ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

PFAPA Syndrome: Evaluation of Clinical Findings, Immunological Alterations, and Treatment Approaches

PHAPA Sendromu: Klinik Bulguların Değerlendirilmesi, İmmünolojik Değişiklikler ve Tedavi Yaklaşımlarının İncelenmesi

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Abstract

Introduction: PFAPA syndrome is an autoinflammatory disease seen in childhood characterized by recurrent fever, aphthous stomatitis, pharyngitis, and cervical adenitis. This study aims to examine the clinical and laboratory features of PFAPA syndrome, assess responses to treatment, and particularly evaluate the disease from an immunological perspective.

Materials and Methods: Forty-nine patients presenting to the Pediatric Immunology and Allergy outpatient clinic and meeting the diagnostic criteria for PFAPA were evaluated. Demographic information, symptoms, physical examination findings, laboratory results, and responses to treatment were meticulously recorded.

Results: Our study included a total of 49 patients, comprising 30 males and 19 females, with a mean age at diagnosis of 3.5 years. Notable findings in immunological assessments included neutrophilia, leukocytosis, and in a few cases, lymphopenia, as well as changes in CD3 and CD19 subsets that highlighted the immunological aspect of the disease, indicating significant alterations in the adaptive immune system. Prednisolone treatment resulted in a response rate of 92.5%, with most patients showing a rapid improvement. Eighty-one point eight percent of patients receiving colchicine prophylaxis reported a decrease in symptoms. The symptoms in 13.5% of patients who underwent tonsillectomy either significantly decreased or completely resolved.

Conclusion: Management of PFAPA syndrome varies in terms of immunological findings and response rates to treatment. Our study elucidates the effectiveness of prednisolone treatment, the benefits of colchicine prophylaxis, and the improvement in symptoms following tonsillectomy. Furthermore, it underscores the necessity of considering immunological factors in the diagnosis and treatment processes of PFAPA syndrome.

Keywords
PFAPA syndrome, periodic fever, autoinflammatory diseases, immunology, prednisolone, colchicine, tonsillectomy

Öz

Giriş: PFAPA sendromu, çocukluk çağında görülen, tekrarlayan ateş, aftöz stomatit, farenjit ve servikal adenit ile karakterize otoinflamatuar bir hastalıktır. Bu çalışmanın amacı, PFAPA sendromunun klinik ve laboratuvar özelliklerini incelemek, tedaviye yanıtları değerlendirmek ve özellikle hastalığı immünolojik bir bakış açısıyla değerlendirmektir.

Gereç ve Yöntem: Pediatrik İmmünoloji ve Alerji polikliniğine başvuran ve PFAPA tanı kriterlerine uyan 49 hasta üzerinde bir değerlendirme gerçekleştirilmiştir. Hastaların demografik özellikleri, semptomları, fizik muayene bulguları, laboratuvar test sonuçları ve tedaviye verdikleri yanıtlar detaylı bir şekilde kayıt altına alınmıştır.

Anahtar kelimeler
PFAPA sendromu, periyodik ateş sendromları, otoinflamatuar hastalıklar, immünoloji, prednizolon, kolşisin, tonsillektomi

Received/Geliş Tarihi : 29.03.2024
Accepted/Kabul Tarihi : 25.07.2024

DOI:10.4274/jcp.2024.36604

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Bulgular: Çalışmamız, ortalama tanı yaşı 3.5 yaş olan, 30'u erkek ve 19'u kız toplam 49 hastayı kapsamaktadır. İmmünolojik değerlendirmeler, nötrofili, lökositoz ve az sayıda vakada lenfopeni gibi dikkate değer bulgular ortaya koymuştur. Prednizolon tedavisi, hastaların %92.5'inde olumlu yanıt alınmasını sağlamış ve çoğu hasta hızlı bir iyileşme sürecine girmiştir. Kolşisin profilaksisi uygulanan hastaların %81.8'i semptomlardaki azalmayı rapor etmiştir. Tonsillektomi yapılan hastaların %13.5'inde semptomlar önemli ölçüde azalmış ya da tamamen ortadan kalkmıştır. Ayrıca, CD3 ve CD19 alt gruplarındaki değişiklikler, hastalığın immünolojik yönünü ön plana çıkararak adaptif bağışıklık sistemindeki önemli değişikliklere dikkat çekmiştir.
Sonuç: PFAPA sendromunun yönetimi, immünolojik bulgular ve tedaviye yanıt oranları açısından değişkenlik gösterir. Çalışmamız, prednizolon tedavisinin etkinliğini, kolşisin profilaksisinin faydalarını ve bademcik ameliyatını takiben semptomlarda görülen iyileşmeyi aydınlatmaktadır. Ayrıca, PFAPA sendromunun tanı ve tedavi süreçlerinde immünolojik faktörlerin dikkate alınmasının gerekliliğini vurgular.

