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Original Article

Evaluation of the clinical characteristics of patients with PFAPA syndrome according to attack triggers

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ABSTRACT

Objective: Based on our clinical observations, this study aimed to evaluate the spectrum of triggers for febrile attacks in children with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) and to investigate whether clinical characteristics differ by trigger presence or type, providing insights relevant for clinicians managing PFAPA.

Methods: The study enrolled children diagnosed with PFAPA by a pediatric rheumatologist according to the European Registry of Autoinflammatory Diseases (EUROFEVER), developed by the Paediatric Rheumatology International Trials Organisation (PRINTO), who had been followed at our tertiary care center for at least six months and were not on prophylaxis. Patients were stratified by the presence of attack triggers. Those with triggers were classified into infection/vaccination, physical/emotional stress, or food intake categories. A comparative analysis of demographic, clinical, and laboratory characteristics was performed between groups during attacks.

Results: Triggers were identified in 31.4% of patients (n = 53), most commonly infection/vaccination (16.0%), followed by physical/emotional stress (8.9%) and food intake-related factors (7.1%). Median breastfeeding duration was significantly shorter in the trigger group (17 vs. 24 months, p=0.032). No significant differences were found in the cardinal PFAPA features (oral aphthae, cervical lymphadenitis, and tonsillitis) by trigger status or type. However, constipation during attacks was more frequent in the group with physical/emotional stress (p=0.020).

Conclusion: The clinical phenotype of PFAPA appears largely independent of trigger type. However, shorter breastfeeding duration among patients with triggers suggests early-life factors may influence trigger susceptibility. Additionally, stress-related triggers may link to other symptoms, such as constipation. Recognizing these patterns may help tailor supportive strategies for PFAPA management.

Keywords: fever, stomatitis, aphthous, triggers

INTRODUCTION

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) represents one of the most common forms of autoinflammatory diseases (AIDs) in the pediatric age group. The syndrome generally presents in early childhood, characterized by recurrent febrile episodes lasting 3 to 7 days and recurring every 2 to 8 weeks. These flares are typically accompanied by pharyngitis, cervical lymphadenopathy, and/or aphthous stomatitis. Between attacks, affected children mostly remain asymptomatic, demonstrating normal growth and development.[1-4]

Although the pathogenesis of PFAPA has not been fully elucidated, it is thought that innate immune system dysregulations and abnormal cytokine responses play

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a role in the development of attacks.[5-7] Clinicians who follow PFAPA are aware that, as in other AIDs such as Familial Mediterranean Fever (FMF), there may be various factors that can trigger attacks in patients. This topic is better defined in FMF, where pyrin activation associated with *MEFV* gene variations has been shown to lower the inflammatory threshold, potentially initiating attacks in response to various environmental or internal triggers.[8-10] In contrast, data on attack triggers in PFAPA are limited. Studies in the literature have reported that emotional stress and changes in the microbial environment may be associated with PFAPA attacks.[11,12]

We hypothesized that specific environmental or physiological triggers may influence the occurrence and clinical characteristics of PFAPA attacks. Based on our biological knowledge and clinical observations, this study aimed to evaluate the factors that trigger attacks in PFAPA patients. We also explored whether clinical characteristics differ by trigger type. Our study aims to make a unique contribution to the literature by examining a wide range of triggers and their clinical effects.

MATERIALS AND METHODS

Patients and data collection

The study enrolled children diagnosed with PFAPA by a pediatric rheumatologist according to the European Registry of Autoinflammatory Diseases (EUROFEVER), developed by the Paediatric Rheumatology International Trials Organisation (PRINTO) who had been followed at our tertiary care center for at least 6 months and were not on prophylaxis.[13] Prophylactic treatment refers to the continuous use of colchicine for attack prevention. Patients who were receiving colchicine prophylaxis at the time of evaluation were excluded from the study. Demographic characteristics and clinical parameters observed during febrile episodes were retrospectively retrieved from patient medical records.

