, most parents reported initiating treatment at ≥38 °C (Group 1: n=188, 94%; Group 2: n=182, 91%); however, definitions of fever thresholds varied significantly. Both groups primarily relied on physician recommendations for determining antipyretic dosages (**Table 4**).

Attitudes and Beliefs about Fever

A larger proportion of healthcare professionals (n=173, 86.5%) perceived fever as harmful than did non-healthcare parents (n^2=158, 79%). The most frequently cited complications were FSs, brain damage, dehydration, and hepatic or renal injury.

Knowledge and Misconceptions Regarding Febrile Seizures

Knowledge of FSs was significantly higher in Group 2. Specifically, more healthcare professionals recognized the age dependency of FSs (n=144, 72%) than did non-healthcare parents (n=65, 32.7%; p<0.001) (**Table 5**). Similarly, understanding of the temperature thresholds for FSs was better among healthcare professionals (n=72, 36%) than among non-healthcare parents (n=47, 23.5%; p=0.006).

However, misconceptions were common in both groups: the belief that FSs inevitably cause brain damage was reported by 71.4% of non-healthcare parents (n=142) and 74.0% of healthcare professionals (n=148) (p=0.597). Knowledge that antiepileptic treatment and neuroimaging are not routinely required was more prevalent in healthcare professionals (antiepileptic treatment: n=136 (68%) vs n=80 (40.2%); p<0.001; neuroimaging: n=64 (32%) vs n=23 (11.6%); p<0.001).

When asked about emergency management practices during an FS, several differences were observed between healthcare professional parents (Group 2) and non-healthcare parents (Group 1). No statistically significant differences were observed between groups regarding the placement of the child in water (35.5% vs. 44%, p=0.1), calling emergency medical services

Table 5.
Knowledge of febrile seizures and their association with epilepsy among groups

		Group 1		Group 2		
		n	%	n	%	p
At what temperature do children have febrile seizures?	38 °C and above	3	1.5	3	1.5	0.054
	38.5 °C and above	5	2.5	8	4	
	39 °C and above	44	22.1	41	20.5	
	40 °C and above	100	50.3	76	38	
	Can occur at any temperature	47	23.6	72	36	
	Correct	47	23.5	72	36	0.006
	Incorrect	153	76.5	128	64	
Is febrile seizure age-dependent?*	Yes	65	32.7	144	72	p<0.001
	No	134	67.3	56	28	
Do you think febrile seizure is a type of epilepsy?	Yes	21	10.6	23	11.5	p<0.001
	No	92	46.2	147	73.5	
	No opinion	86	43.2	30	15	
Do you think febrile seizures lead to epilepsy later?	Yes	46	23.1	70	35	p<0.001
	No	28	14.1	71	35.5	
	No opinion	125	62.8	59	29.5	
Do you think febrile seizures cause brain damage?	Yes	142	71.4	148	74	p<0.001
	No	12	6	32	16	
	No opinion	45	22.6	20	10	
Should children who experience febrile seizures be given epilepsy medication?	Yes	7	3.5	16	8	p<0.001
	No	80	40.2	136	68	
	No opinion	112	56.3	48	24	
Should children who experience febrile seizures undergo brain imaging/EEG (MRI-EEG)?*	Yes	56	28.1	86	43	p<0.001
	No	23	11.6	64	32	
	No opinion	120	60.3	50	25	

*: Knowledge regarding FSs was evaluated according to accepted pediatric neurology definitions and guideline-based management principles. FSs were considered to be associated with febrile illness, typically at temperatures ≥38.0 °C, although no single temperature threshold is universally required for seizure occurrence[22]. FSs are age-dependent events, most commonly occurring between 6 and 60 months of age[23]. Routine prophylactic antiepileptic drug use and routine neuroimaging or electroencephalography are not recommended in the evaluation of children with simple FSs in the absence of atypical features[24,25]. MRI: Magnetic resonance imaging, EEG: Electroencephalography, FS: Febrile seizure

(55.5% vs. 47.5%, p=0.13), administering antipyretic medication (28.5% vs. 23.5%, p=0.30), or immediately transporting the child to the nearest healthcare facility (79% vs. 83.5%, p=0.31). Rarely reported practices, including shaking the child (0.5% vs. 2%, p=0.37), splashing water or cologne on the face (4.5% vs. 6%, p=0.65), and providing mouth-to-mouth ventilation (1% in both groups, p=1), did not differ significantly between groups.

Lateral positioning of the child was reported more frequently by Group 2 than by Group 1 (34% vs. 6%, p<0.001). Similarly, performing cardiopulmonary resuscitation was reported more frequently in Group 2 than in Group 1 (24.5% vs. 5; p<0.001). Attempting to keep the child's mouth open during the event was also reported more frequently in Group 2 (31.5% vs. 18%; p=0.003).

Discussion

Fever remains one of the most frequent reasons for pediatric emergency visits worldwide. Although a physiological response, most commonly to self-limiting viral infections, it continues to provoke considerable anxiety among parents and healthcare professionals. This phenomenon, historically termed "fever phobia" Schmitt[14], stems from misinformation or an inadequate understanding of the causes and implications of fever.

Previous studies, including those by Betz and Grunfled,[6] Crocetti et al.[10] and Esenay et al.[8], have shown that parents often engage in inappropriate fever management practices because of inaccurate or incomplete knowledge. The findings of the present study align with this literature, demonstrating that although healthcare professional parents (Group 2) exhibited higher levels of knowledge in certain areas, misconceptions persisted in both groups. The presence of such gaps even among trained healthcare professionals highlights that professional background alone may not ensure guideline-consistent fever management and underscores the need for ongoing, structured educational interventions.

A major strength of this study is its large, balanced sample of 400 participants, which allows meaningful comparisons between healthcare-professional parents and non-healthcare parents. A substantial proportion of parents in both groups (Group 1: 79; Group 2: 86.5%) perceived fever as harmful, most commonly because of concerns about FSs. These perceptions closely mirror international findings, including those reported by Huang et al.[15], in which FSs were frequently misinterpreted as indicating brain damage or epilepsy.

Parents who are healthcare professionals demonstrated greater accuracy in identifying normal body temperature than non-healthcare parents, which is consistent with previous reports suggesting that higher educational attainment or clinical exposure may be associated with improved fever-related knowledge. Nevertheless, nearly one-quarter of healthcare professionals failed to correctly identify normal body temperature, suggesting that knowledge decay or outdated information may persist even among medically trained individuals.

With respect to fever management practices, both groups commonly reported strategies generally regarded as appropriate, such as the administration of paracetamol or tepid sponging. However, the present study identified higher rates of practices not routinely recommended by current guidelines (such as cold applications or antibiotic use) among parents who are healthcare professionals (**Table 4**). Rather than implying causality, this finding may reflect the complex interaction between professional training, clinical experience, and habitual practices. In addition, frequent home temperature monitoring, sometimes at 15-30-minute intervals, was observed in both groups and appeared more common among healthcare professionals (**Figure 1**), suggesting a tendency toward practicality in clinical settings.

Importantly, our findings support earlier research by Dinçer and Arslan[26] and Peetoom et al.[27], which emphasized that even healthcare professionals lack consistent training in evidence-based fever management. Despite clinical experience, certain misconceptions (such as the perceived need to administer antipyretics at temperatures below 38.5 °C) remain prevalent, indicating that experiential learning may sometimes outweigh guideline-based recommendations.

Concerns regarding FSs were particularly prominent. Regarding FSs, 71.4% of Group 1 believed that FSs cause brain damage, a fear echoed in earlier studies[10,15,28]. In our sample, only 36% of Group 2 correctly identified the body temperature at which FS typically occurs, and only 68% knew that neuroimaging or antiepileptics are not routinely required for FS management (**Table 3**). These findings highlight persistent knowledge gaps and support the need for targeted family-centered education that emphasizes evidence-based seizure management principles.

Our study also revealed socio-demographic nuances. Higher education correlated with better knowledge of body temperature norms, but not necessarily with improved understanding of fever thresholds or FS management. This observation suggests that educational interventions should be tailored not only to professional background but also to educational level and parental experience to effectively address both knowledge- and practice-related gaps.

Study Limitations

This study is subject to several limitations inherent to its cross-sectional, survey-based design. Data were collected using a structured questionnaire administered in face-to-face interviews, rendering the findings dependent on the accuracy of participants' recall and their interpretation of the survey items. Such reliance on self-reported information introduces the potential for recall bias, social desirability bias, and misinterpretation of questions, which may have influenced the validity of the responses. The cross-sectional methodology permits only the characterization of parental knowledge, attitudes, and practices at a single point in time, thereby precluding any inference of causality or temporal change. The heterogeneous composition of the healthcare professional group may have masked differences between specific occupational subgroups;

however, subgroup analyses were not feasible due to limited sample sizes. Additionally, the recruitment of participants from a defined geographic and sociocultural setting, coupled with voluntary participation, may have resulted in selection bias and may have limited the generalizability of the findings to broader populations. Finally, because the dataset was collected in 2017, the results should be interpreted in the context of the prevailing public health environment and clinical practices of that period. While this temporal distance may limit immediate applicability, it confers value as a historical benchmark for longitudinal comparison and trend analysis in future research.

Conclusion

This study confirms that both healthcare and non-healthcare parents experience significant anxiety and misunderstandings about fever, despite widespread access to medical services. Misconceptions, particularly about FS, persist across educational levels and professions. Although healthcare professionals exhibited superior overall knowledge, critical gaps remained, particularly regarding fever thresholds and FS management.

To bridge these gaps, we recommend:

- Developing structured educational modules during pediatric check-ups, targeting both parents and frontline healthcare workers.

- Including visual guides and infographics to correct misconceptions about FS.

- Emphasizing evidence-based fever thresholds and management protocols in nursing and residency training.

- Establishing public health campaigns to dispel “fever phobia” and encourage rational fever management.

By implementing these interventions, families and healthcare professionals can collaborate more effectively to provide safe, informed, and confidently delivered care to febrile children, ultimately reducing unnecessary emergency visits and improving pediatric health outcomes.

Ethics

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of Maltepe University Faculty of Medicine (approval number: 2016-900-57, date: 29.12.2016).

Informed Consent: Institutional permissions were obtained, and written informed consent was secured from all participants prior to enrollment.

Footnotes

Author Contributions: Özomay Baykal G: Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing; Tanju İA: Concept, Design, Writing.

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

Financial Disclosure: The authors declared that this study received no financial support.

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The Impact of Body Mass Index at the Diagnosis on Disease Activity and Lower Extremity Involvement in Juvenile Idiopathic Arthritis

Author(s)

Elif Küçük[1], Feray Kaya[1], Lütfiye Koru[1], Zelal Aydın[1], Eda Nur Dizman[1], Hatice Kübra Dursun[1], Merve Özen Balcı[1], Ufuk Furkan Özdemir[1], Serpil Meriç Toprak[1], Seher Katrancı[2], Kübra Öztürk[1], Fatih Haşlak[1]

Affiliation(s)

[1]İstanbul Medeniyet University Faculty of Medicine, Department of Pediatric Rheumatology, İstanbul, Türkiye

[2]İstanbul Medeniyet University Faculty of Medicine, Department of Pediatrics, İstanbul, Türkiye

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Abstract

Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory disease of childhood, and body mass index (BMI) may influence its course. This study aimed to assess the impact of BMI on disease activity and lower-extremity joint involvement by analyzing demographic, laboratory, and clinical characteristics of children with JIA. A cross-sectional study was conducted in 153 patients who were diagnosed with JIA according to the International League for Rheumatology classification criteria and who attended routine outpatient clinic visits between March 2025 and June 2025. Demographic, clinical, and laboratory characteristics were compared among groups (underweight, normal weight, overweight, and obese). The study included 153 patients (54.9% female, n=84). The prevalence of overweight or obesity among patients with JIA was 30.7%. Underweight patients had an earlier disease onset (p=0.007) and a higher frequency of oligoarticular JIA (p=0.028), whereas overweight patients exhibited a higher frequency of enthesitis-related arthritis (ERA) (p=0.025) and ankle involvement (p=0.030). While underweight patients developed oligoarticular disease at a younger age, overweight or obese patients were more frequently classified as having ERA and exhibited a higher incidence of ankle involvement. Although BMI was not associated with overall disease activity, it may represent an important factor contributing to lower extremity joint stress and inflammation.

Keywords: Ankle, juvenile arthritis, obesity, overweight

Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory disease of childhood, although its etiopathogenesis has not been fully elucidated. The clinical spectrum ranges from mild cases involving only a few joints to severe cases with systemic manifestations[1]. In particular, the knee, ankle, and hip joints are frequently affected in JIA owing to their susceptibility to inflammation and to their role as weight-bearing structures[2-4]. In this context, body

Correspondence: Fatih Haşlak MD, İstanbul Medeniyet University Faculty of Medicine, Department of Pediatric Rheumatology, İstanbul, Türkiye
E-mail: drfatihhaslak@gmail.com **ORCID:** 0000-0002-6963-9668

mass index (BMI) has gained importance as a potential biological variable that may influence the disease course[5,6].

Increased body weight may impose mechanical stress on load-bearing joints, thereby predisposing them to earlier and more severe involvement. Moreover, adipose tissue functions not only as an energy reservoir but also as a metabolically active endocrine organ that contributes to systemic inflammation by secreting pro-inflammatory molecules, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and leptin[5,6]. Conversely, a low BMI may compromise immune-regulatory capacity, potentially exacerbating the inflammatory process[7]. Therefore, both extremes of BMI may contribute to impaired motor development, functional limitations in daily life, and reduced quality of life[6,8].

Highlights

- Underweight juvenile idiopathic arthritis patients had earlier onset and oligoarticular subtype.
- Overweight/obese patients showed more enthesitis-related arthritis and ankle involvement.
- High body mass index may increase lower-extremity stress and inflammation.

Studies have shown that the knee and ankle joints are more frequently and more severely affected in JIA patients with high BMI[6]. Interestingly, the juvenile arthritis disease activity score-27 (JADAS-27) values have been reported to be significantly higher in patients with both high and low BMI[6,8,9]. These findings suggest that the influence of BMI on disease activity is bidirectional and may reflect a clinical parameter directly linked to lower-extremity joint involvement[6,8].

The primary aim of this study was to analyze demographic data, laboratory parameters, and systemic disease characteristics in children with JIA according to BMI. The secondary aim was to evaluate the effects of high BMI on overall disease activity and the pattern of lower-extremity joint involvement.

Materials and Methods

Patients and Data Collection

In this study, the medical records of patients diagnosed with JIA before the age of 16 years who attended routine outpatient clinic visits between March and June 2025 were retrospectively reviewed. Patients who were not diagnosed with JIA at our center, patients with systemic JIA, patients who had received systemic glucocorticoid and/or immunosuppressive treatment before diagnosis, patients with another autoimmune and/or autoinflammatory disease, patients who were non-adherent to treatment, and patients who did not attend outpatient visits regularly were excluded.

Demographic, clinical, and laboratory data were obtained from the medical records of all patients. The BMI was calculated based on the weight (in kilograms) and height (in centimeters) recorded at the time of diagnosis. BMI-for-age percentiles were calculated according to the Centers for Disease Control and Prevention reference standards. A BMI below the 5th percentile was classified as underweight; between the 5th and 85th percentiles, as normal weight; between the 85th and 95th percentiles, as overweight; and at or above the 95th percentile, as obese[10].

The patients were classified as JIA according to the International League for Rheumatology criteria[11]. Disease activity was evaluated using the JADAS-71 at the time of diagnosis[12].

Ethical Approval

This study was approved by the Ministry of Health Göztepe Prof. Dr. Süleyman Yalçın Non-interventional Clinical Research Ethics Committee (approval no.: 2025/0233, date: 23/10/2025). The study complied with the recommendations of the Declaration of Helsinki for human biomedical research.

Statistical Analysis

Statistical processing of the data was performed using IBM SPSS Statistics software (v26.0; Armonk, New York, USA). For categorical parameters, data were presented as absolute numbers and percentages, with intergroup differences analyzed using the χ^2 test. The Kolmogorov-Smirnov test was used to determine the distribution pattern of continuous data. Data conforming to a normal distribution were expressed as mean ± standard deviation, and those deviating from normality were presented as median (minimum-maximum). The independent-samples t-test was used to evaluate differences between the two groups when the assumption of normality was met, whereas non-parametric data were analyzed using the Mann-Whitney U test. When comparisons involved more than two groups, normally distributed variables were assessed using one-way ANOVA, and the Kruskal-Wallis test was applied for data lacking normality. If significant differences were observed in the Kruskal-Wallis or chi-square tests, relevant post-hoc analyses were performed to identify intergroup differences. Across all statistical tests, a p-value less than 0.05 was considered statistically significant.

Results

Demographic, Clinical and Laboratory Findings of the Cohort

The median age of the 153 patients diagnosed with JIA was 12.1 years (range, 1-16), and 54.9% (n=84) were female. The mean BMI at diagnosis was 19.31±5.06 kg/m^2; 9.2% were classified as underweight, 60.1% as normal weight, 18.3% as overweight, and 12.4% as obese. The most common JIA subtype was oligoarticular (n=81, 52.9%). The distribution of other types was as follows: enthesitis-related arthritis (ERA) (31.4%), rheumatoid factor (RF)-negative polyarticular JIA (7.2%), psoriatic arthritis (5.2%), and RF-positive polyarticular JIA (3.3%).

The most commonly affected joint at disease onset was the knee (50.3%), followed by the ankle (28.1%), proximal interphalangeal (PIP) joints of the fingers

(13.1%), the wrist (9.8%), metacarpophalangeal joints (9.2%), metatarsophalangeal joints (4.6%), the hip (3.9%), PIP joints of the toes (3.3%), the elbow (2.6%), distal interphalangeal (DIP) joints of the fingers (2%), DIP joints of the toes (1.3%), cervical vertebrae (0.7%), subtalar joints (0.7%), and tarsometatarsal joints (0.7%). The median number of joints involved was 1 (range, 1-16). Sacroiliitis was found in 27.5% (n=42) of the patients, enthesitis in 17% (n=26), and uveitis in 4.6% (n=7).

At the time of diagnosis, the median C-reactive protein and erythrocyte sedimentation rate levels were 3.8 (0.1-131.5) mg/L and 22 (2-120) mm/hour, respectively. Antinuclear antibody was positive in 34% (n=52) of the patients, human leukocyte antigen-B27 was positive in 13.7% (n=21), RF was positive in 3.9% (n=6), and anti-cyclic citrullinated peptide was positive in 2% (n=3). The mean JADAS-71 score at the time of JIA diagnosis was 11.84±5.06. Detailed data are given in **Table 1**.

Comparison of Groups According to BMI Categories

The age of onset of JIA (6.7 years, range 1.4-16; p=0.007) was significantly lower in the underweight group than in the other groups, whereas the frequency of oligoarticular JIA (n=11, 78.6%; p=0.028) was significantly higher. The frequencies of ERA (n=13, 46.4%; p=0.025) and ankle involvement (n=13, 46.4%; p=0.030) were significantly higher in the overweight group than in the other groups. Detailed data are given in **Table 2**.