Introduction

PFAPA syndrome (Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Cervical Adenitis) is one of the most common periodic fever syndromes, characterized by periodic fever episodes that typically recur every 3 to 8 weeks. It predominantly manifests within the first 5 years of life but generally shows a tendency to resolve spontaneously between the ages of 5 and 10. No specific association with any ethnic origin or race has been identified. The diagnosis is made by observing the typical clinical signs and excluding other potential causes. During episodes, an increase in neutrophils, acute phase reactants, and white blood cells is observed. PFAPA is distinguished from other monogenic autoinflammatory diseases by its regular interval attacks, confinement to upper respiratory tract inflammation, and spontaneous resolution with age. Treatment options include corticosteroids for symptom relief, colchicine, and tonsillectomy, which in some cases can completely eradicate the disease (1). Initially considered a sporadic illness, the reporting of familial clusters in PFAPA syndrome suggests a hereditary component (2,3). Research on its genetic basis has indicated that genes associated with the inflammasome might play a role in this syndrome (4,5). Despite its unclear etiology, PFAPA syndrome is thought to emerge from an autoinflammatory reaction resulting from dysfunctions in both innate and adaptive immune mechanisms. Notably, interleukin-1β is believed to have a significant role in hyperinflammation events. Studies on cytokines have shown an increase in pro-inflammatory cytokines and a decrease in anti-inflammatory cytokines during episodes, along with a dysregulation in IL-1β production. Additionally, significant alterations in the anti-inflammatory activity of monomeric CRP and in neutrophil functions have been observed (6,7,8,9). Although PFAPA syndrome is a common cause of recurrent fever, its true prevalence remains unclear. Patients often receive incorrect diagnoses such as bacterial tonsillitis, leading to unnecessary use of antibiotics. Recently, increased awareness among clinics has led to improvements in diagnostic accuracy (10). This study aims to evaluate the clinical and laboratory characteristics of patients directed to the Pediatric Immunology Clinic with frequent infection complaints and subsequently diagnosed with PFAPA syndrome, as well as to investigate the disease from an immunological perspective.

Materials and Methods

Study Population and Design

The study population includes 49 patients diagnosed with PFAPA (Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Cervical Adenitis) syndrome, according to the diagnostic criteria proposed by Thomas et al. (11), who presented to the Pediatric Immunology and Allergy outpatient clinic. These criteria encompass early-onset fever episodes, absence of upper respiratory tract infection, exclusion of cyclic neutropenia, symptom-free intervals between episodes, and maintained normal growth and development. Data on patients' demographics, disease history, symptoms, physical examination findings, laboratory results, and treatments were collected from hospital records. Informed consents were obtained from the patients for the study. The study was initiated after obtaining approval from the Ondokuz Mayıs University Ethics Committee (date: 29.12.202, decision no: OMÜ/KAEK 2021/601).

Statistical Analysis

Statistical analyses were performed using IBM SPSS software version 21.0. The Chi-square test was utilized for comparing categorical variables between

groups, while the Mann-Whitney U test or Kruskal-Wallis test was employed for continuous variables, selected for variables not normally distributed. The level of statistical significance was set at $p<0.05$.

