Cumhuriyet Medical Journal, 45(3): 73-78, 2023
DOI: http://dx.doi.org/10.7197/cmj.1351454

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

Childhood PFAPA Syndrome Cases in a University Hospital in Turkey: A 10-Year Analysis

Cemile Ece ÇAĞLAR ŞİMŞEK[1*], Mahmut EKİCİ[2]

[1] *Sivas Cumhuriyet University, Medical Facuty, Department of Pediatrics, Sivas, Turkey*

[2] *Sivas Medicana Hospital, Department of Pediatrics, Sivas, Turkey.*

**Corresponding author*

Research Article

History

Received: 07/04/2023
Accepted: 26/09/2023

ABSTRACT

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is characterized by recurrent fever attacks every 3-6 weeks lasting 3-6 days, associated with at least one of the three main symptoms. This study aimed to evaluate the demographic, clinical features, laboratory findings, and effectiveness of the applied treatment in patients with PFAPA syndrome.

A total of 73 patients diagnosed with PFAPA syndrome, aged between 0-18 years, who presented to Sivas Cumhuriyet University Hospital Pediatric Outpatient Clinic between 01.01.2012 and 31.12.2022, were included in this study. Demographic data such as age, gender, symptoms, laboratory findings, treatment and efficacy of the treatment were analysed.

Out of the 73 patients, 34 (46.6%) were female and 39 (53.4%) were male. The mean and median age at diagnosis were 3.85±1.47 years and 3.30 (1.1-7.5) years, respectively. The most common presenting complaint was fever. Fever was present in 64 (87.6%) of the 73 patients. Pharyngitis was observed in 56 (76.7%) patients, cervical adenitis in 26 (35.6%), cryptic tonsillitis in 12 (16.5%), and aphthous stomatitis in 15 (20.6%). Leukopenia and neutropenia were not detected in patients at the time of diagnosis. Neutrophilia was observed in 59 (80.8%) patients, and leukocytosis in 64 (87.7%) patients. Prior to treatment, CRP levels were found to be higher than the reference value of 8 mg/L in all patients. Prior to treatment, ESR values were within normal range (lower than 20 mm/h) in 10 (13.7%) patients and higher than 20 mm/h in 63 (86.3%) patients. Tonsillectomy was performed in 10 (13.7%) of 73 patients.

The possibility of PFAPA syndrome should be considered in the differential diagnosis of patients younger than 5 years of age who present with recurrent episodes of fever and tonsillitis and whose fever does not decrease despite antibiotic treatment. In this way, early diagnosis can be made, unnecessary antibiotic use can be avoided and thus unnecessary investigations, treatment and hospitalisations can be prevented.

Keywords: Periodic fever, PFAPA, children

Türkiye'de Bir Üniversite Hastanesindeki Çocukluk Çağı PFAPA Sendromu Vakaları: 10 Yıllık Analiz

Süreç

Geliş: 07/04/2023
Kabul: 26/09/2023

ÖZ

Ateş, aftöz stomatit, farenjit ve servikal adenit (PFAPA) sendromu , üç ana belirtiden en az biriyle ilişkili, her 3-6 haftada bir tekrarlayan, 3-6 gün süren ateş atakları ile karakterizedir. Bu çalışmada, PFAPA sendromu hastalığının demografik, klinik özellikleri,laboratuvar bulguları ve uygulanan tedavinin etkinliğinin değerlendirilmesi amaçlanmıştır.

Bu çalışmaya Sivas Cumhuriyet Üniversitesi Hastahanesi Pediatri Polikliniğine 01.01.2012-31.12.2022 tarihleri arasında başvuran 0-18 yaş grubu hastalardan PFAPA Sendromu tanısı alan 73 hasta dahil edildi. Çalışmaya dahil edilecek hastalarda yaş, cinsiyet gibi demografik verileri, semptomlar, laboratuvar bulguları, uygulanan tedavi ve tedavinin etkinliği incelendi.

Yetmiş üç hastanın 34'ü (%46,6) kız , 39'u (%53,4) erkekti. Ortalama ve medyan tanı yaşı ise sırasıyla 3,85±1,47 yıl ve 3,30 (1,1–7,5) yıldı. En yaygın başvuru şikayeti ateş idi. 73 hastadan 64'ünde (%87,6) ateş şikayeti mevcuttu. Hastaların 56'sında (%76,7) farenjit, 26'sında (%35,6) servikal lenfadenit, 12'sinde (%16,5) kriptik tonsilit, 15'inde (%20,6) aftöz stomatit mevcuttu. Tanı anında hastalarda lökopeni ve nötropeni saptanmadı. Nötrofil yüksekliği 59 (%80,8) hastada ve lökositoz 64 (%87,7) hastada görüldü. Tedavi öncesi tüm hastaların CRP değeri referans değeri olan 8 mg/L'den yüksek bulundu. Tedavi öncesi ESH değeri hastaların 10 (% 13,7)'unda normal değerlerde (20 mm/h'den düşük), 63 (% 86,3) hastada ise 20 mm/h'den yüksekti. 73 hastadan 10'una (%13,7) tonsillektomi uygulandı.