The frequency of ankle involvement was significantly higher in the overweight/obese group (n=21, 44.7%) than in the underweight/normal-weight group (n=22, 20.8%); p=0.004. There were no significant differences between the two groups in other demographic, clinical, or laboratory parameters (p>0.05, **Table 3**).

Discussion

In this study, we evaluated the role of BMI in the clinical, laboratory, and disease-related characteristics of patients with JIA. Underweight patients had earlier disease onset and more frequently presented with the oligoarticular subtype, whereas overweight and obese patients had significantly higher rates of the ERA subtype and ankle involvement. In addition, ankle involvement was significantly more frequent in the overweight/obese group than in the underweight/normal group, suggesting that BMI may be an important determinant of lower extremity joint involvement.

The relationship between BMI and disease activity in JIA has received increasing attention in recent years[5,6,8]. While existing studies typically evaluate limited parameters, such as specific JIA subtypes or joint involvement patterns[5,6,9,13], our study examines this relationship across a considerably broader clinical and demographic spectrum and reports one of the most comprehensive patient series in the literature. While the prevalence of overweight/obesity in the general pediatric population ranges between 20-25%[14], it has been reported to be between 20% and 45% in patients with JIA[6,15,16]. In our study, the prevalence of overweight/obesity was 30[7].

Table 1.
Demographics, clinical, laboratory, and outcome data of the patients with juvenile idiopathic arthritis

	Total cohort (n=153)
Age (years) [median (min-max)]	14.7 (2.7-20.7)
Age at diagnosis (years) [median (min-max)]	12.1 (1-16)
Female gender (n, %)	84 (54.9%)
Body mass index (kg/m²) (mean ± standard deviation)	19.31±5.06
Underweight (n, %)	14 (9.2%)
Normal (n, %)	92 (60.1%)
Overweight (n, %)	28 (18.3%)
Obese (n, %)	19 (12.4%)
JIA type (n, %)	
Oligoarticular JIA (n, %)	81 (52.9%)
Enthesitis related arthritis (n, %)	48 (31.4%)
RF negative polyarticular JIA (n, %)	11 (7.2%)
Psoriatic arthritis (n, %)	8 (5.2%)
RF positive polyarticular JIA (n, %)	5 (3.3%)
Distribution of the affected joints at disease onset (n, %)	
Knee (n, %)	77 (50.3%)
Ankle (n, %)	43 (28.1%)
PIP (finger) (n, %)	20 (13.1%)
Wrist (n, %)	15 (9.8%)
Metacarpophalangeal (n, %)	14 (9.2%)
Metatarsophalangeal (n, %)	7 (4.6%)
Hip (n, %)	6 (3.9%)
PIP (toe) (n, %)	5 (3.3%)
Elbow (n, %)	4 (2.6%)
DIP (finger) (n, %)	3 (2%)
DIP (toe) (n, %)	2 (1.3%)
Cervical vertebra (n, %)	1 (0.7%)
Subtalar (n, %)	1 (0.7%)
Tarsometatarsal (n, %)	1 (0.7%)
Involved joint at disease onset [median (min-max)]	1 (1-16)
Sacroiliitis (n, %)	42 (27.5%)
Enthesitis (n, %)	26 (17%)
Uveitis (n, %)	7 (4.6%)
Laboratory findings at admission	
ANA positivity (n, %)	52 (34%)
HLA-B27 positivity (n, %)	21 (13.7%)
RF positivity (n, %)	6 (3.9%)
Anti-CCP positivity (n, %)	3 (2%)
CRP (mg/L) [median (min-max)]	3.8 (0.1-131.5)
ESR (mm/h) [median (min-max)]	22 (2-120)
Platelet count (×10⁹/L) [median (min-max)]	349 (200-725)
JADAS-71 (mean ± standard deviation)	11.84±5.06

anti-CCP: Anti-cyclic citrullinated peptide antibody, ANA: Antinuclear antibody, CRP: C-reactive protein, DIP: Distal interphalangeal, ESR: Erythrocyte sedimentation rate, HLA-B27: Human leukocyte antigen-B27, JADAS-71: Juvenile idiopathic arthritis disease activity score-71, JIA: Juvenile idiopathic arthritis, PIP: Proximal interphalangeal, RF: Rheumatoid factor, min-max: Minimum-maksimum

Table 2.
Comparison of groups according to body mass index categories

	Underweight (n=14)	Normal weight (n=92)	Overweight (n=28)	Obese (n=19)	p
Age (years) [median (min-max)]	11.6 (4.2-17.8)	14.7 (3.8-20.7)	14.9 (7.3-19.8)	14.5 (5.9-20.2)	**0.028**[1]
Age at diagnosis (years) [median (min-max)]	6.7 (1.4-16)	12.5 (1-16)	12.2 (4.5-16)	11.9 (2.1-16)	**0.007**[2]
Female gender (n, %)	9 (64.3%)	55 (59.8%)	12 (42.9%)	8 (42.1%)	0.233
JIA type (n, %)					
Oligoarticular JIA (n, %)	11 (78.6%)	51 (55.4%)	9 (32.1%)	10 (52.6%)	**0.028**[3]
Enthesitis related arthritis (n, %)	0 (0%)	29 (31.5%)	13 (46.4%)	6 (31.6%)	**0.025**[4]
RF negative polyarticular JIA (n, %)	0 (0%)	6 (6.5%)	4 (14.3%)	1 (5.3%)	0.419
Psoriatic arthritis (n, %)	1 (7.1%)	3 (3.3%)	2 (7.1%)	2 (10.5%)	0.275
RF positive polyarticular JIA (n, %)	2 (14.3%)	3 (3.3%)	0 (0%)	0 (0%)	0.151
Distribution of the affected joints at disease onset (n, %)					
Knee (n, %)	10 (71.4%)	46 (50%)	10 (35.7%)	11 (57.9%)	0.142
Ankle (n, %)	3 (21.4%)	19 (20.7%)	13 (46.4%)	8 (42.1%)	**0.030**[5]
PIP (finger) (n, %)	1 (7.1%)	11 (12%)	6 (21.4%)	2 (10.5%)	0.556
Wrist (n, %)	1 (7.1%)	10 (10.9%)	3 (10.7%)	1 (5.3%)	0.940
Metacarpophalangeal (n, %)	0 (0%)	9 (9.8%)	4 (14.3%)	1 (5.3%)	0.570
Metatarsophalangeal (n, %)	1 (7.1%)	3 (3.3%)	3 (10.7%)	0 (0%)	0.195
Hip (n, %)	0 (0%)	4 (4.3%)	1 (3.6%)	1 (5.3%)	1.0
PIP (toe) (n, %)	2 (14.3%)	2 (2.2%)	1 (3.6%)	0 (0%)	0.134
Elbow (n, %)	0 (0%)	3 (3.3%)	1 (3.6%)	0 (0%)	1.0
DIP (finger) (n, %)	0 (0%)	2 (2.2%)	1 (3.6%)	0 (0%)	0.785
DIP (toe) (n, %)	0 (0%)	1 (1.1%)	1 (3.6%)	0 (0%)	0.640
Cervical vertebra (n, %)	0 (0%)	0 (0%)	1 (3.6%)	0 (0%)	0.399
Subtalar (n, %)	0 (0%)	0 (0%)	1 (3.6%)	0 (0%)	0.399
Tarsometatarsal (n, %)	0 (0%)	1 (1.1%)	0 (0%)	0 (0%)	1.0
Involved joint at disease onset [median (min-max)]	1 (1-9)	1 (1-16)	2 (1-11)	2 (1-7)	0.348
Sacroiliitis (n, %)	0 (0%)	28 (27.2%)	11 (39.3%)	6 (31.6%)	0.059
Enthesitis (n, %)	1 (7.1%)	16 (17.4%)	7 (25%)	2 (10.5%)	0.425
Uveitis (n, %)	0 (0%)	4 (4.3%)	2 (7.1%)	1 (5.3%)	0.861
Laboratory findings at admission					
ANA positivity (n, %)	8 (57.1%)	29 (31.5%)	8 (28.6%)	7 (36.8%)	0.258
HLA-B27 positivity (n, %)	0 (0%)	13 (17.3%)	5 (20%)	3 (23.1%)	0.465
RF positivity (n, %)	2 (14.3%)	3 (3.3%)	1 (3.6%)	0 (0%)	0.225
Anti-CCP positivity (n, %)	1 (7.1%)	2 (2.2%)	0 (0%)	0 (0%)	0.580
CRP (mg/L) [median (min-max)]	4.6 (0.2-27.2)	4.2 (0.1-131.5)	3.8 (0.3-74.5)	2.1 (0.2-42)	0.972
ESR (mm/h) [median (min-max)]	19.5 (2-116)	22.5 (2-120)	20.5 (2-98)	28 (2-88)	0.883
Platelet count (×10^9/L) [median (min-max)]	402 (272-690)	347 (200-725)	326 (237-502)	383 (315-638)	0.086
JADAS-71 (mean ± standard deviation)	14.5±5.8	12.7±5	13.1±6	11.6±4.9	0.468

[1]"Age" was significantly lower in the underweight group than in the normal-weight and overweight groups.
[2]"Age at diagnosis" was significantly lower in the underweight group than in the normal-weight and overweight groups.
[3]"Oligoarticular JIA" was significantly more frequent in the underweight group than in the overweight group.
[4]"Enthesitis-related arthritis" was significantly more frequent in the overweight group than in the underweight group.
[5]"Ankle involvement" was significantly more frequent in the overweight group than in the normal-weight group.
anti-CCP: Anti-cyclic citrullinated peptide antibody, ANA: Antinuclear antibody, CRP: C-reactive protein, DIP: Distal interphalangeal, ESR: Erythrocyte sedimentation rate, HLA-B27: Human leukocyte antigen-B27, JADAS-71: Juvenile idiopathic arthritis disease activity score-71, JIA: Juvenile idiopathic arthritis, PIP: Proximal interphalangeal, RF: Rheumatoid factor, min-max: Minimum-maksimum

Although this rate is higher than that reported for healthy children, it is consistent with existing data in the literature.

Deviations in BMI are thought to contribute to the inflammatory process in JIA through distinct immunological mechanisms. At higher BMI levels, adipose tissue functions as an active endocrine organ, releasing cytokines such as TNF-α, IL-6, and IL-1β, and enhancing pro-inflammatory Th1 and Th17 helper T-cell responses, which contribute to chronic low-grade inflammation, via leptin and resistin. Reduced adiponectin levels further disrupt the anti-inflammatory balance, promoting synovial infiltration and cartilage damage. Conversely, undernutrition and low BMI suppress T-cell and Treg functions, reduce IL-10 production, and shift the immune response toward a proinflammatory state dominated by IL-6 and TNF-α. Malnutrition-induced hypoleptinemia and micronutrient deficiencies further compromise immune regulation and perpetuate chronic inflammation[17]. The literature reports conflicting findings regarding the relationship between

BMI and JIA disease activity. In addition to studies reporting that high or low BMI was associated with higher JADAS-27 scores[5,15], other studies have reported no such association[18,19]. In our study, no difference was found between BMI groups for JADAS-71 scores, which may be explained by the fact that the contribution of BMI to inflammation is mostly subclinical and is not always reflected in clinical activity scores.

Studies examining the impact of BMI on JIA phenotypes have suggested marked differences in age at diagnosis, subtype distribution, and joint involvement patterns[5,8,15]. It has been reported that the ERA subtype is more common in children with a high BMI, especially when the knee and ankle joints are more severely affected and as the number of involved joints increases[5,15,20,21]. In our study, the rate of ERA was higher and ankle involvement was more common in the overweight group; these findings are consistent with the literature. This may be explained by facilitation of local inflammatory responses caused by increased mechanical stress in load-bearing joints and by promotion of systemic inflammation mediated by adipokines[22,23]. Although these findings are not statistically significant in the literature, it has been reported that age at diagnosis is earlier and the oligoarticular JIA subtype is more common in the low BMI group[8,15,24]. In our study, the underweight group had

Table 3.
Comparison of underweight/normal and overweight/obese groups

	Underweight/normal weight (n=106)	Overweight/obese (n=47)	p
Age (years) [median (min-max)]	14.5 (3.8-20.7)	14.9 (5.9-20.2)	0.445
Age at diagnosis (years) [median (min-max)]	12 (1-16)	12.1 (2.1-16)	0.417
Female gender (n, %)	64 (60.4%)	20 (42.6%)	0.062
JIA type (n, %)			
Oligoarticular JIA (n, %)	62 (58.5%)	19 (40.4%)	0.059
Enthesitis related arthritis (n, %)	29 (27.4%)	19 (40.4%)	0.156
RF negative polyarticular JIA (n, %)	6 (5.7%)	5 (10.6%)	0.314
Psoriatic arthritis (n, %)	4 (3.8%)	4 (8.5%)	0.251
RF positive polyarticular JIA (n, %)	5 (4.7%)	0 (0%)	0.324
Distribution of the affected joints at disease onset (n, %)			
Knee (n, %)	56 (52.8%)	21 (44.7%)	0.450
Ankle (n, %)	22 (20.8%)	21 (44.7%)	**0.004**
PIP (finger) (n, %)	12 (11.3%)	8 (17%)	0.481
Wrist (n, %)	11 (10.4%)	4 (8.5%)	1.0
Metacarpophalangeal (n, %)	9 (8.5%)	5 (10.6%)	0.763
Metatarsophalangeal (n, %)	4 (3.8%)	3 (6.4%)	0.677
Hip (n, %)	4 (3.8%)	2 (4.3%)	1.0
PIP (toe) (n, %)	4 (3.8%)	1 (2.1%)	1.0
Elbow (n, %)	3 (2.8%)	1 (2.1%)	1.0
DIP (finger) (n, %)	2 (1.9%)	1 (2.1%)	1.0
DIP (toe) (n, %)	1 (0.9%)	1 (2.1%)	0.521
Cervical vertebra (n, %)	0 (0%)	1 (2.1%)	0.307
Subtalar (n, %)	0 (0%)	1 (2.1%)	0.307
Tarsometatarsal (n, %)	1 (0.9%)	0 (0%)	1.0
Involved joint at disease onset [median (min-max)]	1 (1-16)	2 (1-11)	0.104
Sacroiliitis (n, %)	25 (23.6%)	17 (36.2%)	0.158
Enthesitis (n, %)	17 (16%)	9 (19.1%)	0.811
Uveitis (n, %)	4 (3.8%)	3 (6.4%)	0.677
Laboratory findings at admission			
ANA positivity (n, %)	37 (34.9%)	15 (31.9%)	0.861
HLA-B27 positivity (n, %)	13 (15.3%)	8 (21.1%)	0.600
RF positivity (n, %)	5 (4.7%)	1 (2.1%)	0.667
Anti-CCP positivity (n, %)	3 (2.8%)	0 (0%)	1.0
CRP (mg/L) [median (min-max)]	4.4 (0.1-131.5)	3.1 (0.2-74.5)	0.986
ESR (mm/h) [median (min-max)]	21.5 (2-120)	22 (2-98)	0.601
Platelet count (×10^9/L) [median (min-max)]	356 (200-725)	345 (237-638)	0.896
JADAS-71 (mean ± standard deviation)	12.9±5.1	12.5±5.6	0.642

anti-CCP: Anti-cyclic citrullinated peptide antibody, ANA: Antinuclear antibody, CRP: C-reactive protein, DIP: Distal interphalangeal, ESR: Erythrocyte sedimentation rate, HLA-B27: Human leukocyte antigen-B27, JADAS-71: Juvenile idiopathic arthritis disease activity score-71, JIA: Juvenile idiopathic arthritis, PIP: Proximal interphalangeal, RF: Rheumatoid factor, min-max: Minimum-maksimum

an earlier age at diagnosis and a significantly higher rate of oligoarticular JIA. This may be related to oligoarticular JIA being the most common subtype in early childhood[11] and to joint swelling being more easily recognized by families of children with low BMI.

Study Limitations

The main limitation of our study was its retrospective and single-center design, which limited the generalizability of the results. BMI was only assessed at diagnosis, and changes over time could not be analyzed. However, our study includes one of the largest JIA cohorts to examine the impact of BMI on clinical characteristics and to compare demographic, laboratory, and disease parameters across BMI categories. To strengthen the generalizability of our findings and their contribution to clinical practice, they require support from prospective studies conducted at multiple centers.

Conclusion

This study demonstrated that BMI significantly influences the disease phenotype in JIA. Underweight patients commonly presented with early-onset oligoarticular disease, whereas overweight and obese patients presented with the ERA subtype and ankle involvement. These findings suggest that increased BMI may contribute to mechanical loading and systemic inflammation, which predispose patients to lower-extremity involvement.

Ethics

Ethics Committee Approval: This study was approved by the Ministry of Health Göztepe Prof. Dr. Süleyman Yalçın Non-interventional Clinical Research Ethics Committee (approval no.: 2025/0233, date: 23/10/2025). The study complied with the recommendations of the Declaration of Helsinki for human biomedical research.

Informed Consent: Because the study was designed retrospectively no written informed consent form was obtained from the patients.

Footnotes

Author Contributions: Küçük E: Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing; Kaya F: Data Collection or Processing, Literature Search; Koru L: Data Collection or Processing, Literature Search; Aydın Z: Data Collection or Processing, Literature Search; Dizman EN: Data Collection or Processing, Literature Search; Dursun HK: Data Collection or Processing, Literature Search; Özen Balcı M: Data Collection or Processing, Literature Search; Özdemir UF: Data Collection or Processing, Literature Search; Meriç Toprak S: Data Collection or Processing, Literature Search; Katrancı S: Data Collection or Processing, Literature Search; Öztürk K: Concept, Design, Analysis or Interpretation, Literature Search; Haşlak F: Concept, Design, Analysis or Interpretation, Literature Search.

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Awareness and Knowledge of PFAPA Syndrome and Familial Mediterranean Fever Among Pediatricians: A Questionnaire-based Study

Author(s)

Betül Öksel, Nihal Şahin, Hafize Emine Sönmez

Affiliation(s)

Kocaeli University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Rheumatology, Kocaeli, Türkiye

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Abstract

Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) and familial Mediterranean fever (FMF) are the most frequent recurrent fever syndromes in children. Both cause episodic inflammatory flares, and appropriate management markedly improves quality of life. Given the limited data on physicians' awareness of these conditions in Türkiye, this study aimed to evaluate the knowledge and attitudes of pediatric specialists and residents regarding PFAPA syndrome and FMF. An online questionnaire consisting of Likert scale and multiple-choice items assessing clinical features, diagnostic approaches, treatment practices, and demographic characteristics was administered. A total of 306 participants were included: 59.5% were women, 40.8% were pediatricians, and 52.9% were employed at university hospitals. The clinical features most commonly considered when diagnosing PFAPA were fever (frequency and duration, 85%), sore throat (58.5%), aphthous ulcers (56.9%), and cervical lymphadenopathy (54.6%). Sixty percent of participants stated that PFAPA can be diagnosed clinically, and participants showed high awareness of treatment options, such as corticosteroids (89.2%) and tonsillectomy (85.9%). In FMF, recurrent fever (97%), abdominal pain (93.8%), and arthritis (76.1%) were well-recognized features, whereas awareness of less common symptoms was lower. While 84% acknowledged the diagnostic importance of *MEFV* mutations, only half knew the appropriate timing for genetic testing. Most participants recognized colchicine as the first-line treatment for FMF, and 78.4% were aware of the use of biologic agents in colchicine-resistant cases. In conclusion, this study is one of the few nationwide assessments of pediatricians' awareness of PFAPA and FMF in Türkiye. Although overall awareness was high, important gaps remain in the recognition of atypical clinical features and the appropriate use of genetic testing, underscoring the need for targeted educational initiatives to support early diagnosis and timely treatment.