Results

Our study encompasses 49 patients with Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Cervical Adenitis (PFAPA) syndrome. The clinical features, laboratory findings, administered treatments, and immunological test results have been evaluated. Of the total 49 patients, 30 were male (61.2%), and 19 were female (38.8%). The average age of the patients was 7 years (min-max: 3-17 years), with the age of diagnosis being 3.5 years (min-max: 1-11.5 years). The median duration of episodes was calculated as 4 days (min-max: 2-7), and the median interval between episodes was found to be 20 days (min-max: 10-120). In 8.3% of the patients, there was a parental consanguinity, and 16% had a family history of fever and recurrent tonsillitis.

All patients (100%) in the study exhibited fever and tonsillitis. Cervical lymphadenopathy was detected in 92.5% (n=37), musculoskeletal pain in 66.7% (n=30), abdominal pain in 63.0% (n=29), and aphthous stomatitis in 52.3% (n=23) (Table 1).

These results highlight the characteristic and heterogeneous clinical features of PFAPA syndrome; fever and tonsillitis are the most prominent and consistent findings. Moreover, other symptoms such as cervical lymphadenopathy, musculoskeletal pain, abdominal pain, and aphthous stomatitis also provide important clues for diagnosis and management.

In laboratory findings, the average white blood cell count was 10,290±2,920 cells/μL, lymphocytes 5,356±1,656 cells/μL, neutrophils 2,670±1,268 cells/μL, and platelet count 382,000 ± 107,310/μL. Immunoglobulin levels were determined as IgG 878.13±240.51 mg/dL, IgA 80.27±46.55 mg/dL, IgM 123.35±106.75 mg/dL, and IgE 61.97±99.63 IU/mL. Additionally, the CRP level was measured at an average of 59 ± 18.9 mg/L (Table 2). In the examined patient group, leukocytosis was observed in 44%, lymphopenia in 4%, and neutropenia in 8%. Furthermore, in immunoglobulin evaluations, decreases were detected in IgG levels in 28%, IgA levels in 26%, and IgM levels in 12%. No microbial growth was identified in the throat culture samples taken. Vitamin D levels were assessed in 14 patients, with 10 of them found to have levels below 30 ng/mL.

Due to frequent infections, specific lymphocyte subgroups such as CD3, CD3CD4, CD3CD8, and CD19 were examined in our patient group (Table 3). Additionally, when compared with age-matched reference values of a healthy control group, some lymphocyte subgroups showed lower or higher values (Figure 1).

Table 1. Clinical findings and treatments applied to patients

		N (%)
Gender	male	30 (61.2)
	female	19 (38.8)
Family history	no	44 (91.7)
	yes	4 (8.3)
Tonsillitis		45 (100)
Fever		46 (100)
Aphthous stomatitis	no	21 (47.7)
	yes	23 (52.3)
Abdominal pain	no	29 (63.0)
	yes	17 (37.0)
Musculoskeletal pain	no	30 (66.7)
	yes	15 (33.3)
Cervical lymphadenopathy	no	3 (7.5)
	yes	37 (92.5)
Diarrhea	no	39 (90.7)
	yes	4 (9.3)
Constipation	no	37 (86.0)
	yes	6 (14.0)
Rash	no	34 (79.1)
	yes	9 (20.9)
Response to colchicine prophylaxis	no	2 (18.2)
	yes	9 (81.8)
Response to prednisolone during attacks	no	3 (7.5)
	yes	37 (92.5)
Tonsillectomy	no	32 (86.5)
	yes	5 (13.5)

Table 2. Findings related to patients' laboratory results	
	Mean ± Standard Deviation
WBC (µL)	10290±2920
Hb(g/dL)	9,72±2,16
Lymphocytes (µL)	5356±1656
Neutrophils (µL)	2670±1268
PLT (x10^3/µL)	382000±107310
IgG (mg/dL)	878.13±24051
IgA (mg/dL)	80.27±46.55
IgM (mg/dL)	123.35±106.75
Total IgE (mg/dL)	61.97±99.63
CRP (mg/L)	59±18.9

WBC: White blood cell, PLT: Platelet, CRP: C-Reactive protein, Ig: Immunoglobuline