This study was conducted in compliance with the Helsinki Declaration and local laws and regulations. Informed consent was obtained from the patients and their legal caregivers. The ethics committee of a tertiary center approved our study (18/07/2024/725).

Grouping of patients and classification of triggers

Patients were interviewed face-to-face during outpatient clinic visits regarding triggers and were asked to respond based on attacks experienced within the last three attacks. They were then stratified into two groups: those with and those without triggers preceding febrile episodes. Triggers were classified into three main categories: (1) infection/vaccination, (2) physical/emotional stress, and (3) food intake. Some patients experienced more than one trigger type during different attacks. Infection was defined as the presence of physician-confirmed or microbiologically proven infection, or at least two infection-related symptoms (e.g., cough, rhinorrhea) in the patient or household members within 7 days prior to the attack; all other episodes were classified as PFAPA flares. In our study, infection-triggered PFAPA attacks were defined as episodes meeting PFAPA criteria but preceded by mild upper respiratory or other infection-related symptoms occurring within seven days before fever onset, either in the patient or household members. These symptoms resolved in parallel with the PFAPA flare, without a pathogen-specific treatment response. In contrast, episodes with clear evidence of active infection requiring antimicrobial therapy or showing pathogen-specific findings were classified as infectious episodes rather than PFAPA attacks. Infection and vaccine-related triggers were grouped due to their shared potential to activate the innate immune response in genetically susceptible individuals.[14] Physical stress (cold exposure, intense exercise) and emotional stress were combined under a single category, as stress-induced neuroimmune alterations may activate similar inflammatory pathways.[15,16] The food intake category consisted of potential triggers, including milk, yogurt, cocoa, and processed packaged foods.

Statistical analysis

We performed the statistical analysis using SPSS for Windows, version 25.0 (SPSS Inc., Chicago, IL). The Kolmogorov–Smirnov test was used to assess the distribution of continuous variables. Variables with a normal distribution were presented as mean ± standard deviation, whereas those with a non-normal distribution were presented as median (minimum–maximum). Categorical variables, expressed as numbers (percentages), were compared using the chi-square test or Fisher's exact test,

as appropriate. Continuous variables were compared using the Student's t-test, Mann–Whitney U test, or Kruskal–Wallis test, depending on the distribution and number of groups. A p-value < 0.05 was considered statistically significant.

RESULTS

Characteristics and comparative analysis of patients with and without triggers

The investigation encompassed 169 children, of whom 53 patients (31.4%) had triggers and 116 (68.6%) had no triggers. The gender distribution was 65.7% (n=111) male and 34.3% (n=58) female. The median age at diagnosis was 4.3 (1.0–9.4) years in patients with triggers and 4.3 (1.1–9.7) years in those without triggers. Breastfeeding duration was significantly shorter in patients with triggers compared to those without triggers (17 (0–48) months *vs*. 24 (0–54) months, $p = 0.032$). No statistically significant differences were observed in other demographic, clinical, or laboratory characteristics between the two groups (Table 1).

Comparative analysis of clinical characteristics and laboratory findings by trigger types

In the overall cohort, the most common trigger type was infection/vaccination (n=27, 16.0%), followed by physical/emotional stress (n=15, 8.9%) and food intake-related triggers (n=12, 7.1%). Among patients with infection- or vaccination-triggered episodes, one patient had an attack following vaccination. Mevalonate kinase deficiency (MKD) was excluded based on clinical evaluation and genetic testing showing no pathogenic MVK variants. Comparative analysis according to trigger types revealed that constipation was significantly more frequent in the physical/emotional stress group ($p = 0.020$). No other statistically significant differences were observed in demographic, clinical, or laboratory characteristics among the trigger type groups (Table 2).