Keywords: Recurrent fever syndromes, pediatrician awareness, PFAPA, FMF

Correspondence: Betül Öksel MD, Kocaeli University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Rheumatology, Kocaeli, Türkiye
E-mail: betuloksel@gmail.com **ORCID:** 0000-0002-8979-4497

Introduction

The most common recurrent fever syndromes in childhood are periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome and familial Mediterranean fever (FMF). Both disorders are characterized by episodic attacks, but with appropriate treatment, patients can experience significant improvements in quality of life. PFAPA syndrome typically affects children under five years of age. It is characterized by recurrent episodes of high fever accompanied by aphthous stomatitis, pharyngitis, and cervical adenitis, with children remaining completely healthy between episodes[1,2]. Because PFAPA is non-infectious in origin and is associated with elevations in acute-phase reactants during attacks, it is an important condition for pediatricians to consider in the differential diagnosis. Early recognition can prevent unnecessary antibiotic use and reduce the need for advanced diagnostic evaluations. FMF is an inherited autoinflammatory disease characterized by recurrent episodes of fever and serositis (peritonitis, pleuritis, and acute synovitis). Diagnosis is primarily clinical but is supported by genetic testing. Colchicine therapy effectively prevents complications in the majority of patients[3-6].

Highlights

- Pediatricians demonstrated high awareness of the key clinical features and treatment approaches for periodic fever, aphthous stomatitis, pharyngitis, and adenitis and familial Mediterranean fever.
- However, notable gaps remain in recognizing atypical symptoms and in understanding the appropriate timing of genetic testing.
- These findings highlight the need to strengthen educational programs to support early diagnosis and effective management.

Both disorders can be recognized early through careful pediatric evaluation. However, delays in diagnosis may lead to unnecessary antibiotic use, increased healthcare burden, and reduced quality of life. Particularly in FMF, delayed diagnosis and treatment are major risk factors for the development of amyloidosis. Therefore, awareness and knowledge among pediatricians are critical.

The aim of this study was to assess the knowledge and awareness of PFAPA and FMF among pediatricians and pediatric research assistants in Türkiye. The findings may provide valuable insights to support the enhancement of clinical practices related to the diagnosis and management of these conditions.

Materials and Methods

The questionnaire used in this study consisted of sections evaluating participants' demographic and professional characteristics, as well as their knowledge and awareness regarding PFAPA and FMF. The survey included multiple-choice items and Likert scale questions.

In the first section, participants were asked about their age, sex, professional title, years of experience, workplace type and location, presence of chronic illnesses, personal or immediate family history of recurrent fever syndromes, the number of patients with recurrent fever syndromes managed in the past year, and their definition of recurrent fever syndromes (**Supplementary File 1**).

The second section included 23 questions assessing clinicians' knowledge of PFAPA. Of these, 14 addressed awareness and attitudes toward PFAPA; 5 focused on atypical presentations and the exclusion of alternative diagnoses; and the remaining 4 assessed the clinical findings used to diagnose PFAPA. A total of 28 questions were asked to assess clinicians' awareness of the clinical and laboratory findings used in the diagnosis of FMF and their attitudes toward FMF. Of these, 14 addressed clinical and laboratory findings, while the remaining 14 focused on awareness and attitudes. All questions were designed using a five-point Likert scale (1= strongly disagree; 2= disagree; 3= uncertain; 4= agree; 5= strongly agree).

The assessment items were independently reviewed and finalized by two pediatric rheumatology specialists, each with over five years' experience. The final, complete list of questions related to diagnostic considerations, atypical findings, exclusion of alternative diagnoses, and awareness and attitude assessments for both PFAPA and FMF is provided in **Supplementary File 2**.

Participation in the study was voluntary, and individuals who agreed to complete the survey were included. The online questionnaire was created using Google Forms and shared through institutional pediatric communication groups via messaging applications and email links. The survey targeted pediatricians across various regions of Türkiye, including residents, specialists, and academic faculty. A random sampling method was employed to administer the survey.

Ethical approval for the study was obtained from the Kocaeli University Ethics Committee (approval number: GOKAEK-2025/14/39, date: 18.06.2025). Written informed consent was obtained electronically from all participating physicians prior to enrollment in the study.

Statistical Analysis

The database was generated using SPSS 29.0 (IBM Corp., Armonk, NY, USA). The normality of variable distributions was assessed using visual methods (histograms and probability plots) and analytical tests (Kolmogorov-Smirnov and Shapiro-Wilk). As the data did not follow a normal distribution, descriptive analyses were presented as median (minimum-maximum) values. Categorical variables were expressed as percentages. The chi-square test was used to compare two independent groups. A p-value <0.05 was considered statistically significant.

Results

A total of 306 participants were included in the study, of whom 182 (59.5%) were women. The age distribution

was as follows: 135 participants (44.1%) were 25-30 years old, 127 (41.5%) were 31-35 years old, 32 (10.5%) were 36-40 years old, and 12 (3.9%) were over 41 years old. Of all participants, 125 (40.8%) were pediatricians, 112 (36.7%) were pediatric research assistants, and 69 (22.5%) were pediatric subspecialists or fellows. Among the participants, 29 (9.5%) were pediatric rheumatology specialists or fellows actively working in pediatric rheumatology. Regarding professional experience, 171 participants (55.9%) had 0-5 years, 105 (34.3%) had 6-10 years, 21 (6.9%) had 11-15 years, and 9 (2.9%) had more than 15 years.

When institution type was evaluated, 162 participants (52.9%) worked at a university hospital, 78 (25.5%) at a training and research hospital, 34 (11.1%) at a private hospital, and 32 (10.5%) at a state hospital. Of the participants, 173 (56.5%) were from the Marmara region; 81 (26.5%) from the Aegean region; 18 (5.9%) from Central Anatolia; 16 (5.2%) from the Black Sea region; and 6 (2%) from each of the Mediterranean, Eastern Anatolia, and Southeastern Anatolia regions (**Table 1**).

Seventeen participants (5.6%) reported having a chronic disease. Six participants (2%) had a personal history of recurrent fever syndrome, and 17 (5.6%) reported a first-degree relative with recurrent fever syndrome.

A total of 220 participants (71.9%) correctly identified the definition of recurrent fever syndrome as "three or more fever episodes within six months, with at least one week of symptom-free interval between episodes." A significant association was found between professional title and the ability to accurately identify the definition of recurrent fever (p=0.038). The correct response rate was 84.1% among subspecialty fellows and specialists, 68.8% among pediatricians, and 67.9% among pediatric residents.

Regarding the clinical features considered in the diagnosis of PFAPA, 260 participants (85%) consistently considered fever frequency and duration. One hundred seventy-nine (58.5%) reported a sore throat. One hundred seventy-four (56.9%) considered aphthous ulcers; and 167 (54.6%) considered cervical lymphadenopathy. For PFAPA, more than half of participants agreed or strongly agreed that the presence of findings such as diarrhea (59.9%), rash (55.8%), chest pain (54%), arthritis (52.9%), and abdominal pain (51%) should prompt consideration of alternative diagnoses.

Table 1.
Demographic characteristics of respondents

Variable	n=306
Sex	
Female, n (%)	182 (59.5%)
Male, n (%)	124 (40.5%)
Academic title	
Pediatricians	125 (40.8%)
Research assistant	112 (36.7%)
Subspecialist/fellow	69 (22.5%)
Professional experience	
0-5 years	171 (55.9%)
6-10 years	105 (34.3%)
11-15 years	21 (6.9%)
>16 years	9 (2.9%)
Type of institution	
University hospital	162 (52.9%)
Training and research hospital	78 (25.5%)
Private hospital	34 (11.1%)
State hospital	32 (10.5%)
Geographic region	
Marmara	173 (56.5%)
Aegean	81 (%6.5%)
Central Anatolia	18 (5.9%)
Black Sea	16 (5.2%)
Mediterranean	6 (2%)
Eastern Anatolia	6 (2%)
Southeastern Anatolia	6 (2%)

Table 2.
Respondents' opinions on PFAPA awareness and attitudes statements

Statements	Strongly disagree n, (%)	Disagree n, (%)	Uncertain n, (%)	Agree n, (%)	Strongly agree n, (%)
PFAPA syndrome is one of the most common causes of recurrent fever in childhood.	17 (5.6)	19 (6.2)	30 (9.8)	82 (26.8)	158 (51.6)
I consider the diagnosis of PFAPA in children presenting with recurrent fever in my clinical practice.	0	0	18 (5.9)	77 (25.1)	211 (69.0)
PFAPA can be easily diagnosed using clinical criteria.	9 (2.9)	40 (13.1)	72 (23.5)	94 (30.7)	91 (29.7)
I have difficulty distinguishing PFAPA from infections.	15 (4.9)	51 (16.7)	122 (39.9)	59 (19.3)	59 (19.3)
I have sufficient knowledge about PFAPA.	3 (1.0)	49 (16.0)	92 (30.1)	112 (36.6)	50 (16.3)
Delayed diagnosis of PFAPA may lead to unnecessary antibiotic use.	0	0	9 (2.9)	64 (20.9)	233 (76.1)
Corticosteroid therapy reduces the frequency of PFAPA attacks.	80 (26.1)	34 (11.1)	59 (19.3)	50 (16.3)	83 (27.1)
I believe that more education and training about PFAPA are needed.	3 (1.0)	0	29 (9.5)	96 (31.4)	178 (58.2)
I think corticosteroid treatment is effective during PFAPA attacks.	6 (2.0)	3 (1.0)	24 (7.8)	85 (27.8)	188 (61.4)
Colchicine is a treatment option for PFAPA.	10 (3.3)	15 (4.9)	68 (22.2)	93 (30.4)	120 (39.2)
I am aware that tonsillectomy can be recommended as a treatment option in PFAPA.	15 (4.9)	10 (3.3)	18 (5.9)	60 (19.6)	203 (66.3)
Tonsillectomy is always the first-line option in the treatment of PFAPA.	134 (43.8)	64 (20.9)	58 (19.0)	21 (6.9)	29 (9.5)
I am aware that probiotics can be used in the treatment of PFAPA.	60 (19.6)	34 (11.1)	107 (35.0)	67 (21.9)	38 (12.4)
PFAPA generally has a good prognosis and does not lead to serious long-term complications.	3 (1.0)	9 (2.9)	55 (18.0)	116 (37.9)	123 (40.2)

PFAPA: Periodic fever, aphthous stomatitis, pharyngitis, and adenitis

Responses regarding PFAPA awareness and attitudes are shown in **Table 2**. Most participants (88.4%) agreed that PFAPA syndrome is one of the most common causes of recurrent fever in childhood. A high proportion of participants (94.1%) considered PFAPA a diagnosis in children presenting with recurrent fever. Awareness of treatment options varied: 69.6% were aware of colchicine, 85.9% of tonsillectomy, and 34.3% of probiotics.

Most participants identified recurrent fever (97%), abdominal pain (93.8%), chest pain (68.6%), and arthritis (76.1%) as significant manifestations of FMF. Additionally, 97% of participants considered FMF as a diagnosis in children presenting with recurrent fever and abdominal pain. Approximately half of the participants were unsure about how often skin rashes occur during FMF attacks. Responses to questions on clinical and laboratory findings relevant to FMF diagnosis are given

Table 3.
Awareness of clinical and laboratory findings in the diagnosis of FMF

Statements	Strongly disagree n, (%)	Disagree n, (%)	Uncertain n, (%)	Agree n, (%)	Strongly agree n, (%)
Recurrent fever attacks	3 (1.0)	3 (1.0)	3 (1.0)	22 (7.2)	275 (89.8)
Abdominal pain (peritonitis attacks)	10 (3.3)	3 (1.0)	6 (2.0)	37 (12.1)	250 (81.7)
Chest pain	22 (7.2)	15 (4.9)	59 (19.3)	57 (18.6)	153 (50.0)
Arthritis	10 (3.3)	12 (3.9)	51 (16.7)	69 (22.5)	164 (53.6)
Erysipelas-like erythema of the lower extremities	19 (6.2)	19 (6.2)	87 (28.4)	64 (20.9)	117 (38.2)
Family history of FMF	0	15 (4.9)	19 (6.2)	63 (20.6)	209 (68.3)
Completely asymptomatic periods between attacks	0	6 (2.0)	24 (7.8)	54 (17.6)	222 (72.5)
Disease onset before 5 years of age	26 (8.5)	46 (15.0)	127 (41.5)	55 (18.0)	52 (17.0)
Scrotal pain and swelling (tunica vaginalis involvement)	13 (4.2)	21 (6.9)	144 (47.1)	61 (19.9)	67 (21.9)
Dramatic response to colchicine therapy	0	6 (2.0)	46 (15.0)	87 (28.4)	167 (54.6)
Elevated serum AA levels	10 (3.3)	12 (3.9)	60 (19.6)	96 (31.4)	128 (41.8)
Detection of *MEFV* mutation in genetic testing	10 (3.3)	9 (2.9)	30 (9.8)	78 (25.5)	179 (58.5)
Conjunctivitis	68 (22.2)	61 (19.9)	134 (43.8)	19 (6.2)	24 (7.8)
Urticarial-like rash	58 (19.0)	56 (18.3)	136 (44.4)	28 (9.2)	28 (9.2)

FMF: Familial Mediterranean fever, AA: Arachidonic acid

Table 4.
Awareness regarding FMF diagnosis, management, and disease characteristics

Statements	Strongly disagree n, (%)	Disagree n, (%)	Uncertain n, (%)	Agree n, (%)	Strongly agree n, (%)
FMF is one of the common autoinflammatory diseases seen in children in our country.	3 (1.0)	4 (1.3)	3 (1.0)	73 (23.9)	223 (72.9)
I consider FMF in children presenting with recurrent abdominal pain and fever.	3 (1.0)	0	6 (2.0)	39 (12.7)	258 (84.3)
Skin rashes are frequently seen during FMF attacks.	31 (10.1)	58 (19.0)	139 (45.4)	52 (17)	26 (8.5)
I know when to request genetic testing for FMF diagnosis.	12 (3.9)	33 (10.8)	108 (35.3)	75 (24.5)	78 (25.5)
FMF can be diagnosed even without genetic testing.	19 (6.2)	38 (12.4)	106 (34.6)	64 (20.9)	79 (25.8)
I have sufficient knowledge about FMF.	3 (1.0)	40 (13.1)	103 (33.7)	104 (34)	56 (18.3)
I experience difficulty diagnosing FMF in my clinical practice.	40 (13.1)	70 (22.9)	116 (37.9)	59 (19.3)	21 (6.9)
Delayed diagnosis of FMF may lead to serious complications.	0	3 (1.0)	42 (13.7)	61 (19.9)	200 (65.4)
I need more education and up-to-date information about FMF.	6 (2.0)	13 (4.2)	61 (19.9)	104 (34.0)	122 (39.9)
Recurrent fever and serositis attacks are the most important clinical findings for FMF diagnosis.	0	3 (1.0)	3 (1.0)	81 (26.5)	219 (71.5)
Colchicine is the first-line treatment for FMF.	3 (1.0)	0	3 (1.0)	63 (20.5)	237 (77.5)
The dose of colchicine should not be increased during an FMF attack.	61 (19.9)	46 (15.0)	91 (29.7)	45 (14.7)	63 (20.6)
Biologic agents may be used in colchicine-resistant patients.	0	12 (3.9)	54 (17.6)	61 (19.9)	179 (58.5)
I agree that measuring serum amyloid a is important in risk assessment for amyloidosis.	6 (2.0)	18 (5.9)	70 (22.9)	71 (23.2)	141 (46.1)

FMF: Familial Mediterranean fever

in **Tables 3 and 4**. Participants indicated uncertainty about early disease onset (<5 years) and scrotal pain or swelling: 41.5% and 47.1% responded "undecided", respectively. The items with the highest correct and incorrect response rates are presented in **Table 5**.

Discussion

In this study, we evaluated pediatric physicians' knowledge, attitudes, and awareness regarding two common recurrent fever syndromes: FMF and PFAPA. Our findings indicate that participants generally had a high level of awareness of both conditions. The fact that PFAPA and FMF were considered in the differential diagnosis of children with recurrent fever in 94.1% and 97% of cases, respectively, reflects strong clinical awareness among physicians. Pediatricians comprised the largest group of participants (40.8%). A significant association between professional title and accurate recognition of the definition of recurrent fever (p=0.038), with subspecialty fellows and specialists demonstrating the highest accuracy (84.1%), suggests that longer training and greater clinical experience are associated with improved diagnostic accuracy.

The clinical findings most often used to diagnose PFAPA were fever frequency and duration, the most frequently reported parameters (85%). This was followed by sore throat (58.5%), aphthous ulcers (56.9%), and cervical lymphadenopathy (54.6%). Similarly, a survey of pediatric rheumatologists and infectious disease specialists reported that both groups agreed at a rate of 95% that recurrent, patterned febrile episodes are characteristic of PFAPA[7].

The atypical features considered by our participants for alternative diagnoses included diarrhea (59.9%), skin rash (55.8%), chest pain (54%), arthritis (52.9%), and abdominal pain (51%). Although the Eurofever/PRINTO 2019 criteria designate diarrhea, chest pain, skin rash, and arthritis as features that rule out PFAPA[2], our results indicate that only about half of the participants were aware of these exclusion criteria. This suggests a need to enhance clinical awareness of specific signs that warrant inclusion in the differential diagnosis. Moreover, 60.4% of our respondents answered "strongly agree" or "agree" to the statement that PFAPA can be diagnosed using clinical criteria. This finding indicates the need to enhance education on the diagnostic value of clinical assessment for PFAPA, particularly among specialists and pediatric rheumatology fellows/residents, who constituted most of the study group.

Regarding PFAPA treatment, most participants were familiar with the available therapeutic options. Corticosteroids (89.2%), tonsillectomy (85.9%), and colchicine (69.6%) were the most frequently selected treatments among our participants. The 2020 CARRA PFAPA Working Group recommends antipyretics, corticosteroids, prophylactic colchicine, and tonsillectomy for PFAPA[8]. However, considering the self-limiting nature of PFAPA and the absence of long-term sequelae, it is recommended to optimize corticosteroid use and reserve tonsillectomy for patients with a true otolaryngological indication or for those with refractory disease. In addition to these treatment modalities, a study evaluating the potential efficacy of *Streptococcus salivarius* K12 in preventing febrile episodes in PFAPA reported that probiotic use may help reduce febrile attacks and the need for additional pharmacological therapy[9]. Although recent evidence supports the use of probiotics in PFAPA, only 34.3% of our survey participants were aware of probiotics as a treatment option. However, recent literature increasingly highlights the role of probiotics, indicating that participants' awareness of current evidence on this topic remains limited[10,11].