Table 3. Evaluation of patients' lymphocyte subgroups	
	% Median %(Min-Max)
CD3	64.5 (48-80)
CD3CD4	36.5 (28-50)
CD3CD8	27 (18-47)
CD 19	19 (7-35)
NK	9 (4-17)
CD3/CD8/TCRGD	17.5 (17-19)
RTE	51.5 (31-60)
CD45RA	70 (6-87)
CD4+CD45RA+	64.5 (15-72)
CD8+CD45RA+	63 (15-76)
CD19+CD27-IgD+	84 (61-93)
CD19+CD27+	4.3 (0-32)
CD19+ CD27+IgD+IgM+	3 (0-14)
CD19+CD27+IgD-IgM-	5 (0-14)

CD3: T cell co-receptor, CD3CD4: Helper T cells, CD3CD8: Cytotoxic T cells, CD19: B cell marker, NK: Natural Killer cells, CD3/CD8/TCRGD: TCR gamma delta T cells, RTE: Recent thymic emigrants, CD45RA: Naive T cell marker, CD4+CD45RA+: Naive CD4+ T cells, CD8+CD45RA+ Naive CD8+ T cells, CD19+CD27-IgD+: Naive B cells, CD19+CD27+: Memory B cells, CD19+CD27+IgD+IgM+: Non-switched memory B cells, D19+CD27+IgD-IgM-: Switched memory B cells

As for treatment methods, prednisolone, colchicine prophylaxis, and tonsillectomy were administered. A response to prednisolone treatment during episodes was observed in 92.5% (n=37) of the patients. Of the patients who received colchicine prophylaxis, 81.8% (n=9) responded positively to the treatment.

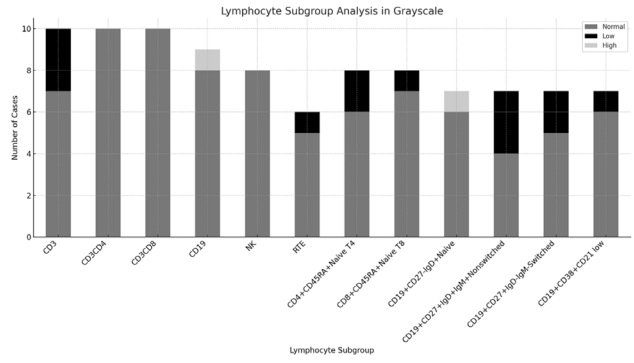

Figure 1. Comparative analysis of lymphocyte subgroups with reference values of the healthy child population (12)
NK: Natural miller cells, RTE: Recent thymic emigrants

Among the patients who underwent tonsillectomy, 13.5% (n=5) showed improvement in symptoms with this intervention. During follow-ups, 2 patients had recurrent complaints. These findings highlight that prednisolone administered during the attack period is an effective option in treating PFAPA syndrome, colchicine prophylaxis is beneficial in managing symptoms for certain patients, and tonsillectomy is a preferred method in selected cases.

Discussion

In our study of patients with PFAPA syndrome, evaluated in terms of clinical and immunological characteristics, the gender distribution was found to be in favor of males, with a ratio calculated at 1.57. The average age at diagnosis of our patients was 3.5 years, with a diagnostic range from 1 to 11.5 years. Initial symptoms generally started before diagnosis, but a diagnosis was often delayed due to a history of frequent infections leading to referrals to our clinic. This suggests a tendency for PFAPA syndrome to be misdiagnosed. In this process, the disease is often confused with bacterial tonsillitis, resulting in patients receiving unnecessary repeated antibiotic treatments.

In our study, tonsillitis and fever were observed in all patients (100%), while the rate of cervical lymphadenopathy was determined to be 92.5%. Aphthous lesions were only detected in 52.3% of patients. These findings indicate that tonsillitis and fever are common among patients, but cervical lymphadenopathy and aphthous lesions are less frequent. In addition to the main symptoms, other symptoms detected in a majority of patients include

abdominal pain (37.0%), musculoskeletal pain (33.3%), rash (20.9%), constipation (14.0%), and diarrhea (9.3%). Studies in the literature show that 76% of patients with PFAPA syndrome may present with additional symptoms accompanying the clinical picture. These symptoms include abdominal pain (40-65%), vomiting (18-41%), arthralgia (11-42%), headache (18-65%), skin rashes (12%), and neurological symptoms (3%) (12). The most common additional finding in our study was abdominal pain, with large series studies conducted in our country reporting the frequency of abdominal pain in PFAPA patients as 41%-45.1%. The wide range of symptoms associated with PFAPA syndrome plays a critical role in the accurate diagnosis and determination of appropriate treatment strategies. While fever and tonsillitis are key indicators of PFAPA syndrome, other symptoms such as cervical lymphadenopathy, musculoskeletal pain, abdominal pain, and aphthous stomatitis highlight the heterogeneous nature of the disease and the individual differences among patients. These symptoms complicate the clinical course of the disease and necessitate different treatment approaches for each patient.