DISCUSSION

In this study, we evaluated triggers for PFAPA flares, including their distribution and association with clinical, demographic, and laboratory characteristics. These parameters were compared by trigger presence/absence and, among patients with triggers, by trigger type. The most frequent trigger was infection/vaccination, followed by physical/emotional stress and food intake. The sole significant difference between the groups was a shorter breastfeeding duration in patients with triggers. When stratified by trigger type, constipation was more frequently observed in the physical/emotional stress group. These findings suggest that the presence or type of trigger in PFAPA may be associated with certain clinical features, although the overall clinical profile remains largely consistent.

To our knowledge, no previous study has systematically evaluated such a broad spectrum of triggers in PFAPA; in this respect, our work represents one of the most comprehensive analyses to date. Previous reports have generally focused on a single trigger, most often infectious exposures or stress, and have not described their relative frequencies.[11,12] In our study, the most frequent trigger was infection or vaccination, followed by physical/emotional stress, and, less commonly, food-related factors. This trigger profile is not unique to PFAPA but shares common features with infectious triggering mechanisms described in certain AIDs.[17,18] In these disorders, the primary pathology involves excessive or inappropriate activation of the innate immune system.[18] Pattern-recognition receptors (e.g., Toll-like receptors, NOD-like receptors) detect viral or bacterial components and activate the inflammatory cascade in a regulated manner. In AIDs, however, the activation threshold of this system is lowered.[17,18] Although a genetic mutation is rarely identified in PFAPA, it is likely that defects in regulatory mechanisms and epigenetic alterations lead to similarly low-threshold activation of the innate immune system, with infection or vaccination serving as potent stimuli for flare initiation. Vaccination, in particular, is a temporally distinct and easily recognizable event for caregivers, increasing the likelihood that it will be recalled and linked to the onset of an episode. Additionally, although infrequently reported, food intake-related triggers are noteworthy. Dietary antigens may modulate inflammatory responses through the mucosal immune system, and alterations in gut microbiota composition can influence the severity of IL-1–mediated inflammation.[19,20] These biological mechanisms, together with the high detectability of such events by caregivers, may account for the prominence of these triggers among patients.

When patients with triggers were compared with those without, the only statistically significant difference was a shorter breastfeeding duration in the trigger group. Although the clinical relevance of this finding is not entirely clear, early cessation of breastfeeding may lead to alterations in gut microbiota composition, inadequate maturation of the mucosal immune system, and reduced oral tolerance.[21,22] Human milk oligosaccharides in breast

Table 1. Comparison of clinical and demographic characteristics of patients with and without attack triggers

	Patients with triggers (n=53)	Patients without triggers (n=116)	*p* value
Male gender (n, %)	38 (71.7%)	73 (62.9%)	0.265
*Age at diagnosis (Year) Median	4.3 (1.0-9.4)	4.3 (1.1-9.7)	0.819
*Number of monthly attacks	1 (0-5)	1.5 (0-4)	0.628
*Duration of attack (Day)	4 (2-10)	4.5 (1-10)	0.215
*Highest fever value in the attack (^{0}C)	40 (38-41)	40 (38-41)	0.594
*Time between attacks (Day)	15 (7-90)	25 (7-90)	0.688
Clinical findings during the attack (n, %)			
Sore throat	53 (100%)	113 (97.4%)	0.553
Oral aphthae	29 (54.7%)	59 (50.9%)	0.642
Lymphadenitis	44 (83%)	83 (71.6%)	0.110
Abdominal pain	34 (64.2%)	67 (57.8%)	0.432
Headache	15 (28.3%)	29 (25%)	0.650
Diarrhea	9 (17%)	24 (20.7%)	0.573
Constipation	4 (7.5%)	4 (3.4%)	0.260
Family history (n, %)			
Periodic fever syndrome	33 (62.3%)	75 (64.7%)	0.764
Tonsillectomy	27 (50.9%)	53 (45.7%)	0.526
*Breastfeeding duration (months)	17 (0-48)	24 (0-54)	0.032
Vaccination status (n, %)	45 (84.9%)	109 (94.0%)	0.078
Genetic and laboratory findings			
MEFV variation (n, %)	17 (51.5%)	36 (50%)	0.885
M694V variation (n, %)	5 (15.2%)	13 (18.1%)	0.714
Exon 10 variation (n, %)	11 (33.3%)	19 (26.8%)	0.491
,CRP (mg/L)*	44 (8.7-156)	60.6 (7.9-338)	0.091
,ESR (mm/h)*	25.5 (4-56)	25 (10-89)	0.945
,Neutrophil count (×10^9/L)*	8.9 (2.2-27.1)	9 (1.2-23.9)	0.750
,Lymphocyte count*	2.5 (1.1-9.8)	3.1 (0.9-7.7)	0.086
,Platelet count (×10^9/L)*	295 (212-526)	301 (171-603)	0.506