According to the Yalçinkaya et al.[12] criteria, the presence of two or more of the following features—fever, abdominal pain, chest pain, arthritis, and a family history of FMF—allows for a diagnosis of FMF with 86.5% sensitivity and 96.3% specificity. In our survey cohort, most participants acknowledged the diagnostic relevance of clinical manifestations, including recurrent

Table 5.
Items with the highest rates of correct and incorrect responses

	Agree-strongly agree				
	In all participants %	In pediatric research assistants %	In pediatricians %	In subspecialists or fellows %	p
Correct					
1. Recurrent fever and serositis attacks are the most important clinical features in the diagnosis of FMF.	98	94.6	100.0	100.0	0.02
2. Colchicine is the first-line treatment for FMF.	98	100.0	95.2	100.0	0.09
3. Delayed diagnosis of PFAPA may lead to unnecessary antibiotic use.	97.1	92.0	100.0	100.0	<0.001
Incorrect responses					
1. I am aware that probiotics can be used in the treatment of PFAPA.	34.3	33.0	29.6	44.9	<0.001
2. In FMF diagnosis, erysipelas-like erythema on the lower extremities is an important clinical finding.	59.1	49.1	56.0	81.2	<0.001
3. PFAPA can be easily diagnosed using clinical criteria.	60.4	59.8	62.4	58.0	0.04

FMF: Familial Mediterranean fever, PFAPA: Periodic fever, aphthous stomatitis, pharyngitis, and adenitis

fever (97%), abdominal pain (93.8%), arthritis (76.1%), and chest pain (68.6%). When asked whether disease onset before the age of 5 years is typical for FMF, a considerable proportion of participants either agreed or expressed uncertainty. Although FMF most commonly begins in childhood, there is no strict age threshold, and disease onset may occur later in adolescence or even adulthood[13]. Therefore, onset before the age of 5 years should not be considered a defining or obligatory feature of FMF. The high rate of agreement with this statement suggests a misconception regarding the typical age of disease onset rather than accurate clinical knowledge. This finding highlights an important gap in disease-related awareness and underscores the need for clearer educational messaging regarding the variable age at onset of FMF. Awareness of less common FMF-related clinical features was significantly lower. When asked about the diagnostic value of symptoms such as scrotal pain and swelling, rash, and conjunctivitis, about half of the participants responded "uncertain." This indicates that participants lacked sufficient knowledge of the clinical signs that may accompany other, rarer autoinflammatory diseases. These findings highlight the importance of emphasizing in educational programs the atypical clinical features of FMF and other autoinflammatory diseases for consideration in the differential diagnosis.

The 2019 Eurofever/PRINTO classification criteria incorporated genetic testing into the diagnostic process for FMF for the first time[2]. In our study, knowledge and awareness regarding genetic testing were evaluated through three separate questions. Although most participants (84%) acknowledged the diagnostic significance of *MEFV* mutations, only half (50%) reported knowing when to request genetic testing. Additionally, 46.7% agreed that FMF can be diagnosed without genetic testing. This indicates recognition of the central role of clinical evaluation in the diagnostic process, but also highlights heterogeneity in knowledge regarding the appropriate use of genetic testing.

Low awareness of atypical clinical features and of genetic testing practices may reflect that atypical manifestations are less frequently encountered in routine pediatric practice and are often overshadowed by more typical clinical presentations. As a result, such features may be underemphasized during clinical training and daily practice. Moreover, earlier diagnostic approaches for FMF relied largely on clinical findings, whereas the Eurofever/PRINTO classification criteria incorporate genetic findings into the classification process[2]. This shift from a predominantly clinical framework to one that also considers genetic data may not yet be fully reflected in routine clinical practice, potentially contributing to uncertainty regarding the appropriate use and timing of genetic testing.

Nearly all participants were aware that colchicine is the first-line treatment for FMF, reflecting widespread recognition of this therapy, which has been the cornerstone of FMF management for nearly half a century[6]. Furthermore, 78.4% of respondents expressed support for the use of biologic agents in colchicine-resistant cases, indicating a high level of awareness of additional therapeutic options. Awareness of potential complications was high: 85.3% recognized that delayed diagnosis of FMF can lead to severe outcomes, such as amyloidosis, underscoring the importance of early diagnosis and appropriate treatment[14]. In addition, the fact that 69.3% agreed with the statement "measuring serum amyloid a is important in evaluating amyloidosis" indicates that awareness of monitoring for complications is generally adequate.

Study Limitations

This study has several limitations. The use of Likert scale questions may have led some participants to select "agree" or "uncertain" without fully comprehending the statements. The absence of open-ended questions limited our ability to gauge participants' depth of knowledge regarding PFAPA and FMF. As no pilot study was conducted, the findings should be interpreted with this limitation in mind. In addition, potential ambiguity in some questionnaire items may have influenced participant responses, underscoring the importance of employing clearer, more explicit wording in future survey-based studies. Participants' institutional pediatric rheumatology practice or involvement during training was not specifically assessed, limiting the ability to correlate awareness levels with clinical practice. Furthermore, the majority of participants were employed at tertiary care centers, including university hospitals and training and research hospitals, which may limit the generalizability of our findings to primary care pediatric practice. Since more complex and atypical cases are more frequently referred to tertiary care centers, the level of awareness observed in our study may be higher than that of pediatricians working in primary or secondary care settings. Moreover, the online, voluntary nature of the survey may have introduced selection and response biases, potentially favoring physicians who are more interested in recurrent fever syndromes or more confident in their knowledge, which may have contributed to higher observed overall awareness. Because no previous studies have assessed awareness of PFAPA and FMF, we based the questionnaire design and interpretation of our findings on comparisons with existing clinical criteria, therapeutic approaches, and guideline recommendations. Despite these limitations, this study represents one of the first efforts in Türkiye to assess pediatricians' awareness of and attitudes toward PFAPA and FMF.

Conclusion

Even in Türkiye, where FMF and PFAPA are highly prevalent, our findings indicate that significant gaps remain in awareness and education regarding these conditions. In diseases with heterogeneous clinical presentations, even rare features that contribute to the differential diagnosis are important. Particularly in recurrent fever syndromes, where early diagnosis can significantly improve quality of life, timely and accurate recognition and management are critical. Furthermore, staying up to date with the current literature is essential for

implementing innovative approaches in clinical practice. Encouraging active involvement in the management of PFAPA and FMF cases during residency training, along with structured postgraduate educational programs for pediatric specialists, may help translate updated knowledge into daily clinical practice.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Kocaeli University Ethics Committee (approval number: GOKAEK-2025/14/39, date: 18.06.2025).

Informed Consent: Written informed consent was obtained electronically from all participating physicians prior to enrollment in the study.

Footnotes

Author Contributions: Öksel B: Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing; Şahin N: Concept, Analysis or Interpretation; Sönmez HE: Concept, Analysis or Interpretation.

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Micronutrient Deficiencies and Thyroid Function in Children with Protein-energy Malnutrition

Author(s)

Utku Dönger[1], Osman Fırat Çalışkan[2]

Affiliation(s)

[1]Defne State Hospital, Clinic of Pediatrics, Hatay, Türkiye

[2]Hatay Mustafa Kemal University Faculty of Medicine Hospital, Department of Pediatrics, Hatay, Türkiye

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Abstract

Protein-energy malnutrition (PEM) remains a significant public health problem in childhood and is frequently accompanied by multiple micronutrient deficiencies and metabolic alterations. This study aimed to simultaneously evaluate micronutrient status and thyroid function in children diagnosed with PEM. A retrospective analysis was conducted of the medical records of children aged 0-17 years who were admitted to Defne State Hospital between December 2023 and May 2025 with a diagnosis of PEM. Demographic characteristics, anthropometric measurements, and laboratory parameters, including hemoglobin, serum iron, ferritin, vitamin B12, vitamin D, blood urea nitrogen, creatinine, thyroid-stimulating hormone, and free T4 were recorded. Nutritional status was assessed using World Health Organization growth standards. A total of 65 children (32 males and 33 females) were included. Mild, moderate, and severe malnutrition were identified in 38.46%, 44.62%, and 16.92% of patients, respectively. Anemia and vitamin D deficiency were the most common abnormalities observed in 23.08% and 18.46% of patients, respectively. In contrast, vitamin B12 deficiency and abnormal thyroid function test results were detected at lower rates (3.08% and 4.62%, respectively). No significant differences were observed between genders in anthropometric measurements or malnutrition severity. The relatively low prevalence of thyroid dysfunction, compared with previous studies, may be attributable to the predominance of mild-to-moderate malnutrition in the study population. These findings suggest that the impact of PEM on micronutrient metabolism and endocrine function varies according to disease severity, and highlight the importance of a comprehensive clinical approach that includes assessment of both micronutrient and hormonal status in children with PEM.

Keywords: Anemia, micronutrient deficiency, protein-energy malnutrition, thyroid function, vitamin D

Correspondence: Utku Dönger MD, Defne State Hospital, Clinic of Pediatrics, Hatay, Türkiye
E-mail: utkudonger@gmail.com **ORCID:** 0000-0002-7489-0136

Introduction

Malnutrition is a clinical condition resulting from inadequate intake of one or more nutrients, leading to impairment of growth, development, and metabolic balance[1]. Protein-energy malnutrition (PEM) remains a major health problem among children, particularly in low- and middle-income countries, and is associated with increased morbidity and mortality[2]. In our country, PEM continues to be an important public health concern within the pediatric population.

Iron deficiency anemia (IDA), thyroid dysfunction, and vitamin B12 deficiency are clinical conditions closely associated with childhood malnutrition. Recent evidence indicates that PEM is not a uniform disease entity but rather a heterogeneous condition comprising clinically variable subtypes related to different patterns of nutritional deficiency[3].

Childhood malnutrition and micronutrient deficiencies, especially IDA, constitute a major global health problem affecting millions of children. IDA is the most common nutritional disorder and the leading cause of anemia in children. If left untreated, it may lead to long-term adverse effects on neurodevelopment, immune function, and physical growth[4]. Recent comprehensive reviews have demonstrated that in children with acute malnutrition, anemia frequently coexists with other micronutrient deficiencies, thereby increasing disease severity[5].

Children diagnosed with severe acute malnutrition exhibit a markedly increased susceptibility to infections. Anemia, which is frequently observed in these patients, develops as a consequence of malnutrition and contributes to morbidity and mortality through both direct and indirect mechanisms[6,7]. This increased risk is thought to result from the combined effects of protein deficiency, micronutrient depletion, and impaired immune function[5].

Vitamin B12 is an essential micronutrient for motor, language, and cognitive development in children. In malnourished children, vitamin B12 deficiency may lead to developmental delay and severe anemia[8,9]. Emerging evidence suggests that vitamin B12 deficiency may persist despite nutritional rehabilitation and have lasting adverse effects on neurodevelopmental outcomes[5,8].

As the severity of malnutrition increases, serum levels of triiodothyronine (T3) and thyroxine (T4) may decline. This phenomenon is considered an adaptive response aimed at reducing energy expenditure. In PEM, decreased synthesis of carrier proteins such as albumin and T4-binding globulin contributes to lower circulating thyroid hormone levels. These hormonal changes resemble the non-thyroidal illness response observed in other severe conditions and may become clinically significant in prolonged or severe PEM[10].

Although numerous studies have examined PEM subtypes and micronutrient deficiencies, data integrating micronutrient status and thyroid function within the same pediatric PEM cohort remain limited[5,11].

Therefore, this study aimed to evaluate the levels of serum vitamin D, vitamin B12, blood urea nitrogen (BUN), creatinine, thyroid-stimulating hormone (TSH), and free T4 (fT4) in children diagnosed with PEM and determine the prevalence of anemia based on complete blood count data. By adopting an integrated approach, this study seeks to provide clinically relevant insights into the combined assessment of micronutrient deficiencies and thyroid function alterations in pediatric PEM.

Highlights

- Anemia (23.08%) and vitamin D deficiency (18.46%) were the most common micronutrient abnormalities observed in children with protein-energy malnutrition (PEM).
- Vitamin B12 deficiency (3.08%) and abnormal thyroid function test results (4.62%) were detected at relatively low frequencies.
- Moderate malnutrition accounted for the majority of cases, which may explain the low prevalence of thyroid dysfunction.
- Hematological parameters and vitamin D metabolism were affected more frequently than was thyroid function in pediatric PEM.
- These findings emphasize the importance of incorporating micronutrient and endocrine evaluations into the routine clinical assessment of children with PEM.

Materials and Methods

This retrospective study included children aged 0-17 years admitted to Defne State Hospital, located in the Hatay province, Türkiye, diagnosed with PEM between December 2023 and May 2025. Demographic characteristics, anthropometric measurements, and laboratory data were obtained from the hospital's electronic medical record system.

Anthropometric assessment included measurements of body weight and height, which were performed according to standardized clinical procedures. Nutritional status was evaluated in accordance with the World Health Organization (WHO) Child Growth Standards.

In children younger than five years of age (0-59 months), nutritional status was primarily assessed using weight-for-age Z-scores (WAZ), calculated based on the WHO Child Growth Standards (2006). Weight-for-age was preferred because it is the most stable and comparable indicator of overall nutritional status in children under five years of age[12]. Malnutrition severity was classified as follows: mild malnutrition, WAZ between -1 and -2 standard deviations (SDs) moderate malnutrition, WAZ between -2 and -3 SD; and severe malnutrition, WAZ below -3 SD.

In children and adolescents aged 5-19 years, nutritional status was assessed using body mass index (BMI)-for-age Z-scores (BAZ), in accordance with the WHO reference standard[13]. Accordingly, thinness was defined as a BAZ between -2 and -1 SD, moderate thinness as a BAZ between -3 and -2 SD, and severe thinness as a BAZ below -3 SD.

The study excluded children with the following conditions: metabolic disorders, urinary tract infections, malabsorption syndrome (e.g., celiac disease), protein-

losing enteropathy, nephrotic syndrome, chronic liver or kidney disease, and significant congenital anomalies.

Patients who had used medications known to affect thyroid function tests (e.g., amiodarone, corticosteroids, lithium, anticonvulsants, iodides) were excluded.

Patients with vitamin B12 levels below 200 pg/mL were designated as deficient, while those with levels between 200 and 300 pg/mL were classified as borderline[14].

Anemia was defined as a decrease in hemoglobin (Hb) concentration, hematocrit (Hct), or red blood cell count per cubic millimeter. The presence of anemia in patients was assessed as present if values were below the anemia threshold, which was defined as two SDs below the mean value for the age group[15].

In assessing thyroid function test results in patients, serum TSH and sT4 levels were evaluated according to patient age; TSH values were reported in µIU/mL and sT4 in ng/dL[16].

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Hatay Mustafa Kemal University (approval number: 05, date: 18.06.2025). As this was a retrospective study based on existing medical records, informed consent was waived by the ethics committee.

Statistical Analysis

All statistical analyses were performed using SPSS v27.0 (IBM Corp., Armonk, NY, USA). The normality of the variables was assessed using the Shapiro-Wilk test. Descriptive statistics were reported using the mean, SD, median, minimum, and maximum values for continuous variables. Continuous variables with a normal distribution are presented as mean ± SD, whereas non-normally distributed variables are presented as median and interquartile range (IQR), according to normality testing. For variables that did not follow a normal distribution, comparisons between the two groups were performed using the Mann-Whitney U test. For variables that exhibited a normal distribution, comparisons between the two groups were conducted using the t-test. Categorical variables were presented as frequencies and percentages, and differences between groups were tested using the Pearson chi-square test. Statistical significance was set at $p<0.05$.

Results

The study comprised a total of 65 children diagnosed with PEM, of whom 32 (49.2%) were male and 33 (50.8%) were female. No statistically significant differences were observed between male and female patients in age, height, weight, or BMI; all $p>0.05$. The median age was 4.07 years (IQR: 6.41) in males and 4.42 years (IQR: 9.22) in females (p=0.990). Mean heights were 103.59±24.46 cm in males and 103.55±32.96 cm in females (p=0.995), while mean BMIs were 13.85±1.57 kg/m² in males and 13.61±1.27 kg/m² in females (p=0.496) (**Table 1**).

The severity of malnutrition was evaluated by gender. Mild malnutrition was observed in 25 patients (38.46%), moderate malnutrition in 29 patients (44.62%), and severe malnutrition in 11 patients (16.92%). Among male patients, 43.75% had mild malnutrition, 43.75% moderate malnutrition, and 12.50% severe malnutrition. In female patients, the corresponding rates were 33.33%, 45.46%, and 21.21%, respectively. No statistically significant difference was observed in the distribution of malnutrition severity between genders (p=0.549; **Table 2**).

The laboratory findings of the study population are summarised in **Table 3**. The mean Hb level was 12.19±1.02 g/dL, and the mean Hct value was 36.95±3.29%. The mean serum iron concentration was 68.59±30.93 µg/dL, while the median ferritin level was 34.49 ng/mL (IQR: 25.32 ng/mL). The median vitamin B12 and vitamin D levels were 463 pg/mL (IQR: 262) and 26 ng/mL (IQR: 17), respectively. Thyroid function parameters showed a median TSH level of 1.91 µIU/mL (IQR: 1.40 µIU/mL), with mean free T3 and fT4 levels of 4.18±0.69 ng/dL and 1.34±0.19 ng/dL, respectively. The mean blood urea nitrogen (BUN) and creatinine levels were 10.86±3.65 mg/dL and 0.38±0.11 mg/dL, respectively.

Evaluations of micronutrient deficiencies and abnormal thyroid function test results are presented in **Table 4**. Anemia was detected in 15 patients (23.08%), whereas 47 (72.31%) were not anemic. Serum iron deficiency and low ferritin levels were identified in 2 (3.08%) and 4 (6.15%) patients, respectively. The prevalence of vitamin B12 deficiency was 3.08% (2 patients), whereas that of vitamin D deficiency was 18.46% (12 patients). Abnormal thyroid function test results and low BUN levels were each present in 3 patients (4.62%).

Discussion

PEM is frequently associated with deficiencies of multiple micronutrients, such that a deficiency in one nutrient often coexists with deficiencies in others[17].