These varied symptoms are crucial in diagnosing the disease correctly and establishing suitable treatment strategies. For instance, a study observed aphthous stomatitis in 66.7% of PFAPA patients, cervical adenopathy in 94.8%, and abdominal pain in 23.1% (13,14).

The consanguinity rate between mothers and fathers was determined to be 8.3% in our study. In 16% of the cases, similar histories were found in the family. Studies have shown that a history of recurrent fever, tonsillitis, and/or tonsillectomy among parents and first-degree relatives can be found, indicating a polygenic genetic origin of the disease (15,16).

PFAPA Syndrome typically follows a benign course, with symptoms tending to decrease spontaneously by the age of 7-8. However, in some of our patients, symptoms have continued even after adolescence. While it is a common belief that this syndrome is exclusive to childhood, the increasing reports of PFAPA Syndrome cases in adults are challenging this viewAccording to the study by Rigante et al. (17), the occurrence of PFAPA syndrome in adults challenges the common belief that the disease is limited to childhood. The study found that while the duration of febrile attacks was longer in adults, the frequency of attacks was higher in children. Adults exhibited a broader range of inflammatory symptoms compared to children, including joint pain, myalgia, headache, fatigue, ocular signs, and rashes. Corticosteroids were found to be effective in 98.82% of children and 88.2% of adults. NSAIDs were more effective in adults, and colchicine treatment yielded successful results in three adult patients. Tonsillectomy was rarely performed and was effective in only one adult patient. These findings suggest that PFAPA syndrome may present a more complex clinical picture in adults and that diagnostic criteria may need to be reevaluated (17).

In the laboratory findings of our patients, leukocytosis, neutrophilia, and, less frequently, lymphopenia were observed. The literature suggests that inflammation in PFAPA results from the activation of the innate immune system, with increases in neutrophil and monocyte counts during fever episodes, while lymphocyte counts typically decrease. Dytrych and colleagues have associated the peripheral lymphopenia observed during attacks with the accumulation of polyclonal T cells in the tonsils of patients (18).

In our study, an analysis of lymphocyte subgroups was conducted. Low values were detected in the CD3 subgroup in 3 out of 10 patients (30%), suggesting the adaptive immune system may be affected in these patients, although it is important to note that we do not have a sufficient number of patients for these results. High values were observed in the CD19 subgroup in 1 out of 9 patients (11.1%), indicating that B cells were more prevalent than expected in this case, which could signify a potential immune response or an autoimmune condition. Low values were found in CD19+ CD27+ IgD+ IgM+ non-switched B cells in 3 patients (42.9%). When considered together with the low levels of immunoglobulins, these findings could point to a deficiency in a specific B cell population and potentially a decrease in specific antibody responses. Decreases of 25% and 12.5% were observed in CD4+CD45RA+ Naive T4 and CD8+CD45RA+ Naive T8 cells, respectively, which might indicate an impairment in the immune response to new antigens, critical for fighting new infections. Due to the small number of patients, no statistical evaluation was made, and the lack of abundant data in the literature makes comparisons challenging. However, studies have

shown an increase in inflammatory cells and immune system molecules in the tonsils of patients with PFAPA syndrome, particularly in the numbers of CD8+ T cells, CD19+ B cells, and memory B cells (19). Furthermore, markers of inflammation such as IL-1β were found to be increased in the tonsils of PFAPA patients compared to those of a recurrent bacterial pharyngitis control group, with high levels of inflammation markers like IL1RN and TNF, indicating that the NF-κB signaling pathway is continually active. These findings suggest ongoing inflammation in the tonsils of patients with PFAPA syndrome (19). Another study evaluated paraffinized tonsil samples from 26 PFAPA and 29 control patients, revealing statistically significant higher counts of CD8+ and CD4+ T-cells in PFAPA patients compared to controls (20). Additionally, tonsils removed from PFAPA patients through tonsillectomy, when compared with those from children undergoing tonsillectomy for hypertrophic tonsils or obstructive sleep apnea, showed smaller germinal centers, wider squamous epithelial surfaces, less IL-4 expression, lower B lymphocyte ratios, and higher T lymphocyte ratios (21).