*: Median (Min-Max)
**: During the attack
CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; MEFV: Mediterranean fever gene.

milk support the colonization of beneficial gut bacteria, while bioactive components such as immunoglobulin A, lactoferrin, and antimicrobial peptides play a critical role in protecting against infections and modulating inflammatory responses.[23,24] The absence of these protective mechanisms may increase susceptibility to infectious or other environmental stimuli, thereby lowering the threshold for disease flares. Indeed, in a study of 150 PFAPA patients, Rigante *et al.*[25] demonstrated that breastfeeding for ≥6 months was associated with lower attack frequency and severity, higher rates of spontaneous remission, and that prolonged breastfeeding was an independent protective factor against disease activity in PFAPA. In our study, the shorter breastfeeding duration observed in patients with triggers suggests that the diminished protective effect of breastfeeding might increase the likelihood of trigger-related attacks. Moreover, the association between shorter breastfeeding duration and the development of allergic and autoimmune diseases has been demonstrated in multiple epidemiological studies, potentially predisposing the immune system toward a more reactive phenotype in response to environmental stimuli.[26-28] As an early-life factor, inadequate breast milk intake may shape gut microbiota development, immune tolerance, and

Table 2. Comparison of clinical and genetic features according to trigger types in PFAPA patients

	Attack Trigger Types (n, %)			
	Infection/Vaccination (27, 16%)	**Physical/Emotional Stress (15, 8.9%)**	**Food intake (12, 7.1%)**	***p***
Male gender (n, %)	20 (76.9%)	10 (66.7%)	8 (66.7%)	0.582
*Age at diagnosis (Year)	5 (1.1-8.2)	3.5 (1.1-9.4)	3.8 (1-6.7)	0.889
*Number of monthly attacks	1 (1-5)	1.5 (0-3)	1 (1-2)	0.958
*Duration of attack (Day)	4 (2-10)	4 (2-10)	4 (3-7)	0.541
*Highest fever value in the attack (^{0}C)	40 (38.6-42)	40 (38.5-41)	40 (38-41)	0.924
*Time between attacks (Day)	15 (7-60)	20 (10-90)	20 (15-30)	0.809
Clinical findings during the attack (n, %)				
Sore throat	26 (100%)	15 (100%)	12 (100%)	0.707
Oral aphthae	15 (57.7%)	7 (46.7%)	7 (58.3%)	0.859
Lymphadenitis	23 (88.5%)	12 (80%)	9 (75%)	0.326
Abdominal pain	19 (73.1%)	10 (66.7%)	5 (41.7%)	0.257
Headache	8 (30.8%)	6 (40%)	1 (8.3%)	0.279
Diarrhea	4 (15.4%)	3 (20%)	2 (16.7%)	0.930
Constipation	0 (0%)	3 (20%)	1 (8.3%)	0.020
Family history (n, %)				
Periodic fever syndrome	17 (65.4%)	10 (66.7%)	6 (50%)	0.775
Tonsillectomy	17 (65.4%)	6 (40%)	4 (33.3%)	0.188
*Breastfeeding duration (months)	17 (0-42)	15 (1-30)	22 (0-48)	0.149
Vaccination status (n, %)	21 (80.8%)	13 (86.7%)	11 (91.7%)	0.173
Genetic and laboratory findings				
MEFV variation (n, %)	7 (26.9%)	9 (60%)	1 (8.3%)	0.532
*, **CRP (mg/L)	54.7 (8.7-156)	42 (13.3-119.6)	37.8 (18.7-98)	0.267
*, **ESR (mm/h)	16.5 (4-38)	28 (21-51)	34 (17-56)	0.414
*, **Neutrophil count (×10^9/L)	8.3 (2.2-27.1)	6.6 (2.5-14.3)	10.9 (3.6-21.2)	0.262
*, **Lymphocyte count (×10^9/L)	2.1 (1.1-5.0)	2.7 (1.2-4.4)	2.6 (1.7-9.8)	0.164
*, **Platelet count (×10^9/L)	304 (227-525)	280 (212-526)	370 (219-433)	0.312