Table 1.
Demographic characteristics and anthropometric measurements of patients by gender

	Gender		p
	Male	Female	
n (%)	32 (49.20)	33 (50.80)	
Age (years)[a]	4.07; 6.41	4.42; 9.22	0.990*
Height (cm)[β]	103.59±24.46	103.55±32.96	0.995**
Weight (kg)[a]	12.75; 9.95	12.50; 14.40	0.689*
BMI[β]	13.85±1.57	13.61±1.27	0.496**

α Median; IQR
β Mean ± Standard deviation
*: p<0.05, Mann-Whitney U test
**: p<0.05, Independent samples t-test
BMI: Body mass index, IQR: Interquartile range

Table 2.
Degree of malnutrition according to gender

	Gender				Total		p
	Male		Female				
	n	%	n	%	n	%	
Mild	14	43.75	11	33.33	25	38.46	
Moderate	14	43.75	15	45.46	29	44.62	0.549*
Severe	4	12.50	7	21.21	11	16.92	
Total	32	100.00	33	100.00	65	100.00	

*: p<0.05, Pearson chi-square test

In our cohort, anemia and vitamin D deficiency were the most prominent abnormalities, a pattern that has also been reported in other settings. For example, research from India involving 104 children with PEM identified these two deficiencies as the most frequent findings[18]. Likewise, a Pakistani study of 150 malnourished children aged 6-60 months documented anemia in nearly 80% participants; most cases were attributable to iron deficiency. The study also reported rickets in more than a third of patients, vitamin A deficiency in 14% of patients, and zinc or B-complex vitamin deficiencies in more than a quarter of patients[19]. These results highlight the multifactorial nature of nutritional compromise in PEM. Similarly, among 428 children diagnosed with IDA

Table 3.
Laboratory findings of the patients

Hemoglobin (g/dL)[β]	12.19±1.02
Hematocrit (%)[β]	36.95±3.29
Serum iron (µg/dL)[β]	68.59±30.93
Ferritin (ng/mL)[α]	34.49; 25.32
Vitamin B12 (pg/mL)[α]	463; 262
Vitamin D (ng/mL)[α]	26; 17
TSH (µIU/mL)[α]	1.91; 1.40
Free T3 (ng/dL)[β]	4.18±0.69
Free T4 (ng/dL)[β]	1.34±0.19
Blood urea nitrogen (mg/dL)[β]	10.86±3.65
Creatinine (mg/dL)[β]	0.38±0.11

α Median ; IQR
β Mean ± Standard deviation
TSH: Thyroid-stimulating hormone, T3: Triiodothyronine, T4: Thyroxine

Table 4.
Evaluation of micronutrient deficiencies and abnormal thyroid function test results

Parameter	Status	n	%
Anemia	Present	15	23.08
	Absent	47	72.30
	Not tested	3	4.62
Low serum iron	Present	2	3.08
	Absent	48	73.84
	Not tested	15	23.08
Low ferritin	Present	4	6.15
	Absent	46	70.77
	Not tested	15	23.08
Vitamin B12 deficiency	Present	2	3.08
	Absent	49	75.38
	Not tested	14	21.54
Vitamin D deficiency	Present	12	18.46
	Absent	35	53.85
	Not tested	18	27.69
Abnormal thyroid function tests	Present	3	4.62
	Absent	47	72.30
	Not tested	15	23.08
Low BUN levels	Present	3	4.62
	Absent	55	84.62
	Not tested	7	10.76
Total		65	100.0

BUN: Blood urea nitrogen

the combined prevalence of vitamin D insufficiency or deficiency was 62%. This finding corroborates evidence that micronutrient deficiencies are prevalent in the context of malnutrition[20].

Endocrine involvement, particularly disturbances in thyroid function, is another important consequence of PEM. Energy and protein deficiencies, limited production of transport proteins, altered peripheral conversion of hormones, and impaired iodine metabolism are among the proposed mechanisms. As nutritional status deteriorates, serum T3 and T4 concentrations fall while TSH levels tend to rise. Initially, the alterations reflect deficits in the binding protein, but with progression, hormone synthesis becomes impaired. Additional nutrient deficiencies, such as hypoalbuminemia, and micronutrient deficiencies (e.g., zinc and iodine) further compromise thyroid function. While this represents an adaptive attempt to conserve energy, the compensatory response may eventually fail in severe or prolonged cases[21-24].

Several studies corroborate this relationship. An Indian study of 60 malnourished children aged 1-5 years reported declines in T3 and T4 with increasing severity of malnutrition, accompanied by a parallel rise in TSH[23]. Another study in Türkiye compared malnourished children with healthy controls and found that T4 levels remained stable in mild-to-moderate PEM but were markedly reduced in severe PEM. T3 was suppressed across all PEM groups, whereas TSH levels remained relatively stable. These findings suggest a stepwise suppression of thyroid function, most evident for T3, with advancing malnutrition[22].

In contrast, abnormal results on thyroid function tests were detected in only three children (4.62%) in our study. When compared with previously reported rates, this proportion appears to be relatively low. The most plausible explanation for this finding is the predominance of mild and moderate, rather than severe, PEM in our study population. Mild and moderate forms of malnutrition may be insufficient to trigger marked hormonal disturbances, which may help explain the discrepancy between our findings and those reported in the existing literature.

In this context, another important consideration when interpreting thyroid function results in children with PEM is the euthyroid sick syndrome (ESS) characterized by alterations in thyroid hormone homeostasis in the absence of intrinsic thyroid disease. ESS has been described in various non-thyroidal conditions, including malnutrition, infections, renal and hepatic disorders, and other states of metabolic stress. The typical biochemical pattern of ESS includes reduced serum T3 levels, normal or low fT4 levels, and normal or mildly altered TSH levels. In the present study, thyroid function assessment was limited to TSH and fT4 measurements, as serum T3 levels were not available for a substantial proportion of patients. Therefore, the presence of ESS could not be reliably evaluated or excluded. This limitation should be considered when interpreting the relatively low prevalence of abnormal thyroid function observed in our cohort. However, the predominance of moderate rather than severe malnutrition in the study population

may partly explain the limited extent of thyroid hormone alterations detected.

Study Limitations

One of the main strengths of this study is that it is among the few studies to simultaneously assess micronutrient deficiencies and thyroid dysfunction in children with PEM. The inclusion of a broad age range enabled the analysis of age-related variations, while the use of retrospective data from the hospital's electronic medical records helped minimize measurement errors. Furthermore, the application of a standardized anthropometric classification based on the WHO criteria strengthened the methodological robustness of the study.

However, this study also has some limitations. It is a single-center, retrospective study, which limits the generalizability of the findings. The relatively small sample size may have reduced the statistical power, particularly in detecting low-frequency conditions such as thyroid dysfunction. Additionally, the prevalence of moderate malnutrition in the study population may have limited the ability to observe the full hormonal impact of severe malnutrition. Important micronutrients, such as vitamin A, zinc, and selenium, were not evaluated. The lack of T3 measurements in a substantial proportion of patients limited the full assessment of thyroid function. The lack of long-term follow-up data also prevented the assessment of the persistence of deficiencies and hormonal alterations.

Conclusion

The findings of this study indicate that, when micronutrient deficiencies and thyroid dysfunction are evaluated together in children diagnosed with PEM, anemia and vitamin D deficiency are relatively common, with prevalence rates of 23.08% and 18.46%, respectively. In contrast, vitamin B12 deficiency and abnormal thyroid function test results were observed at lower rates (3.08% and 4.62%, respectively). The lower frequency of thyroid dysfunction, compared with that reported in previous studies, may be attributable to the predominance of moderate malnutrition in the study population. These results suggest that the effects of PEM on micronutrient metabolism and the endocrine system vary according to the severity of malnutrition. Therefore, childhood malnutrition should be addressed through a comprehensive approach that includes not only assessment of macronutrient status but also evaluation of micronutrient and hormonal status.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Hatay Mustafa Kemal University (approval number: 05, date: 18.06.2025).

Informed Consent: Because the study was designed retrospectively no written informed consent form was obtained from the patients.

Footnotes

Author Contributions: Dönger U: Medical Practices, Concept, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing; Çalışkan OF: Medical Practices, Analysis or Interpretation, Literature Search.

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

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Inflammation-Based Prognostic Markers in Pediatric Continuous Renal Replacement Therapy

Author(s)

Gültaç Evren[1], Sultan Okur Acar[2]

Affiliation(s)

[1]University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital, Clinic of Pediatric Intensive Care Unit, İzmir, Türkiye

[2]Dokuz Eylül University Research and Application Hospital, Department of Pediatric Hematology and Oncology, İzmir, Türkiye

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Abstract

Acute kidney injury is a major cause of morbidity and mortality in critically ill children, and continuous renal replacement therapy (CRRT) is often required in severe cases. Inflammation-based indices such as the neutrophil percentage-to-albumin ratio (NPAR) and the C-reactive protein (CRP)-to-albumin ratio (CAR), as well as procalcitonin (PCT), have been proposed as prognostic markers; however, evidence in pediatric CRRT remains limited. We retrospectively included children aged 29 days to 18 years who underwent CRRT in the Pediatric Intensive Care Unit at Manisa City Hospital from February 2021 to May 2025. Demographic and clinical data and laboratory values obtained within 24 hours prior to CRRT initiation were collected. NPAR was calculated as neutrophil percentage (%) / albumin (g/dL) and CAR as CRP (mg/L) / albumin (g/dL). A total of 41 patients were included; 29 (70.7%) survived and 12 (29.3%) died. Non-survivors had significantly higher Pediatric Risk of Mortality (PRISM) III scores (p=0.008), NPAR values (p=0.03), and PCT levels (p=0.01), while CAR did not differ between groups (p=0.79). In the receiver operating characteristic analysis, PCT [area under the curve (AUC): 0.737] and NPAR (AUC: 0.713) showed moderate discrimination for predicting mortality, whereas CAR showed poor discrimination (AUC: 0.474). NPAR and PCT may support early risk stratification in pediatric patients requiring CRRT; larger multicenter studies are warranted.

Keywords: CAR, continuous renal replacement therapy, NPAR, pediatric intensive care, procalcitonin, prognosis

Correspondence: Gültaç Evren MD, University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital, Clinic of Pediatric Intensive Care Unit, İzmir, Türkiye
E-mail: gultacevren@gmail.com **ORCID:** 0000-0002-0614-0894

Introduction

Acute kidney injury (AKI) is a frequent and clinically important problem in children managed in the pediatric intensive care unit (PICU) and is associated with increased morbidity and mortality. In patients who do not respond adequately to conservative measures, continuous renal replacement therapy (CRRT) is commonly initiated to control fluid balance and correct electrolyte and acid-base disturbances, particularly when hemodynamic instability limits the use of intermittent modalities[1]. Despite its widespread use, the mortality rate among pediatric patients undergoing CRRT remains high, typically ranging from 30% to 40%, depending on underlying comorbidities and illness severity[2]. Identifying prognostic markers that enable early risk stratification is therefore critical. The prognosis of patients undergoing CRRT is influenced by multiple factors, including the accumulation of uremic toxins, electrolyte imbalances, and reduced clearance capacity resulting from impaired renal function[3]. Inflammation plays a pivotal role in both AKI pathogenesis and the overall course of critical illness in children. Biomarkers such as C-reactive protein (CRP), procalcitonin (PCT), albumin, and neutrophil percentage are commonly used to reflect systemic inflammatory status.

Highlights

- Neutrophil percentage-to-albumin ratio and procalcitonin can be used as prognostic biomarkers for mortality in critically ill children requiring continuous renal replacement therapy.
- These markers may support earlier risk stratification and inform clinical decision-making in the pediatric intensive care unit.
- C-reactive protein-to-albumin ratio was not associated with mortality.

Combined inflammatory indices, including the neutrophil percentage-to-albumin ratio (NPAR) and the CRP-to-albumin ratio (CAR), have recently emerged as stronger prognostic indicators , as they capture both the inflammatory response and the nutritional status. Albumin, a negative acute-phase reactant, decreases during systemic inflammation and serves as a marker of malnutrition; both low albumin and malnutrition are associated with poor outcomes in critical illness[4]. Previous studies have demonstrated that NPAR is closely associated with prognosis in severe sepsis and AKI[5]. However, no study to date has specifically evaluated the relationship between NPAR and outcomes in pediatric patients undergoing CRRT.

Given the high morbidity and mortality in this patient group, the potential utility of inflammation-based markers in prognostic assessment is of particular interest. Therefore, this study aims to investigate the prognostic significance of NPAR, CAR, and PCT in pediatric patients treated with CRRT, particularly their association with short-term outcomes and mortality. We hypothesized that NPAR, CAR, and PCT may be associated with adverse outcomes in this population.

Materials and Methods

This study was approved by the Bakırçay University Hospital Non-Interventional Clinical Research Ethics Committee (approval number: 1688, date: 10.07.2024) and conducted in accordance with the ethical principles of the Declaration of Helsinki. This retrospective analysis included all hospitalized patients who underwent CRRT in the PICU at Manisa City Hospital from February 2021 to May 2025. Demographic and clinical variables, including age, sex, laboratory results, Pediatric Risk of Mortality (PRISM) III[6] score at CRRT initiation, duration of mechanical ventilation, PICU length of stay, and indication for CRRT, were recorded. Laboratory values collected at CRRT initiation included neutrophil percentage, CRP, albumin, and PCT. Patients aged 29 days to 18 years who received CRRT during their PICU admission and had complete data available were included. CRRT indications included: AKI, fluid overload exceeding 10% of body weight, electrolyte imbalances, severe metabolic acidosis, and acute metabolic disorders. The total percent fluid overload (percent fluid overload) was calculated using the following formula: [(total fluid intake - total fluid output) (in liters) / admission body weight (kg)]×100. The vasopressor index score (VIS) was calculated as the dopamine dose (g/kg/min), dobutamine dose (g/kg/min), 100 times the epinephrine dose (g/kg/min), 10 times the milrinone dose (g/kg/min), 10,000 times the vasopressin dose (U/kg/min), and 100 times the norepinephrine dose (g/kg/min)[7].

Percutaneous insertion of double-lumen central venous catheters is often performed through the right internal jugular vein. While subclavian vein access was used in one patient due to thrombosis, femoral vein access was preferred in three patients. The PRISMAFLEX hemofiltration system was used for CRRT. Modifications were applied to the CRRT parameters, with blood flow rates ranging from 4 to 10 cc/kg/min. After reaching a clearance dose of 2000 mL/h/1.73 m^2, dialysate and replacement settings were adjusted[8]. Unfractionated heparin was used for anticoagulation.

Laboratory results included CRP (immunoluminometric assay; reference 0-8 mg/L), albumin (colorimetric assay; reference 3.4-5.4 g/dL), and PCT (ng/mL). Values obtained within the 24 hours before CRRT initiation were analyzed. NPAR was calculated by dividing neutrophil percentage (10^3/μL) by albumin (g/dL); CAR (mg/g) was calculated by dividing CRP (mg/L) by albumin (g/dL). The PRISM III probability of death (PRISM-3 death probability) was also recorded.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics version 20.0 (SPSS Inc., Chicago, IL, USA). Distributional characteristics were examined visually (histograms) and tested using the Kolmogorov-Smirnov test. Because several continuous variables deviated from normality, results are presented as the median [interquartile range (IQR)] for continuous variables and as number (percentage) for categorical variables. Comparisons

between two independent groups were performed using the Mann-Whitney U test, while comparisons across more than two groups were carried out with the Kruskal-Wallis test. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Receiver operating characteristic (ROC) curve analysis was used to assess the ability of NPAR, CAR, and PCT, measured at intensive care unit admission, to predict mortality. Discriminative performance was quantified by the area under the ROC curve (AUC) with 95% confidence intervals (CIs). Optimal cut-off points were identified using the Youden index. A two-sided p-value of <0.05 was considered statistically significant.

Results

A total of 41 pediatric patients underwent CRRT during the study period. Of these, 29 patients (70.7%) survived, while 12 (29.3%) died. The demographic and clinical characteristics of both groups are summarized in **Table 1**. There were no statistically significant differences between survivors and non-survivors in terms of age, sex, presence of underlying metabolic or genetic disorders, or PICU admission diagnosis. However, PRISM III scores were significantly higher among non-survivors (median 34, IQR: 15-56) than among survivors (median 25, IQR: 8-54; p=0.008). NPAR values were also significantly elevated in non-survivors (median 26, IQR: 22.3-32.6) compared to survivors (median 22, IQR: 17.6-26.4; p=0.03). Similarly, PCT levels were markedly higher in the non-survivor group (median 45.5 ng/mL, IQR: 10.5-100) than in survivors (median 8 ng/mL, IQR: 1-49; p=0.01). In contrast, CAR did not differ significantly between the groups (p=0.79). survivors had significantly longer durations of mechanical ventilation (p=0.01) and PICU stay (p=0.009) than non-survivors. However, no significant differences were observed between groups in the use of vasoactive agents or in VIS (**Table 1**).

ROC curve analysis demonstrated that PCT had the highest discriminatory ability for mortality, with an AUC of 0.737 (95% CI: 0.575-0.899), followed by NPAR with an AUC of 0.713 (95% CI: 0.536-0.889). CAR showed poor performance in predicting mortality, with an AUC of 0.474 (95% CI: 0.266-0.682) (**Figure 1**, **Table 2**).

Discussion

In this study, we evaluated the prognostic value of NPAR, PCT, and CAR for predicting mortality in pediatric patients undergoing CRRT. Our findings demonstrate a statistically significant association of elevated NPAR and PCT levels with increased mortality. In contrast, CAR was not associated with patient outcomes.

Consistent with this biological rationale, one of the most notable findings of our study was a significant association between the NPAR and mortality in critically ill pediatric patients undergoing CRRT. Inflammation plays a central role in the pathogenesis of AKI and in the progression of multiorgan dysfunction in critically ill children. Neutrophil activation represents one of the earliest events in systemic inflammatory responses and contributes to kidney injury through endothelial damage, increased

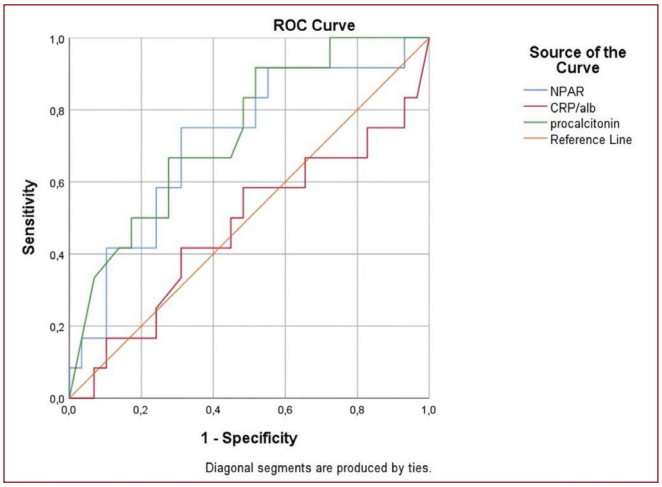

Figure 1. ROC analysis of biomarkers predicting mortality

Comparison of ROC curves of NPAR, CRP/alb ratio and Procalcitonin levels of mortality

ROC: Receiver operating characteristic, NPAR: Neutrophil percentage-to-albumin ratio, CRP: C-reactive protein

Table 1.
Demographic and clinical features of pediatric patients admitted to the PICU who either survived or did not survive

Patients (n=41)	Survivors (n=29)	Non-survivors (n=12)	p
Age (month), median (IQR)	27 (2-192)	10 (2-192)	0.14
Gender female, n (%)	11 (37.9)	6 (50)	0.50
PRISM III score, median (IQR)	25 (8-54)	34 (15-56)	0.008
Underlying metabolic / genetic disease, n (%)	11 (37.9)	4 (33.3)	0.53
PICU admission diagnosis sepsis/septic shock, n (%)	14 (48.3)	5 (41.7)	0.62
PICU admission diagnosis, pulmonary disease, n (%)	7 (24.1)	3 (25)	0.74
NPAR, median (IQR)	22 (17.6-26.4)	26 (22.3-32.6)	0.03
CRP-to-albumin ratio (CAR)	12.6 (2.9-34.5)	19.7 (1.6-31.3)	0.79
PCT, median (IQR)	8 (1-49)	45.5 (10.5-100)	0.01
Vasoactive use, n (%)	21 (72.4)	11 (91.7)	0.24
VIS score, median (IQR)	35 (20-90)	40 (30-90)	0.50
Duration of mechanical ventilation (days), median (IQR)	14 (4-32)	7 (3-26)	0.01
Duration of PICU stay (days), median (IQR)	15 (7-30)	7 (4-23)	0.009

PICU: Pediatric intensive care unit, PRISM III: Pediatric risk of mortality score III, IQR: Interquartile range, NPAR: Neutrophil percentage-to-albumin ratio, CRP: C-reactive protein, VIS: Vasopressor index score, PCT: Procalcitonin

Table 2.
Area under the curve (AUC) of receiver-operating characteristic curve (ROC) and respective confidence interval (CI) values of the biological markers and mortality predictors

Patients (n=41)	Survivors (n=29)	Non-survivors (n=12)	p	AUC	CI (95%)
NPAR, median (IQR)	22 (17.6-26.4)	26 (22.3-32.6)	0.034	0.713	0.536-0.889
CRP / albumin ratio, median (IQR)	12.6 (2.9-34.5)	19.7 (1.6-31.3)	0.796	0.474	0.266-0.682
PCR, median (IQR)	8 (1-49)	45.5 (10.5-100)	0.018	0.737	0.575-0.899

AUC: Area under the curve, ROC: Receiver operating characteristic, CI: Confidence interval, NPAR: Neutrophil percentage-to-albumin ratio, CRP: C-reactive protein, IQR: Interquartile range, PCR: Procalcitonin

vascular permeability, microvascular congestion, and the release of pro-inflammatory cytokines and reactive oxygen species. Activated neutrophils may also promote intrarenal microthrombus formation and tubular injury, thereby aggravating renal dysfunction and limiting recovery, particularly in patients requiring CRRT[9].