Prednisolone is an effective option in the treatment of PFAPA syndrome, with its use during flare-ups leading to rapid symptom relief and improved quality of life for Patients. Colchicine prophylaxis is beneficial for managing symptoms, particularly in patients who experience frequent attacks and do not respond well to other treatments. Tonsillectomy, on the other hand, offers a long-term solution by significantly reducing or completely eliminating symptoms in selected cases. PFAPA attacks dramatically improve with corticosteroid treatment. Dosages of 0.6-2 mg/kg prednisone/prednisolone (or 0.1-0.2 mg/kg betamethasone) can be used in therapy. Steroids can reduce the production of pro-inflammatory cytokines, including IL-1β, through the modulation of gene expression. In our research, the response rate to prednisolone during attacks was observed to be 92.5%. Studies have reported a complete response rate within a few hours to be between 63-97%. However, some patients may require an additional dose. While corticosteroid therapy is not effective in preventing subsequent attacks, patients continue to respond to corticosteroids in future attacks. The interval between attacks may shorten after starting corticosteroid use (22,23).

Literature has shown that colchicine, the primary treatment option for Familial Mediterranean Fever, can be beneficial in partially reducing the frequency of attacks in children with PFAPA syndrome. In our study, the response rate to colchicine prophylaxis was found to be 81.8%. There are studies reporting a strong association between PFAPA syndrome and Familial Mediterranean Fever (FMF). A study by Butbul-Aviel et al. (24). involving 270 PFAPA patients and a large series study conducted in our country found mutations in the MEFV gene in 59.9% of patients diagnosed with PFAPA, with the most common mutation being M694V (29.3%) (25). In a similar study previously conducted in our clinic, an MEFV gene mutation was found in 66.0% of children (26). These patients were simultaneously treated with colchicine, and the most frequently detected mutation was M694V. Given the prevalence of FMF in our country, it is important to investigate PFAPA patients from this perspective. Colchicine therapy, used in doses of 0.5-1.2 mg/day for children aged 4-6 and 1-1.8 mg/day for children over 6, has reported success rates in attack treatment of 40-80%. Patients treated with colchicine have significantly fewer attacks compared to those treated with corticosteroids (27). In our clinic, we apply colchicine treatment as a second option for patients who do not respond to prednisolone or have frequent attacks. Our response rate for colchicine prophylaxis aligns with the current literature, suggesting that long-term use of colchicine can be effective. However, our tonsillectomy results are significantly lower than findings in the literature regarding its effectiveness

Tonsillectomy was performed in 13.5% (n.5) of our patients. Two patients experienced attacks during follow-up. Tonsillectomy is generally considered an effective method for stopping fever attacks in patients with PFAPA syndrome, with an efficacy rate ranging between 63% and 100% (28). The most comprehensive observational study on the effectiveness of tonsillectomy in PFAPA treatment was conducted by Licameli et al. (29) In this study, 102 patients were followed for an average of 43 months after tonsillectomy, and it was reported that PFAPA attacks completely disappeared in 99 of them (97%). However, fever attacks may continue in some PFAPA patients after tonsillectomy. In such cases, there is evidence that an underlying MEFV mutation may be present and that colchicine treatment could be more effective in these patients.