*: Median (Min-Max)

**: During the attack

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; MEFV: Mediterranean fever gene.

resistance to infections, thereby providing a biological basis for increased trigger sensitivity in PFAPA patients. Moreover, alterations in gut microbiota composition have been suggested to play a role in PFAPA pathogenesis by influencing mucosal immune responses and oral tolerance. In this context, approaches targeting the gut microbiota, including probiotic supplementation, may potentially help in modulating disease activity.[29]

When evaluated by trigger presence/absence or trigger type, no significant differences were observed in the cardinal PFAPA manifestations during attacks (oral aphthae, cervical lymphadenitis, tonsillitis). PFAPA shares some clinical features with FMF, such as recurrent fever, aphthous stomatitis, and abdominal pain, which may sometimes complicate the differential diagnosis. However, PFAPA attacks are usually shorter and exhibit more regular periodicity. MEFV gene variants may also contribute to overlapping inflammatory phenotypes between PFAPA and FMF.[30,31] In our previous study, these findings were also similar regardless of *MEFV* variation status or early response to colchicine.[32] These parallel results suggest that the core clinical phenotype of PFAPA may be largely independent of genetic factors, trigger history, and early treatment response. However, the significantly higher frequency of constipation during attacks in patients reporting

stress as a trigger suggests that stress may influence the gastrointestinal system through alterations in gut motility and neuroimmune interactions.[33] Therefore, although the fundamental clinical phenotype may remain unchanged, supportive interventions targeting stress-related triggers, particularly those potentially associated with additional symptoms such as constipation, should be considered in PFAPA management.

The main limitation of our study is its retrospective design, which risks recall bias, as trigger presence and type were based on patient or caregiver reports. For infectious triggers, mild symptoms could have been overlooked or misremembered. The absence of standardized trigger definitions may have introduced subjectivity in classification, and microbiological confirmation was not systematic in all patients. The relatively small number of patients in each trigger subgroup may also have limited the statistical power, and the observed difference in constipation should therefore be interpreted with caution. Despite these limitations, the study benefits from a large, well-characterized cohort and a systematic comparison of clinical features by trigger presence and type, thereby strengthening the reliability of our observations. The main strength of our study lies in being the first to examine attack triggers in children diagnosed with PFAPA syndrome.

In conclusion, our findings show that PFAPA's core clinical phenotype is largely independent of trigger type. However, higher constipation frequency in patients with stress-related triggers suggests additional symptoms may emerge in this subgroup. The shorter duration of breastfeeding in patients with triggers implies that early-life factors may influence trigger development. Infections, vaccinations, and certain foods were identified as triggers, highlighting the importance of evaluating trigger history in PFAPA's clinical management.

Ethical approval

This study has been approved by the Istanbul Medeniyet University Göztepe Training and Research Hospital (approval date 18/07/2024, number 725). Written informed consent was obtained from the participants.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: LK, FK, EK; data collection: ESYE, ZA, END, HKD; analysis and interpretation of results: FH, MÖB, UFÖ; draft manuscript preparation: LK, KÖ. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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