Serum albumin, conversely, is a well-established negative acute-phase reactant that reflects nutritional status, the severity of systemic inflammation, and hepatic synthetic function. Hypoalbuminemia is associated with reduced plasma oncotic pressure, intravascular volume depletion, impaired renal perfusion, and decreased glomerular filtration. Moreover, albumin possesses antioxidant and anti-inflammatory properties; thus, reduced albumin levels may further amplify inflammatory injury in critically ill patients[10,11]. Taken together, these complementary pathophysiological mechanisms provide a strong biological basis for the use of composite inflammatory indices such as NPAR, which integrates markers of both acute inflammation and systemic physiological reserve[5].

Previous studies in adult populations, including patients with diabetic kidney disease, have identified NPAR as a valuable biomarker for predicting all-cause and cardiovascular mortality[12,13]. Similarly, studies conducted in adult intensive care settings have demonstrated that elevated NPAR is a novel predictor of poor prognosis in patients with severe sepsis or septic shock, often outperforming neutrophil count or albumin level alone[5,14]. While neutrophil parameters primarily reflect acute inflammatory activity, albumin levels additionally capture nutritional status and hepatic function; therefore, NPAR may offer a more comprehensive reflection of overall disease burden. However, data regarding the prognostic utility of NPAR in pediatric populations remain limited. By demonstrating a significant association between NPAR and mortality in critically ill children, our study contributes preliminary pediatric evidence and supports the potential role of NPAR as a prognostic marker in pediatric intensive care.

PCT levels were also significantly higher in non-survivors, consistent with previous reports linking elevated PCT to poor prognosis in sepsis. In children receiving CRRT for AKI, PCT levels ≥3 ng/mL have been associated with worse outcomes than lower levels[15]. Although absolute PCT values alone may not consistently predict mortality, persistently elevated or markedly high levels are generally indicative of severe systemic illness, organ dysfunction, and an increased risk of death[16]. Importantly, timely and effective interventions may still improve outcomes in these patients, highlighting the role of PCT as both a diagnostic and prognostic biomarker.

In contrast, CAR did not show prognostic value in our cohort. This result differs from adult studies, in which the CRP / albumin ratio has been reported as a strong predictor of mortality, particularly in septic patients[17]. Pediatric studies, however, have produced more heterogeneous results. For example, in a large cohort of 942 critically ill children, the CRP / albumin ratio outperformed CRP alone but was less predictive than albumin; the AUC was 0.751[18]. Several factors may explain the discrepancy in our findings: age-related differences in immune response among children, our limited sample size reducing statistical power, and the single measurement of biomarkers within 24 hours of CRRT initiation, which may not capture dynamic changes over time. Collectively, these limitations suggest that CAR may be less reliable in pediatric populations and highlight the need for larger studies with serial biomarker assessments.

Higher PRISM III scores among non-survivors in our study support the reliability of established pediatric mortality prediction models. Differences in clinical outcomes between survivors and non-survivors, such as the duration of mechanical ventilation and the length of PICU stay, further underscore the multifactorial nature of prognosis in critically ill children. Although NPAR and PCT were significantly associated with mortality, these findings should be interpreted with caution. Given the small sample size and limited number of mortality events, multivariable regression analysis was not performed due to the high risk of model overfitting. As a result, it remains unclear whether these biomarkers provide prognostic information independent of established severity scores such as PRISM III. Therefore, our results should be considered exploratory and hypothesis-generating rather than confirmatory. In addition, albumin-based ratios may be influenced by fluid overload and hemodilution, which are common in patients undergoing CRRT. This may partially affect the performance of albumin-derived indices and further support the need for cautious interpretation.

Study Limitations

This study has several strengths, including the evaluation of multiple inflammatory markers within the same cohort. Nonetheless, limitations must be acknowledged. The relatively small sample size and single-center design restrict the generalizability of the findings. The retrospective nature of the study also introduces potential bias, such as incomplete data collection and unmeasured confounders. Moreover, while biomarker levels were obtained in the 24 hours

before CRRT initiation, these measurements may not coincide with peak inflammatory responses, limiting their predictive accuracy. The absence of multivariable analysis represents an important limitation of this study. Although PRISM III scores differed significantly between survivors and non-survivors, adjustment for illness severity was not performed due to sample size constraints. Larger prospective studies are required to determine whether inflammation-based biomarkers such as NPAR and PCT provide prognostic information beyond established severity scores. Finally, although NPAR and PCT showed significant associations with mortality, the relatively wide CIs in the ROC analysis call for cautious interpretation.

Overall, our results suggest that both NPAR and PCT may serve as clinically relevant prognostic indicators in pediatric patients undergoing CRRT. Further multicenter, prospective studies with larger cohorts are warranted to validate these findings and clarify the clinical utility of these biomarkers.

Conclusion

Our findings highlight the potential value of NPAR and PCT as prognostic biomarkers for mortality in critically ill children requiring CRRT. These markers may support earlier risk stratification and assist clinical decision-making in the PICU. In contrast, CAR did not demonstrate predictive utility in our cohort, underscoring the need for further research in pediatric populations. Larger, multicenter prospective studies are necessary to validate these observations and establish the role of these biomarkers in routine pediatric intensive care practice.

Ethics

Ethic Committee Approval: This study was approved by the Bakırçay University Hospital Non-Interventional Clinical Research Ethics Committee (approval number: 1688, date: 10.07.2024) and conducted in accordance with the ethical principles of the Declaration of Helsinki.

Informed Consent: Because the study was designed retrospectively no written informed consent form was obtained from the patients.

Footnotes

Author Contributions: Evren G: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing; Okur Acar S: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.

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

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Impact of a Structured Educational Intervention on Heimlich Maneuver Awareness Among Parents of Individuals with Autism Spectrum Disorder: A Survey Study

Author(s)

Abdullah Akkuş[1], Fatih Ercan[2], Nefise Betül Ercan[3], Mehtap Yücel[4], Hurşit Ferahkaya[5], Zeynep Naz Yılmaz[6], Çağla Nur Yılmaz[6], Elif Ceyda Yılmaz[6], Şeyda Yılmaz[6], Sümeyye Yılmaz[6], Gülşen İrem Zorlu[6], İkbal Bahar Yılmaz[6], Tuba Yurtseven[6], Muhammed Orkun Yılmaz[6], Mert Yılmaz[6], Kaan Kadir Damkacı[6], Mustafa Büyükavcı[7]

Affiliation(s)

[1]Necmettin Erbakan University Faculty of Medicine, Department of Pediatrics, Konya, Türkiye

[2]Necmettin Erbakan University Faculty of Medicine, Department of Pediatric Pulmonology, Konya, Türkiye

[3]Konya Provincial Directorate of Health Department of Family Medicine, Konya, Türkiye

[4]Necmettin Erbakan University Faculty of Medicine, Department of Public Health, Konya, Türkiye

[5]Necmettin Erbakan University Faculty of Medicine, Department of Child and Adolescent Psychiatry, Konya, Türkiye

[6]Necmettin Erbakan University Faculty of Medicine, Student in Faculty of Medicine, Konya, Türkiye

[7]Necmettin Erbakan University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Hematology and Oncology, Konya, Türkiye

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Abstract

The objective of this study was to evaluate baseline knowledge and awareness of the Heimlich maneuver among parents of individuals with autism spectrum disorder (ASD) and to assess the effectiveness of a structured educational intervention on airway obstruction recognition, prevention, and first aid practices. This survey-based pre-post interventional study included 66 parents of individuals with ASD. A 19-item questionnaire assessing knowledge of the causes and symptoms of airway obstruction, preventive measures, and Heimlich maneuver techniques for infants, children, and adults was administered before and after an educational session delivered by intern physicians under specialist supervision. At baseline, 87.9% of participants had never received training on the Heimlich maneuver, and only 31.8% correctly identified differences among infant, child, and adult techniques. After training, the

Correspondence: Abdullah Akkuş MD, Necmettin Erbakan University Faculty of Medicine, Department of Pediatrics, Konya, Türkiye
E-mail: abdullahakkus29@gmail.com **ORCID:** 0000-0002-0642-8759

correct identification rate increased to 95.5% (p<0.001). The proportion of participants anticipating difficulty in performing the maneuver decreased from 53.0% to 34.8%, while those reporting it as generally easy increased to 59.1% (p<0.001). Knowledge of the causes of airway obstruction, signs of partial and complete obstruction, appropriate first-aid responses, and preventive measures improved significantly across most items (p<0.05). Knowledge of the application of the infant Heimlich maneuver increased from 30.3% to 100% following training. Parents of individuals with ASD demonstrated limited baseline knowledge of the Heimlich maneuver. A brief, structured educational intervention significantly improved awareness, confidence, and knowledge related to airway obstruction management, highlighting the importance of targeted caregiver education in this high-risk population.

Keywords: Airway obstruction, autism spectrum disorder, child, Heimlich maneuver, parent

Introduction

Autism spectrum disorder (ASD) is a lifelong neurodevelopmental condition characterized by differences in communication, social interaction, and behavior. The global prevalence of ASD has increased markedly in recent decades, leading to growing attention to the specific health and safety needs of affected individuals and their families[1]. Children and adults with ASD may be at increased risk of accidental injuries and medical emergencies due to sensory sensitivities, behavioral challenges, impaired hazard awareness, and feeding-related difficulties[2,3].

Foreign body aspiration and acute airway obstruction remain among the leading causes of preventable morbidity and mortality in childhood worldwide[4]. Feeding selectivity, oral sensory processing differences, rapid eating, and atypical chewing patterns—frequently observed in individuals with ASD—may further elevate the risk of choking in this population[5]. In such emergencies, early recognition of airway obstruction and the prompt application of appropriate first aid measures are critical for survival.

The Heimlich maneuver is a well-established first aid technique recommended for the management of complete airway obstruction in conscious infants, children, and adults; however, its application varies according to age group and clinical scenario[6]. Despite its lifesaving potential, multiple studies have shown that caregivers and parents often have insufficient knowledge regarding the correct indications for and techniques of the Heimlich maneuver, particularly in distinguishing between partial and complete airway obstruction[7,8].

Parents of individuals with ASD frequently serve as the primary caregivers and are often the first responders in emergency situations occurring at home or in community settings. Nevertheless, there is a paucity of research specifically focusing on parents' awareness and practical knowledge of the application of the Heimlich maneuver for individuals with ASD, as well as on the effectiveness of structured educational interventions in this population[9]. Addressing this gap is essential, given the potentially increased choking risk and the critical role of caregivers in immediate emergency response.

Therefore, the present study aimed to evaluate the baseline knowledge and perceptions of parents of individuals with ASD regarding the Heimlich maneuver, assess changes in awareness following a structured educational intervention, and determine the effectiveness of training in improving knowledge of airway obstruction recognition, prevention, and appropriate first-aid practices.

Highlights

- Parents of individuals with autism spectrum disorderhad low baseline Heimlich awareness.
- Most parents lacked prior formal training and confidence.
- Structured education significantly improved Heimlich knowledge.
- Recognition of age-specific techniques improved markedly.
- Correct identification increased from 31.8% to 95.5%.

Materials and Methods

Study Design

This study was designed as a pre-post educational intervention and was conducted as part of a social responsibility project. The study aimed to evaluate changes in knowledge and awareness regarding the Heimlich maneuver among parents of children with ASD following a structured educational program.

Study Population, Sample Size, and Post-Hoc Power Analysis

The study population consisted of parents who attended an educational session organized by the SOBE Foundation (*Selçuklu Otizmli Bireyler Eğitim Vakfı*) in Konya, Türkiye, and who had children with ASD. Participation was voluntary, and all parents who attended the session and agreed to participate were included in the study. No exclusion criteria were applied; no participants were excluded from the analysis.

All parents who attended the educational session were invited to participate in the study. Of these, 66 consented and completed both pre- and post-training questionnaires, and no participants were lost to follow-up.

Given the paired categorical design, a post hoc power analysis was conducted using G*Power (version 3.1.9.7). The analysis was based on a representative dichotomous outcome variable (knowledge of differences in Heimlich maneuver application between infants, children, and adults), evaluated using the McNemar and McNemar-Bowker tests (for 2 and ≥3 variables, respectively; α=0.05). Using the observed discordant proportions (p01=0.64, p10=0.00) and a total sample size of 66 participants, the achieved statistical power was approximately 99%, indicating that the study was sufficiently powered to detect pre-post differences.

Ethical Considerations

Ethical approval was obtained from the Ethics Committee for Non-pharmaceutical and Non-medical Device Research (approval no: 2025/5699, date: 25.04.2025).

In addition, institutional permission to conduct the study and educational activities was obtained from the SOBE Foundation prior to data collection.

Participation was entirely voluntary. All participants were informed about the study procedures and provided verbal informed consent. Confidentiality and anonymity were ensured by not collecting personal identifiers.

Educational Intervention

The educational intervention consisted of a 45-minute structured theoretical training session, followed by hands-on practical training. The theoretical component covered airway obstruction, indications for the Heimlich maneuver, age-specific differences in application, and common incorrect practices.

Following the theoretical session, participants practiced the Heimlich maneuver on infant, pediatric, and adult mannequins. Intern physicians performed demonstrations under the supervision of specialist physicians, and each participant was encouraged to perform the maneuver to reinforce learning.

Data Collection Tool

The data collection form was developed following a comprehensive literature review and consisted of 19 structured questions. The questionnaire assessed practical knowledge related to the recognition of airway obstruction and the correct application of the Heimlich maneuver in infants, children, and adults. All variables were categorical.

Pre-Post Matching Procedure

To enable accurate matching of pre-training and post-training responses while preserving anonymity, participants were asked to generate an identification code (pseudonym) on the pre-training questionnaire and write the same code on the post-training questionnaire. No personal identifying information was collected.

Statistical Analysis

Data entry and statistical analyses were performed using the SPSS for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA) software package. Frequency distributions and percentages were used to summarize categorical data. The McNemar test was used for paired dichotomous variables (yes/no, true/false). For nominal variables with three or more response categories (e.g., difficult/easy/unsure), the McNemar-Bowker symmetry test was applied. The correct response rate was calculated separately for each information item, and the pre- and post-training changes were compared using these tests. The significance level was set at $p<0.05$. Results were statistically significant ($p<0.05$).

Patient and Public Involvement: Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Reporting Guideline: STROBE checklist[10].

Results

Analysis of the participants' descriptive characteristics revealed that the largest proportion belonged to the 46-55 age group (45.5%) and that the majority of respondents were housewives (71.2%). 87.9% of the participants had not previously received any training on the Heimlich maneuver. When sources of information regarding the maneuver were examined, the most frequently reported response was "no source/unknown" (51.5%), followed by the internet (25.8%) and educational seminars (24.2%) (**Table 1**).

Evaluation of perceived difficulty in performing the Heimlich maneuver showed that, prior to training, 53.0% of participants anticipated difficulty, whereas this proportion decreased to 34.8% after the educational intervention ($p<0.001$). The proportion of respondents who stated that the maneuver was "generally easy" increased significantly following training, to 59.1%. With regard to knowledge of differences in the application of the Heimlich maneuver to infants, children, and adults, the rate of correct responses increased from 31.8% before training to 95.5% after training, and this improvement was statistically significant ($p<0.001$) (**Table 2**).

Knowledge related to the causes of airway obstruction showed a statistically significant increase across all items following the educational intervention. Post-training, the proportion of participants who correctly identified foreign bodies such as coins, buttons, marbles, pen caps, and nuts as potential causes of airway obstruction increased significantly (all $p<0.05$).

When signs of partial airway obstruction were assessed, correct response rates for the ability to cough, breathe, and speak increased significantly after training (all $p<0.001$), whereas recognition of wheezing sounds did not change significantly ($p=0.169$).

Regarding appropriate actions for partial airway obstruction, the proportion of correct responses to the

Table 1.
Descriptive information and resources of information regarding the Heimlich maneuver of the participants (n=66)

Variable	n (%)
Age group (years)	
18-25	3 (4.5)
26-35	23 (34.8)
36-45	-
46-55	30 (45.5)
Over 56	10 (15.2)
Occupation	
Housewife	47 (71.2)
Government official	7 (10.6)
Private sector	12 (18.2)
Previous training for Heimlich maneuver	
Yes	8 (12.1)
No	58 (87.9)
Resources of information regarding Heimlich maneuver*	
No source / unknown	34 (51.5)
Internet	17 (25.8)
Educational seminars	16 (24.2)
Healthcare professionals	9 (13.6)
Educational books	5 (7.6)

*: Some participants chose more than one

Table 2.
Comparison of general knowledge and application perceptions regarding the Heimlich maneuver before and after training (n=66)

Variables	Before training n (%)	After training n (%)	p*
Perceived difficulty in performing Heimlich maneuver			
Yes, may be difficult sometimes	35 (53.0)	23 (34.8)	**<0.001**
No, generally easy	5 (7.6)	39 (59.1)	
Unsure	26 (39.4)	4 (6.1)	
Knowledge of differences between infants, children and adults			
No	45 (68.2)	3 (4.5)	**<0.001**
Yes	21 (31.8)	63 (95.5)	

*: McNemar-Bowker test

item "encouraging coughing" increased markedly after training (p<0.001). The incorrect response "giving water" did not change after training (p=0.999), whereas the response for "back blows" changed significantly (p=0.002).