There are studies in the literature indicating that tonsillectomy may alleviate symptoms in some cases but may not be an effective method for every patient. For instance, a Cochrane review reported that results from two small randomized controlled trials showed significant benefits of surgery in terms of immediate and complete symptom resolution, but these results carry moderate certainty due to the small sample sizes and some concerns about applicability. The review emphasized the need for further research to strengthen these findings. Therefore, parents and caregivers of children with PFAPA syndrome must carefully weigh the risks of surgery against the benefits of alternative medication treatment (29,30)

Conclusion

Our study demonstrates that PFAPA syndrome is often misdiagnosed as an infection in our patient population, leading to delayed diagnosis. This highlights the importance of PFAPA diagnosis and underscores the need for increased awareness and a more careful approach in diagnostic processes. Furthermore, the pathogenesis of PFAPA syndrome is still not fully understood, indicating a great need for further research to elucidate the immunological basis of this complex condition. Therefore, future studies are expected to contribute to a deeper understanding of the disease and, consequently, the development of more effective treatment methods.

Study Limitations

The study has several limitations. First, the small sample size of 49 patients may limit the generalizability of the findings to broader populations. Second, the study relies on retrospective data collection. Another limitation is that all patients were referred to the immunology clinic due to frequent infections, which may suggest that the study population has a predisposition to more severe immune system issues compared to the general population.

Ethics

Ethics Committee Approval: The study was initiated after obtaining approval from the Ondokuz Mayıs University Ethics Committee (date: 29.12.2022, decision no: OMÜ/KAEK 2021/601).

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

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

References

1. Rydenman K, Fjeld H, Hätting J, Berg S, Fasth A, Wekell P. Epidemiology and clinical features of PFAPA: a retrospective cohort study of 336 patients in western Sweden. Pediatr Rheumatol Online J. 2022;20:82.
2. Sampaio IC, Rodrigo MJ, Monteiro Marques JG. Two siblings with periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA) syndrome. Pediatr Infect Dis J. 2009;28:254-5.
3. Valenzuela PM, Majerson D, Tapia JL, Talesnik E. Syndrome of periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) in siblings. Clin Rheumatol. 2009;28:1235-7.
4. Akelma AZ, Cizmeci MN, Kanburoglu MK, Mete E, Bozkaya D, Tufan N, et al. Is PFAPA syndrome really a sporadic disorder or is it genetic? Med Hypotheses. 2013;81:279-81.
5. Cheung MS, Theodoropoulou K, Lugrin J, Martinon F, Busso N, Hofer M. Periodic Fever with Aphthous Stomatitis, Pharyngitis, and Cervical Adenitis Syndrome Is Associated with a CARD8 Variant Unable To Bind the NLRP3 Inflammasome. J Immunol. 2017;198:2063-9.
6. Glomba-Kraszewska B, Matkowska-Kocjan A, Szenborn L. The pathogenesis of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome: a review of current research. Mediators Inflamm. 2015;2015:563876.
7. Stojanov S, Hoffmann F, Kéry A, Renner ED, Hartl D, Lohse P, et al. Cytokine profile in PFAPA syndrome suggests continuous inflammation and reduced anti-inflammatory response. Eur Cytokine Netw. 2006;17:90-7.
8. Stojanov S, Lapidus S, Chitkara P, Feder H, Salazar JC, Fleisher TA, et al. Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) is a disorder of innate immunity and Th1 activation responsive to IL-1 blockade. Proc Natl Acad Sci U S A. 2011;108:7148-53.
9. Grimwood C, Kone-Paut I, Piram M, Rossi-Semerano L, Hentgen V. Health-related quality of life in children with PFAPA syndrome. Orphanet J Rare Dis. 2018;13:132.
10. Thomas KT, Feder HM Jr, Lawton AR, Edwards KM. Periodic fever syndrome in children. J Pediatr. 1999;135:15-21.
11. Besci Ö, Başer D, Öğülür İ, Berberoğlu AC, Kıykım A, Besci T, et al. Reference values for T and B lymphocyte subpopulations in Turkish children and adults. Turk J Med Sci. 2021;51:1814-24.
12. Hofer M, Pillet P, Cochard MM, Berg S, Krol P, Kone-Paut I, et al. International periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis syndrome cohort: description of distinct phenotypes in 301 patients. Rheumatology (Oxford). 2014;53:1125-9.
13. Rydenman K, Fjeld H, Hätting J, Berg S, Fasth A, Wekell P. Epidemiology and clinical features of PFAPA: a retrospective cohort study of 336 patients in western Sweden. Pediatr Rheumatol Online J. 2022;20:82.
14. Yıldız M, Haslak F, Adrovic A, Ülkersoy İ, Gücüyener N, Şahin S, et al. Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis Syndrome: A Single-Center Experience. Turk Arch Pediatr. 2022;57:46-52.