Tekrarlayan ateş ve tonsilit atakları ile getirilen, antibiyotik tedavisine rağmen ateşi düşmeyen 5 yaşından küçük hastalarda ayırıcı tanıda PFAPA sendromu olasılığı göz önünde bulundurulmalıdır. Bu sayede erken tanı konabilir, gereksiz antibiyotik kullanımından kaçınılabilir ve böylelikle gereksiz tetkik, tedavi ve hastaneye yatışların önüne geçilebilir.

Anahtar sözcükler: Periyodik ateş, PFAPA, çocuklar

[1] *ececaglar1987@hotmail.com* *https://orcid.org/ 0000-0002-4860-6613* [2] *drmekici@yahoo.com* *https://orcid.org/ 0000-0001-7434-578X*

How to Cite: Şimşek Ç, Ekici M (2023) Childhood PFAPA Syndrome Cases in a University Hospital in Turkey: A 10-Year Analysis,Cumhuriyet Medical Journal, September 2023, 45(3): 73-78

Introduction

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is characterized by recurrent fever attacks lasting 3-6 days, occurring every 3-6 weeks, and associated with at least one of the three main symptoms.[1,3] Fever attacks usually have minimal or no response to antipyretic medications. Patients are asymptomatic between attacks and have normal growth and development. Other symptoms that may occur during fever attacks include headache, joint pain, myalgia, nausea, vomiting, and abdominal pain [4,6]. PFAPA syndrome usually begins before school age and lasts until around 10-11 years old, although some cases are diagnosed in adults. Despite being the most common cause of recurrent fever in children, the true incidence of PFAPA syndrome is unknown due to the rarity of its diagnosis and frequent misdiagnosis, such as bacterial tonsillitis, leading to unnecessary administration of antibiotics [7,8]. The genetic origin of PFAPA syndrome is a matter of debate and several studies suggest that inflammation-related genes may play a role in this autoinflammatory syndrome. Although the exact pathogenesis is unknown, there is an increase in inflammatory cytokines in the blood and affected tissues and dysregulation of the receptors of these cytokines [9,10]. The diagnosis of PFAPA syndrome is based on clinical criteria and excluding other possible causes of recurrent fever in children [11]. During febrile episodes, neutrophils, acute phase reactants and white blood cells are elevated. All inflammatory parameters are normal between attacks [11,12]. In the treatment of PFAPA syndrome attacks, the administration of a single or two doses of steroids during an attack leads to a dramatic improvement in symptoms [13,14]. The aim of this study was to evaluate the demographic and clinical characteristics, laboratory findings and efficacy of the treatment of PFAPA syndrome.

Material Method

In this study, 73 patients aged 0-18 years who were admitted to Sivas Cumhuriyet University Hospital Paediatrics Outpatient Clinic between 01.01.2012-31.12.2022 and diagnosed with PFAPA Syndrome were included. Demographic data such as age, gender, symptoms, laboratory findings, treatment and efficacy of the treatment were analysed. In complete blood count, leukocyte, lymphocyte, neutrophil, platelet and haemoglobin values were evaluated according to normal values determined according to age. Normal platelet count is 150-450x109 litres. Platelet count below 150x109 /L was considered for thrombocytopenia. Platelet count above 450x109 /L was considered for thrombocytosis. For anaemia, the guidelines of the National Health and Nutrition Examination Survey (NHANES-III) were used as the basis. Leukopenia was defined as a total leukocyte count <4,000/µL. Neutropenia was defined as a total neutrophil count <1500/µL. For C-Reactive Protein (CRP) analyzed in the Biochemistry Laboratory of the Cumhuriyet University Faculty of Medicine Research and Application Hospital, the normal values are 0-8 mg/L. For Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT), the normal values are 0-40 U/L. For Erythrocyte Sedimentation Rate (ESR), the normal values are between 0-20 mm/hour.

Ethics of the Study

The study was approved by the Clinical Research Ethics Committee of Sivas Cumhuriyet University (2022-12/10) and conducted in accordance with the principles of the Helsinki Declaration.

Statistical Analysis

SPSS Windows Version 22 package program was used for statistical analysis. The data obtained from our study were loaded into the SPSS 22.0 programme and Wilcoxon test was used to compare two measurement values obtained at different times in the same individuals since the data did not conform to normal distribution, and Chi Square Test and Fisher Exact Test were used in 2x2 layouts and multi compartment layouts in the evaluation of the data obtained by counting. Our data were expressed as arithmetic mean, median, standard deviation, number of individuals and % (percentage) in the tables and the error level was taken as 0.05.