With respect to signs of complete airway obstruction, correct recognition of signs such as clutching the throat, cyanosis, and loss of consciousness increased significantly after training (all p<0.001). No statistically significant difference was found for the item "inability to speak" (p=0.143).

Evaluation of appropriate interventions for complete airway obstruction demonstrated significant post-training improvements in correct responses related to ensuring scene safety and to providing first aid until emergency teams arrived (both p<0.001). No significant changes were observed for the items "calling emergency services" and the incorrect option "giving water" (**Table 3**).

A statistically significant improvement in knowledge regarding the Heimlich maneuver in infants was observed following the educational intervention. Prior to training, only 30.3% of participants reported knowing how to perform the maneuver on infants, whereas this rate increased to 100% after training. Correct response rates for all infant-specific technique components—including tapping the soles of the feet, positioning the infant prone, tilting the head forward, delivering back blows, and applying chest compressions—showed significant post-training increases (all p<0.001). When the application of the Heimlich maneuver in children and adults was evaluated, knowledge levels increased significantly across all assessed items following training. Correct responses relating to checking consciousness, standing behind and encircling the torso, placing the fist appropriately, and applying five abdominal compressions increased markedly following the intervention (all p<0.001). In addition, the proportion of correct responses regarding situations in which the maneuver could be self-administered increased significantly after training (p<0.001) (**Table 4**).

When preventive measures for airway obstruction were evaluated, knowledge levels regarding eating in small bites, avoiding talking while food is in the mouth, burping infants after feeding, and not offering nuts before the age of five increased significantly after the educational

Table 3.
A comparison of pre- and post-training approaches to the causes, symptoms, and partial/complete airway obstruction (n=66)

Variables	Before training n (%)	After training n (%)	p*
Most common cause of airway obstruction	21 (31.8%)	63 (95.5%)	**<0.001**
Coins	37 (56.1)	61 (92.4)	**<0.001**
Buttons	35 (53.0)	60 (90.9)	**<0.001**
Candy	47 (71.2)	60 (90.9)	**0.011**
Chewing gum	32 (48.5)	51 (77.3)	**0.001**
Marbles	31 (47.0)	57 (86.4)	**<0.001**
Pen caps	22 (33.3)	52 (78.8)	**<0.001**
Nuts	48 (72.7)	63 (95.5)	**0.001**
Toy parts	50 (75.8)	61 (92.4)	**0.013**
Symptoms of partial airway obstruction			
Ability to cough	44 (66.7)	64 (97.0)	**<0.001**
Ability to breath	20 (30.3)	53 (80.3)	**<0.001**
Ability to talk	11 (16.7)	44 (66.7)	**<0.001**
Grunting	45 (68.2)	53 (80.3)	0.169
What to do in partial obstructions			
Encouraging coughing	31 (47.0)	58 (87.9)	**<0.001**
Giving water	2 (3.0)	1 (1.5)	0.999
Delivering back blows	45 (68.2)	27 (40.9)	**0.002**
Symptoms of complete airway obstruction			
Clutching the throat	43 (65.2)	62 (93.9)	**<0.001**
Cyanosis of the lips	40 (60.6)	63 (95.5)	**<0.001**
Inability to talk	53 (80.3)	60 (90.9)	0.143
Loss of consciousness	30 (45.5)	59 (89.4)	**<0.001**
What to do in complete obstructions			
Calling emergency services	60 (90.9)	65 (98.5)	0.125
Ensuring scene safety	27 (40.9)	54 (81.8)	**<0.001**
First aid until arrival of medical teams	33 (50.0)	59 (89.4)	**<0.001**
Giving water	2 (3.0)	2 (3.0)	0.999
Delivering back blows	30 (45.5)	35 (53.0)	0.511
Encouraging coughing	19 (28.8)	32 (48.5)	**0.019**

*: McNemar-Bowker test

intervention (p<0.05). Although awareness of keeping small objects and toys out of children's reach, this change did not reach statistical significance (p=0.180) (**Table 5**).

Discussion

This study demonstrated that parents of individuals with ASD had limited baseline knowledge and awareness regarding the Heimlich maneuver and the management of airway obstruction; however, a short, structured

Table 4.
Comparison of correct knowledge and application techniques regarding the Heimlich maneuver in infants and children/adults before and after training (n=66)

Variables	Before training	After training	p*
	n (%)	n (%)	
Having knowledge about Heimlich maneuver in infants	53 (80.3)	66 (100.0)	-
Knowing how to perform Heimlich maneuver in infants	20 (30.3)	66 (100.0)	-
What to pay attention while performing Heimlich maneuver in infants			
Tapping the soles of the feet	4 (6.1)	65 (98.5)	**<0.001**
Positioning the infant prone	22 (33.3)	62 (93.9)	**<0.001**
Tilting the head forward	33 (52.4)	59 (93.7)	**<0.001**
Delivering back blows	34 (54.0)	59 (93.7)	**<0.001**
Chest compressions	25 (39.7)	56 (88.9)	**<0.001**
Having knowledge about Heimlich maneuver in children	59 (89.4)	66 (100.0)	-
Knowing how to perform Heimlich maneuver in children	21 (31.8)	66 (100.0)	-
What to pay attention while performing Heimlich maneuver in children			
Checking consciousness	29 (43.9)	63 (95.5)	**<0.001**
Standing behind and encircling the torso	34 (51.5)	62 (93.9)	**<0.001**
Appropriate fist placement	37 (56.1)	64 (97.0)	**<0.001**
Applying five chest compressions	42 (63.6)	61 (92.4)	**<0.001**
Compressing the upper part of the abdomen to solid objects for effective thrusts when alone	26 (39.4)	58 (87.9)	**<0.001**

*: McNemar-Bowker test; p-values were not calculated for variables with 100% post-training responses due to complete separation

Table 5.
Comparison of pre- and post-training knowledge of preventing airway obstruction with Heimlich maneuver in children and adults (n=66)

What are the preventing measures for airway obstruction?	Before training	After training	p*
	n (%)	n (%)	
Eating small bites	49 (74.2)	66 (100.0)	-
Avoiding talking while food is in the mouth	54 (81.8)	63 (95.5)	**0.022**
Keeping small objects and toys out of children's reach	58 (87.9)	63 (95.5)	0.180
Burping infants after feeding	43 (65.2)	60 (90.9)	**<0.001**
Not offering nuts before the age of 5 years	19 (28.8)	60 (90.9)	**<0.001**

*: McNemar-Bowker test; p-values were not calculated for variables with 100% post-training responses due to complete separation

educational intervention resulted in substantial and statistically significant improvements across nearly all assessed domains. Prior to training, 87.9% of participants reported that they had never received Heimlich maneuver education, and more than half indicated either that they had no information source or that they were unaware of how to access reliable information. These findings are consistent with previous studies reporting insufficient first aid training among caregivers, despite their critical role as first responders in household emergencies[7,8,11].

A key finding of the present study was a significant reduction in perceived difficulty in performing the Heimlich maneuver. Before training, almost half of the participants believed that the maneuver would be difficult to perform; this proportion decreased significantly after training, accompanied by a marked increase in participants who considered the maneuver generally easy. Similar improvements in caregiver confidence following targeted first aid education have been reported, suggesting that perceived barriers can be effectively addressed through structured training delivered by healthcare professionals[11,12].

Knowledge of age-specific differences in the application of the Heimlich maneuver exhibited one of the most pronounced improvements. Only 31.8% of parents correctly identified differences between infant, child, and adult techniques prior to training; this proportion increased dramatically after training ($p<0.001$). This finding is particularly important, as inappropriate technique selection may lead to ineffective intervention or injury. Previous literature emphasizes that age-adapted instruction and visual demonstration are critical components of effective first aid education[6,12], supporting the educational approach used in this study.

Awareness of the causes and symptoms of airway obstruction also improved significantly following the intervention. Post-training, the correct identification of common choking hazards such as coins, buttons, pen caps, nuts, and toy parts increased to over 90% for most items. Recognition of partial airway obstruction signs—such as coughing, breathing, or speaking—also improved markedly (all $p<0.001$), although recognition of wheezing sounds did not change significantly. This aligns with previous studies indicating that certain clinical signs are more difficult for lay caregivers to interpret accurately[13].

Importantly, the training significantly enhanced correct responses regarding appropriate interventions during partial and complete airway obstruction. The proportion of parents correctly identifying that coughing should be encouraged during partial obstruction significantly increased ($p<0.001$), while incorrect practices, such as back blows during partial obstruction, decreased significantly. However, misconceptions such as offering water during choking episodes persisted in a small subset of participants, consistent with prior reports suggesting that deeply rooted first-aid myths may require repeated reinforcement to be fully corrected[13].

Knowledge of the infant-specific Heimlich maneuver showed the most striking improvement. While only 30.3% of participants reported knowing how to perform the maneuver on infants before training, all participants reported correct knowledge post-training, with significant improvements across all technical components (all $p<0.001$). Similar improvements were observed in Heimlich maneuver techniques for children and adults, including correct body positioning, fist placement, and application of abdominal thrusts. These findings underscore the effectiveness of focused, scenario-based training in improving both conceptual understanding and procedural knowledge[12].

Preventive knowledge related to choking risk also improved significantly. Awareness of safe feeding practices, avoidance of talking while eating, use of appropriate burping techniques for infants, and delay of nut consumption until after five years of age increased significantly after training ($p<0.05$). Given that feeding difficulties and atypical eating behaviors are common in individuals with ASD[5,14], strengthening preventive knowledge among caregivers is particularly relevant and may contribute to reducing choking incidence in this vulnerable population.

Individuals with ASD often exhibit sensory processing differences, feeding selectivity, rapid eating, and behavioral rigidity, which may increase the risk of choking and complicate emergency responses. During distressing situations, heightened anxiety, resistance to physical contact, and difficulty following verbal instructions may further challenge the effective delivery of first aid. These ASD-specific factors underscore the importance of caregiver-focused, hands-on training approaches tailored to the unique needs of this population[9].

Study Limitations

This study has several limitations. The sample size was relatively small and derived from a single center, which may limit generalizability. Additionally, the assessment focused on knowledge and self-reported perceptions rather than direct observation of practical skills. Long-term retention of knowledge and real-life application of the Heimlich maneuver were not evaluated. Moreover, participants were not systematically queried regarding prior real-life choking events or performance of the Heimlich maneuver. Such experiences could have influenced baseline knowledge and responsiveness to training, and therefore represent an additional limitation. This study employed a single-group pre-post design without a control group, which limits causal interpretation of observed improvements and may introduce measurement or observer bias. Future multicenter studies with larger samples, practical skill assessments, and long-term follow-up are warranted.

Conclusions

Parents of individuals with ASD demonstrated low baseline awareness of the Heimlich maneuver and the management of airway obstruction. This structured educational model could be readily integrated into routine caregiver education programs for families of individuals with ASD, as well as into school-based health and safety curricula. Incorporating such training into existing rehabilitation and special education services may enhance emergency preparedness and reduce caregiver anxiety.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee for Non-pharmaceutical and Non-medical Device Research (approval no: 2025/5699, date: 25.04.2025).

Informed Consent: All participants were informed about the study procedures and provided verbal informed consent.

Footnotes

Author Contributions: Akkuş A: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing; Ercan F: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing; Ercan NB: Data Collection or Processing, Analysis or Interpretation; Yücel M: Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing; Ferahkaya H: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search; Yılmaz ZN: Data Collection or Processing, Analysis or Interpretation; Yılmaz ÇN: Data Collection or Processing, Analysis or Interpretation; Yılmaz EC: Data Collection or Processing, Analysis or Interpretation; Yılmaz Ş: Data Collection or Processing, Analysis or Interpretation; Yılmaz S: Data Collection or Processing, Analysis or Interpretation; Zorlu Gİ: Data Collection or Processing, Analysis or Interpretation; Yılmaz İB: Data Collection or Processing, Analysis or Interpretation; Yurtseven T: Data Collection or Processing, Analysis or Interpretation; Yılmaz MO: Data Collection or Processing, Analysis or Interpretation; Yılmaz M: Data Collection or Processing, Analysis or Interpretation; Damkacı KK: Literature Search.

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Case Report

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Macrophage Activation Syndrome and Lung Disease Presenting at Onset in a Child with Systemic Juvenile Idiopathic Arthritis

Author(s)

Chandra Prabha, Nishant Verma, Sakshi Singh, Ajitesh Singh

Affiliation(s)

King George's Medical University, Department of Pediatrics, Lucknow, India

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Abstract

Macrophage activation syndrome (MAS), a form of secondary hemophagocytic lymphohistiocytosis, is commonly encountered in pediatric rheumatologic emergencies. Recognition of MAS in a child with systemic juvenile idiopathic arthritis (sJIA) is challenging because the prominent inflammatory expression of sJIA obscures its subclinical forms. Lung disease detected in these children is characterized by a distinct immunological and clinical feature. We describe a boy aged 13 years presenting with fever for 3 months followed by polyarthralgia, maculopapular rash, non-productive cough, and constitutional symptoms including anorexia, weight loss, and generalized paleness of the body. On examination, the child had pallor, grade-1 clubbing, pedal edema, hepatomegaly, and fine crepitations in the right lower lung field. The child fulfilled Pediatric Rheumatology International Trials Organisation criteria for MAS in sJIA and was managed by pulse methylprednisolone, immunoglobulin, and cyclosporine, which showed a significant response. The child was successfully treated and discharged home. MAS in the clinical setting of sJIA is life-threatening; prompt initiation of immunosuppressive therapy can be life-saving.

Keywords: Hemophagocytic lymphohistiocytosis, immunosuppressive therapy, rheumatic diseases

Introduction

Macrophage activation syndrome (MAS) is a secondary form of hemophagocytic lymphohistiocytosis (sHLH) and represents a frequent pediatric rheumatic crisis[1]. MAS can cause severe, life-threatening presentations in about 10% of children with systemic juvenile idiopathic arthritis (sJIA), and up to 30% may have subclinical MAS.

This case highlights the significance of extremely high ferritin levels as a predictor of MAS in sJIA and presents associated findings suggesting a newly recognized entity designated sJIA- lung disease (LD), an inflammatory LD. The emphasis on early initiation of immunosuppressive therapies to mitigate the underlying cytokine storm cannot be overstated.

Case Report

A thirteen-year-old male, who was underweight, was admitted with chief concern of prolonged high-grade intermittent fever for 3 months followed by polyarthralgia along with restriction of range of motion (ROM) across the temporomandibular joint, bilateral hip joint and cervical spine, accompanied by an erythematous maculopapular

Correspondence: Chandra Prabha, King George's Medical University, Department of Pediatrics, Lucknow, India
E-mail: Dr.chandraprabha9@gmail.com **ORCID:** orcid.org/0000-0001-8364-2372

rash over the trunk with non-productive cough for 2 weeks with associated constitutional symptoms of anorexia, weight loss, generalized paleness and weakness of the body.

Prior to this hospital admission, he was treated as an outpatient by multiple practitioners for similar complaints. Upon persistence and worsening of symptoms, the patient required 4 hospital admissions during which he was transfused 3 units of packed red blood cells (PRBC).

Highlights

- We report a case of systemic juvenile idiopathic arthritis (sJIA) complicated by macrophage activation syndrome (MAS) and lung disease, highlighting the importance of timely recognition and prompt initiation of immunosuppressive treatment, which can be life-saving.
- A high index of suspicion for MAS in any child with fever and an underlying or suspected rheumatologic disease facilitates timely recognition.
- In resource-limited settings, cyclosporine plays a well-defined role in the management of MAS and in controlling systemic features in children with sJIA.

General physical examination revealed pallor, grade 1 clubbing, and bilateral pitting edema of the feet, with no icterus, cyanosis, or lymphadenopathy. Erythematous, non-pruritic maculo-papular rash over the trunk was present. Tenderness and restriction of ROM were present during active and passive movements of the bilateral hip joints, temporomandibular joints, and cervical spine. The abdomen was soft, non-distended, and non-tender. His liver was enlarged and palpable 5 cm below the right costal margin, with a liver span of 16 cm and a firm consistency. The spleen was not palpable. There was no shifting dullness or fluid thrill. Respiratory system examination revealed clear breath sounds with fine crepitations in the right lower lung. Examination of the cardiovascular and central nervous systems was unremarkable. The child was admitted and started on broad-spectrum antibiotics. Anti-tubercular treatment (ATT), initiated elsewhere, was continued.

On the basis of the clinical presentation and the exclusion of infectious etiologies, inflammatory disorders, malignancy, and other rheumatologic conditions, a provisional diagnosis of sJIA was made. Later in the course of the illness, the patient developed icterus in the clinical setting of prolonged, high-spiking fever with markedly elevated inflammatory markers, deranged liver enzymes, coagulopathy, and a clinical picture consistent with cytokine storm, leading to suspicion of secondary HLH in the setting of sJIA.

Complete blood count demonstrated persistent anemia, leucocytosis with total leukocyte count of 14.3×10^{9}/L, and thrombocytosis with a maximum documented count of 4.25×10^{12}/L.

Liver function tests were initially within normal limits, but during the hospital stay liver enzymes became elevated, with total serum bilirubin of 1.11 mg/dL, direct bilirubin of 0.52 mg/dL, serum glutamic oxaloacetic transaminase of 1166.8 U/L, serum glutamic pyruvic transaminase of 1219 U/L, and alkaline phosphatase of 333.8 U/L. The coagulation profile was abnormal, with a prolonged prothrombin time (31.7 s) and an elevated international normalized ratio (2.41) (**Table 1**).

In the setting of suspected sJIA, inflammatory markers were elevated, including C-reactive protein (243.2 mg/L), hyper-ferritinemia (449438.20 pmol/L), hypertriglyceridemia (2.5 mmol/L), hypofibrinogenemia (3.3 g/L), leukopenia, and elevated aspartate aminotransferase (AST) (1166.8 U/L); these findings fulfilled the Paediatric Rheumatology International Trials Organisation (PRINTO) criteria for MAS in sJIA (**Table 2**). Immunologically, the patient was negative for rheumatoid factor. In addition, indirect and direct Coombs tests were negative. Bone marrow aspiration revealed reactive granulocytic hyperplasia. Procalcitonin was markedly elevated (39,220 ng/L), and serum galactomannan was negative. Cardiac markers revealed raised Pro B-type natriuretic peptide (142.95 pmol/L), electrocardiography showed sinus tachycardia, and two-dimensional echocardiography suggested mild left ventricular systolic dysfunction with a left ventricular ejection fraction of 52%, moderate pulmonary artery hypertension, and moderate tricuspid regurgitation with mild global hypokinesia.

The chest X-ray showed opacities in both lung fields, with cephalization of the pulmonary vasculature (**Figure 1**). High-resolution computed tomography of the thorax showed ill-defined patches of ground-glass attenuation in both lungs, more marked peripherally, with right-sided fissural thickening, suggestive of LD in sJIA.