15. Manthiram K, Nesbitt E, Morgan T, Edwards KM. Family History in Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis (PFAPA) Syndrome. Pediatrics. 2016;138:e20154572.
16. Adrovic A, Sahin S, Barut K, Kasapcopur O. Familial Mediterranean fever and periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome: shared features and main differences. Rheumatol Int. 2019;39:29-36.
17. Rigante D, Vitale A, Natale MF, Lopalco G, Andreozzi L, Frediani B, et al. A comprehensive comparison between pediatric and adult patients with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenopathy (PFAPA) syndrome. Clin Rheumatol. 2017;36:463-8.
18. Dytrych P, Krol P, Kotrova M, Kuzilkova D, Hubacek P, Krol L, et al. Polyclonal, newly derived T cells with low expression of inhibitory molecule PD-1 in tonsils define the phenotype of lymphocytes in children with Periodic Fever, Aphtous Stomatitis, Pharyngitis and Adenitis (PFAPA) syndrome. Mol Immunol. 2015;65:139-47.
19. Luu I, Sharma A, Guaderrama M, Peru M, Nation J, Page N, et al. Immune Dysregulation in the Tonsillar Microenvironment of Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis (PFAPA) Syndrome. J Clin Immunol. 2020;40:179-90.
20. Türkuçar S, Bülbül G, Ünsal E, Özer E, Erdağ TK, Erkoç E, et al. Exploring the immunological basis of periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome: immunohistochemical staining features of palatine tonsils. Clin Rheumatol. 2023;42:1911-6.
21. Manthiram K, Correa H, Boyd K, Roland J, Edwards K. Unique histologic features of tonsils from patients with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome. Clin Rheumatol. 2018;37:1309-17.
22. Wurster VM, Carlucci JG, Feder HM Jr, Edwards KM. Long-term follow-up of children with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome. J Pediatr. 2011;159:958-64.
23. Yazgan H, Gültekin E, Yazıcılar O, Sagun ÖF, Uzun L. Comparison of conventional and low dose steroid in the treatment of PFAPA syndrome: preliminary study. Int J Pediatr Otorhinolaryngol. 2012;76:1588-90.
24. Butbul Aviel Y, Harel L, Abu Rumi M, Brik R, Hezkelo N, Ohana O, et al. Familial Mediterranean Fever Is Commonly Diagnosed in Children in Israel with Periodic Fever Aphthous Stomatitis, Pharyngitis, and Adenitis Syndrome. J Pediatr. 2019;204:270-4.
25. Yildiz M, Adrovic A, Ulkersoy I, Gucuyener N, Koker O, Sahin S, et al. The role of Mediterranean fever gene variants in patients with periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome. Eur J Pediatr. 2021;180:1051-8.
26. Celiksoy MH, Ogur G, Yaman E, Abur U, Fazla S, Sancak R, et al. Could familial Mediterranean fever gene mutations be related to PFAPA syndrome? Pediatr Allergy Immunol. 2016;27:78-82.
27. Butbul Aviel Y, Tatour S, Gershoni Baruch R, Brik R. Colchicine as a therapeutic option in periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) syndrome. Semin Arthritis Rheum. 2016;45:471-4.
28. Garavello W, Romagnoli M, Gaini RM. Effectiveness of adenotonsillectomy in PFAPA syndrome: a randomized study. J Pediatr. 2009;155:250-3.
29. Licameli G, Lawton M, Kenna M, Dedeoglu F. Long-term surgical outcomes of adenotonsillectomy for PFAPA syndrome. Arch Otolaryngol Head Neck Surg. 2012;138:902-6.
30. Burton MJ, Pollard AJ, Ramsden JD, Chong LY, Venekamp RP. Tonsillectomy for periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome (PFAPA). Cochrane Database Syst Rev. 2019;12:CD008669.