Given the absence of clinical improvement and negative labs, ATT was discontinued after one week of hospitalization. Once a working diagnosis of sJIA disease was made, the patient was started on oral prednisolone 60 mg once daily. Fever persisted and his inflammatory markers continued to rise. After establishing a diagnosis of MAS, the patient was started on pulse intravenous methylprednisolone at 30 mg/kg/day for 5 days, along with oral cyclosporine at 4 mg/kg/day. Intravenous immunoglobulin (IVIG) was also administered at a dose of 2 g/kg. During illness, the child required 4 units of PRBC transfusion.

Fever spike frequency decreased one day after initiation of pulse methylprednisolone and cyclosporine. Cytopenia and transaminitis improved, and inflammatory markers were eventually reduced. The child remained well and was discharged with oral prednisolone 60 mg daily (2 mg/kg/day) and oral cyclosporine 100 mg (4 mg/kg/day).

The patient was followed as an outpatient and had inactive disease while on prednisolone and cyclosporine. Prednisolone was tapered and discontinued over 8 weeks, and cyclosporine was continued for 6 months. Eventually, lab parameters showed normal levels of hemoglobin, white blood cell count, ferritin, triglycerides, and fibrinogen.

Informed consent was obtained from the parents of the patients.

Figure 1. Chest radiograph showing bilateral lung infiltrates

Discussion

MAS is a rare and potentially complication of pediatric chronic rheumatic disorders, particularly sJIA. MAS can produce severe, rapidly progressive symptoms in about 10% of children with sJIA, whereas as many as 30% may have subclinical MAS[2]. The syndrome, with an estimated prevalence of 10% among sJIA patients, may also present subclinically in an additional 30-40%[3]. Early histopathology may not reveal hemophagocytosis[4].Lung involvement is increasingly identified in children with sJIA, particularly in those with MAS[5]. Children with sJIA and severe ongoing LD are at higher risk of death. This newly recognized LD may affect more than 5% of sJIA patients[6].

During the early phase of the disease, MAS is difficult to diagnose and at times may mimic a flare of the primary illness[5].Using PRINTO criteria, a febrile child with confirmed or suspected sJIA is classified as MAS when ferritin exceeds 684 ng/mL and at least two of the following laboratory values are abnormal: platelets ≤181×10^9/L, AST>48 U/L, triglycerides >156 mg/dL, and fibrinogen ≤360 mg/dL. These abnormalities should not be better explained by the patient's other conditions, such as concomitant immune thrombocytopenia, hepatitis, leishmaniasis, or familial hyperlipidemia[5]. Hyperferritinemia has the highest sensitivity and specificity in diagnosing MAS, followed by elevated lactate dehydrogenase, hypertriglyceridemia, and hypofibrinogenemia[7]. Our patient presented with daily non-remitting fever, bicytopenia, reduced fibrinogen levels, and markedly elevated ferritin, which prompted us to consider a diagnosis other than an sJIA flare.

Table 1.
Routine blood investigation

Parameter	At admission	Day-7	Day-15	Day 18	Day-20
Hemoglobin	7 g/dL	6.2 g/dL	3 .9 g/dL	5.6 g/dL	8.1 g/dL
Total leucocyte count	6.8×10^9/L	6.1×10^9/L	0.8×10^9/L	3.7×10^9/L	14.3×10^9/L
Neutrophils Lymphocytes Eosinophils Monocytes Basophils	76% 22% 01% 02% 0%	76% 20% 02% 01% 0%	37% 58% 01% 02% 0%	55% 42% 01% 02% 0%	80% 17% 01% 01% 0%
Platelet count	4.25x10^{12}/L	2.64x10^{12}/L	1.80x10^{12}/L	2.23x10^{12}/L	2.63x10^{12}/L
Red blood cell count	3.2 M/µL	3.1 M/µL	2.4 M/µL	2.8 M/µL	3.4 M/µL
Mean cell volume MCH MCHC RDW Hematocrit	76 fL 28.5 pg 33.6 g/dL 25.8% 19.5%	85.5 fL 30.2 pg 36.3 g/dL 25.6% 18.1 %	73 fL 28.6 pg 40 g/dL 25.2% 9.7%	75 fL 28.5 pg 38 g/dL 25.9 % 14.8 %	76.5 fL 30.8 pg 40.2 g/dL 25.1% 20.2 %
Total bilirubin Direct bilirubin SGOT SGPT Alkaline phosphatase	0.8 mg/dL 0.4 mg/dL 31 IU/L 18.6 IU/L 350 IU/L		0.60 mg/dL 0.36mg/dL 41.5 IU/L 29.8 IU/L 376.8 IU/L	1.11mg/dL 0.52mg/dL 119 IU/L 452.4 IU/L 333.8	0.81mg/dL 0.52mg/dL 68.8IU/L 20.1IU/L 243.2
Albumin Protein	2.77 gm/dL 4.76 gm/dL				
Sodium Potassium Calcium	134.2 mEq/L 3.88 mEq/L 4.28 mEq/L		130.6 mEq/L 4.08 mEq/L 4.56 mEq/L	130.7 mEq/L 5.24 mEq/L 5.12 mEq/L	
Prothrombin time International normalised ratio		27.9 s 2.11	31.7 s 2.41	13.3 s 0.98	

MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, RDW: Red cell distribution width, SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase

Table 2.
Special investigations

Parameter	At admission	Day-7	Day- 15	Day-18	Day-20
C-reactive protein	243.2 mg/L	59.22 mg/L	18.46 mg/L	141.3 mg/L	
Ferretin	51424.84 pmol/L	217646.66 pmol/L	449438.20 pmol/L	224700 pmol/L	88277.26 pmol/L
Procalcitonin	4.16 µg/L	39.22 µg/L			
Fibrinogen	330 mg/dL				
Triglyceride	221 mg/dL				
Rheumatoid factor	1.1 IU/mL				
Serum creatinine kinase MB	8 IU/L				
Galactomannan	0.516 (negative)				
Direct Coombs test	Negative				
Pro BNP	142.95 pmol/L				
Electrocardiogram	Sinus tachycardia				
Echocardiogram	Mild left ventricular systolic dysfunction with a left ventricular ejection fraction of 52%, moderate pulmonary artery hypertension, moderate tricuspid regurgitation with mild global hypokinesia				
Bone marrow examination	Reactive granulocytic hyperplasia				
Blood culture Urine culture	Sterile Sterile				
Gastric aspirate for Acid Fast Bacilli and CBNAAT	Negative				
RT-PCR COVID19	Negative				
Fundus examination Slit lamp examination	Chronic resolving superficial hemorrhage (left eye) over macula No evidence of uveitis				
HIV ELISA, HBsAg, HCV ELISA Anti hepatitis A virus IgM antibody Anti hepatitis E IgM antibody	Non-reactive Negative Negative				
Anti-CMV IgM antibody Ebstein bar virus PCR Parvo B-19 DNA RT-PCR for CMV	Negative Not detected Detected Not detected				

HIV: Human immunodeficiency virus, HBsAg: Hepatitis B surface antigen, HCV: Hepatitis C virus, ELISA: Enzyme-linked immunosorbent assay, CMV: Cytomegalovirus, PCR: Polymerase chain reaction, MB: Myocardial band, BNP: B-type natriuretic peptide, CBNAAT: Cartridge-based nucleic acid amplification test, IgM: Immunoglobulin M, DNA: Deoxyribonucleic acid, RT-PCR: Reverse transcription polymerase chain reaction, S: Serum

The most widely used first-line therapy in MAS is intravenous pulse methylprednisolone for 3 to 5 days, followed by oral prednisolone[8].Oral steroids are initiated at a dose of 2 mg/kg/day and are gradually tapered while clinical and laboratory parameters are monitored.

The addition of cyclosporine to corticosteroids results in rapid control of the underlying cytokine storm, thereby limiting excessive corticosteroid use. Given the lack of consensus regarding duration, cyclosporine is administered for varying lengths of time in MAS, typically ranging from 3 months to 2 years[9].Cyclosporine may be considered a less costly alternative to biological agents in resource-limited settings, particularly when systemic features predominate[10]. Biological agents such as anti-IL (interleukin)-1 therapies (anakinra) are typically contemplated early when there is no improvement after IVIG, with dosing starting at 2 mg/kg/day and increasing to 8 mg/kg/day for refractory situations[1]. Rituximab, a cluster of differentiation 20 monoclonal antibody, may be used to treat MAS brought on by Epstein-Barr virus. Under these circumstances, a dose of 375 mg/m^2 administered once weekly for four weeks resulted in positive outcomes[11]. Etoposide is used to treat severe MAS-HLH refractory to conventional anti-inflammatory medications[12].

In patients who fail conventional therapy, such as high-dose glucocorticoids with or without anti-IL-1 and/or cyclosporine, emapalumab, a fully human immunoglobulin G1 anti-interferon-gamma monoclonal antibody, has demonstrated effectiveness[13].

Our child demonstrated ground-glass opacities and fissural thickening in the right lung, together with grade-1 clubbing, all of which were consistent with the entity sJIA-LD described by Schulert et al[14]. in a retrospective study of eighteen patients with sJIA. sJIA-LD is a new autoinflammatory disease seen in patients with disease onset before 2 years of age, in patients with recurrent MAS, and in patients treated with IL-1 and IL-6-blocking biologic agents[14].

Conclusion

MAS is a near-fatal complication, and very high ferritin levels are predictive of it in the setting of sJIA. This case also emphasizes that timely initiation of immunosuppressive treatment can be lifesaving. sJIA-LD is a newly recognized entity increasingly detected in children with sJIA, particularly in association with MAS. We concluded that high suspicion, early detection, and prompt treatment of MAS improve patient outcomes.

Ethics

Informed Consent: Informed consent was obtained from the parents of the patients.

Footnotes

Author Contributions: Prabha C: Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.; Verma N: Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.; Singh S: Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.; Singh A: Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.

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Incidental Detection of Wyburn-Mason Syndrome Mimicking Extranodal Involvement in a Patient with Hodgkin Lymphoma: A Diagnostic Challenge

Author(s)

Yeşim Yiğit[1], Celal Çınar[2], Seher Bahar[3], Ali Aykan Özgüven[4]

Affiliation(s)

[1]University of Health Sciences Türkiye, Balıkesir Atatürk City Hospital, Clinic of Pediatric Hematology and Oncology, Balıkesir, Türkiye

[2]Ege University Hospital, Department of Radiology, İzmir, Türkiye

[3]University of Health Sciences Türkiye, Balıkesir Atatürk City Hospital, Clinic of Radiation Oncology, Balıkesir, Türkiye

[4]Manisa Celal Bayar University Faculty of Medicine, Hafsa Sultan Hospital, Department of Pediatric Oncology, Manisa, Türkiye

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Abstract

Wyburn-Mason syndrome (WMS) is an extremely rare congenital, non-hereditary neurocutaneous disorder characterized by arteriovenous malformations (AVMs) involving the retina, midbrain, and occasionally the facial structures. Although often asymptomatic, such vascular anomalies may incidentally mimic malignant lesions on functional imaging. A sixteen-year-old girl was diagnosed with stage IIB nodular sclerosis-type Hodgkin lymphoma (HL). During initial staging, positron emission tomography-computed tomography (PET-CT) revealed increased fluorodeoxyglucose uptake and thickening along the left optic nerve, suggesting extranodal involvement. Orbital magnetic resonance imaging demonstrated a stable vascular lesion consistent with WMS. No histopathologic confirmation was possible due to the lesion's location. Following standard European Network for Paediatric HL-C1 therapy (oncovin, etoposide, prednisone, adriamycin / cyclophosphamide, oncovin, prednisone, dacarbazine) and standard involved-site radiotherapy, the lesion remained unchanged. To our knowledge, the coexistence of WMS and HL has not been previously reported. This case highlights the diagnostic challenge posed by congenital AVMs that can mimic malignant infiltration on functional imaging. Recognition of this potential overlap is crucial to avoid overstaging and unnecessary therapeutic escalation. This case highlights a diagnostic pitfall in pediatric oncology and emphasizes the importance of correlating multimodal imaging findings to differentiate congenital vascular malformations from malignant extranodal disease, thereby avoiding overstaging or unnecessary treatment escalation.

Keywords: Wyburn-Mason syndrome, Hodgkin lymphoma, arteriovenous malformation, PET-CT, orbital MRI, diagnostic pitfall

Correspondence: Yeşim Yiğit, University of Health Sciences Türkiye, Balıkesir Atatürk City Hospital, Clinic of Pediatric Hematology and Oncology, Balıkesir, Türkiye
E-mail: yesimdr@hotmail.com **ORCID:** orcid.org/0000-0002-0255-1266

Introduction

Wyburn-Mason syndrome (WMS) is a rare neurocutaneous disorder characterized by unilateral vascular malformations involving the retina, midbrain, and sometimes facial structures[1,2]. The condition arises from an embryologic defect in the development of the optic pathway and its associated vasculature.

Hodgkin lymphoma (HL) is a highly curable pediatric malignancy in which accurate staging is critical for risk-adapted therapy. Fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) is the cornerstone of initial staging and response assessment in HL and plays a decisive role in treatment stratification[3]. However, FDG uptake is not specific to malignancy and may also be observed in inflammatory or vascular conditions. Although rare, congenital vascular malformations may mimic extranodal lymphoma involvement and pose a significant diagnostic challenge[4].

Case Presentation

A sixteen-year-old girl presented with left supraclavicular lymphadenopathy measuring 3 cm. Excisional biopsy revealed nodular sclerosis-type HL. Laboratory studies, including erythrocyte sedimentation rate, were within normal limits. She reported no fever or night sweats but had a 12% weight loss in one month. Staging FDG PET-CT demonstrated increased uptake and thickening along the left optic nerve, raising concern for extranodal involvement. Quantitative maximum standardized uptake value measurements were not available, as the PET-CT images were reviewed retrospectively and the original report did not include numerical metabolic values. Orbital magnetic resonance imaging (MRI) revealed contrast-enhancing vascular structures in the same region, consistent with a congenital arteriovenous malformation (AVM) (**Figure 1**).

According to the Ann Arbor staging system, the patient was classified as stage IIB and was treated with the European Network for Paediatric HL-C1 protocol, consisting of two cycles of oncovin, etoposide, prednisone, adriamycin followed by two cycles of cyclophosphamide, oncovin, prednisone, dacarbazine chemotherapy. Involved-site radiotherapy (21.6 Gy in 12 fractions) to the mediastinal and cervical regions was administered as part of standard treatment for stage IIB HL, rather than because of an inadequate metabolic response.

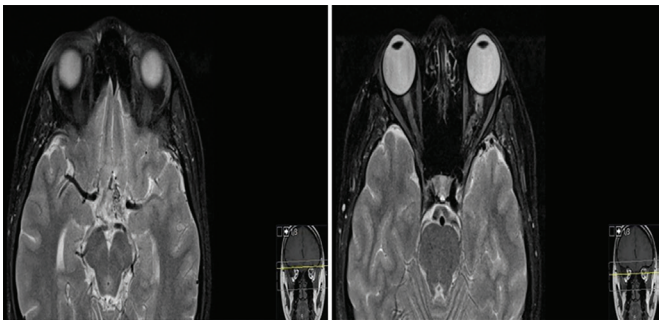

Figure 1. Axial T2-weighted orbital MRI images demonstrating vascular malformation along the left optic nerve, consistent with Wyburn-Mason syndrome
MRI; Magnetic resonance imaging

Follow-up MRI showed no change in the optic lesion, confirming a congenital etiology. Given the asymptomatic nature of WMS, no specific treatment was initiated. Written informed consent was obtained from the patient's parents for publication of this case report and accompanying images.

Discussion

WMS is an exceptionally rare, non-hereditary congenital vascular disorder characterized by AVMs involving the retina, brain, and occasionally orbital or facial structures. Fewer than 100 cases have been reported in the literature, and the clinical presentation varies widely depending on the location and extent of vascular involvement[5-7]. Many patients remain asymptomatic, and the condition is often detected incidentally during imaging performed for unrelated reasons.

The clinical spectrum varies depending on the site and extent of AVMs. Ocular or orbital lesions may cause proptosis or visual disturbances, but many patients remain asymptomatic[7,8].

In pediatric HL, FDG PET-CT plays a central role in initial staging and response assessment, directly influencing risk stratification and treatment planning. However, FDG uptake is not specific to malignancy. Increased metabolic activity may also be observed in inflammatory processes or benign vascular anomalies, creating potential diagnostic pitfalls. In this case, focal FDG uptake along the optic nerve initially raised concern for extranodal involvement by lymphoma, which could have led to disease upstaging and treatment intensification if it had been interpreted in isolation.

Subsequent orbital MRI demonstrated imaging features consistent with a congenital vascular malformation, and the lesion showed no radiologic progression during chemotherapy and follow-up. Importantly, the optic nerve lesion remained morphologically unchanged despite the administration of systemic chemotherapy and standard involved-site radiotherapy, which were given as part of routine treatment for stage IIB HL, rather than in response to inadequate metabolic remission. This stability strongly supported a benign congenital etiology and argued against malignant infiltration.

The underlying mechanism of FDG uptake in AVMs is not fully understood, but is thought to be related to increased regional blood flow, endothelial metabolic activity, and low-grade inflammatory processes rather than true neoplastic involvement. Similar cases of benign vascular lesions mimicking malignancy on PET-CT have been reported sporadically in adults; reports in pediatric patients, particularly in association with HL, are exceedingly rare[6].

This case underscores the importance of multimodal imaging correlation in pediatric oncology. Functional imaging findings should always be interpreted alongside high-resolution anatomic imaging, especially when lesions are located in atypical sites for lymphoma involvement. Awareness of congenital vascular malformations as potential mimics of extranodal disease is essential to prevent overstaging, unnecessary invasive procedures, or overtreatment.

Although angiography remains the diagnostic gold standard for vascular malformations, a non-invasive diagnostic approach was considered appropriate in this asymptomatic pediatric patient. The characteristic MRI findings, combined with long-term radiologic stability during and after lymphoma therapy, supported the diagnosis of WMS without exposing the patient to additional procedural risk.

To our knowledge, this is one of very few reported pediatric cases of incidental detection of WMS during staging for HL. The case highlights an important diagnostic consideration for pediatric oncologists and radiologists, and emphasizes the need for cautious interpretation of FDG PET-CT findings in the presence of rare congenital vascular anomalies.

Conclusion

This case illustrates an important diagnostic pitfall in pediatric HL, where a rare congenital vascular malformation may mimic extranodal disease on FDG PET-CT. The incidental detection of WMS in our patient underscores the limitations of functional imaging when used in isolation. Careful correlation with high-resolution anatomic imaging, particularly MRI, is essential to distinguish benign congenital anomalies from malignant involvement. Awareness of such rare mimickers is crucial to avoid disease overstaging, unnecessary invasive procedures, and inappropriate treatment escalation in pediatric oncology practice.

Ethics

Informed Consent: Written informed consent was obtained from the patient's parents for publication of this case report and accompanying images.

Footnotes

Author Contributions: Yiğit Y: Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing; Çınar C: Surgical and Medical Practices, Concept; Bahar S: Literature Search; Özgüven AA: Literature Search.

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