Results

Out of seventy-three patients, thirty-four (46.6%) were female and thirty-nine (53.4%) were male. The mean and median age of diagnosis were 3.85±1.47 years and 3.30 (1.1-7.5) years, respectively. The most common presenting complaint was fever. Among the seventy-three patients, sixty-four (87.6%) had a complaint of fever. When we referred to the period in which fever attacks occurred and the frequency of the attacks, we found information on forty-seven patients in their files, which was as follows: twenty-five (34.2%) patients (53.19% of the forty-seven patients) had attacks every thirty days, and twenty-two (30.1%) patients (46.80% of the forty-seven patients) had attacks between fifteen and thirty days. In the patients, fifty-six (76.7%) had

pharyngitis, twenty-six (35.6%) had cervical lymphadenitis, twelve (16.5%) had cryptic tonsillitis, and fifteen (20.6%) had aphthous stomatitis (Table 1).

Table 1. Demographic characteristics, clinical findings and symptoms of the patients

Gender	**n (%)**
Male	39 (53,4)
Girl	34 (46,6)
Age at diagnosis	**Year**
Mean±SD	3,85 ±1,47
Median (range)	3,30 (1,1-7,5)
Symptoms	**n (%)**
Fever	64 (87,6)
Abdominal pain	12 (16,4)
Sore throat	11 (15)
Vomiting	8 (11)
Sores in the mouth	6 (8,2)
Nausea	4 (5,5)
Cough	2 (2,7)
Results	**n (%)**
Fever	64 (87,6)
Pharyngitis	56 (76,7)
Cervical adenitis	26 (35,6)
Aphthous stomatitis	15 (20,6)
Cryptic tonsillitis	12 (16,5)

* SD: standard deviation

All patients received outpatient treatment. Seventeen (23.3%) patients had a history of frequent tonsillitis attacks in their first-degree relatives. During the attacks, 1 mg/kg of intravenous/intramuscular methylprednisolone was used for treatment, and all patients had a dramatic response. Laboratory tests were examined before (during the attack) and after treatment. Before treatment (during the attack), the mean white blood cell count was 14.55±4.26 /mm3, and the mean neutrophil count was 10.04±3.65 /mm3. After treatment, the mean white blood cell count was 8.45±2.10 /mm3, and the mean neutrophil count was 4.41±1.81 /mm3. Leukopenia and neutropenia were not detected in patients at the time of diagnosis. Neutrophilia was observed in fifty-nine patients (80.8%), and leukocytosis was observed in sixty-four patients (87.7%). The number of patients with normal leukocyte count was nine (12.3%), and the number of patients with normal neutrophil count was thirteen (17.8%). After treatment, no cases of leukopenia or neutropenia were observed. Thirty-three patients (45.2%) had normal white blood cell count, and six patients (8.2%) had leukocytosis. After treatment, the neutrophil count was normal in thirty-seven patients (50.7%) and high in two patients (2.7%).

Before treatment (during the attack), the average CRP value was 69.17±48.60 mg/dl, and the average ESR value was 36.44±16.16 ml/h. After treatment, CRP values were examined in 34 patients and ESR values in 24 patients. The average CRP value was 7.30±7.01 mg/dl, and the average ESR value was 11.33±4.10 ml/h. The biochemical values of the patients, including liver and kidney function tests, were normal before and after treatment (Table 2 and Table 3). Before treatment (during the attack), the CRP value of all patients (100%) was found to be higher than the reference value of 8 mg/L. After treatment, CRP value was found to be lower, i.e., normal, than the reference value of 8 mg/L in 24 (32.9%) patients, and higher in 10 (13.7%) patients. Before treatment, the ESR value was within the normal range (less than 20 mm/h) in 10 (13.7%) patients, and higher than 20 mm/h in 63 (86.3%) patients. After treatment, the ESR value was lower than the reference value of 20 mm/h in 24 (32.9%) patients, and there were no patients with high ESR values. Tonsillectomy was performed in 10 (13.7%) of 73 patients.

Table 2. Laboratory findings of the patients before treatment (during the attack)

Mean±SD	Median	Min.-max.	Total number of patients	
Leukocytes (/mm3)	14,55±4,26	13,61	6,07-26,89	73/73
Neutrophils (/mm3)	10,04±3,65	9,40	3,10-20,70	73/73
Haemoglobin (g/dl)	12,48±0,78	12,50	10,5-14,2	73/73
Platelets (/mm3)	318,47±83,80	312	179-596	73/73
ALT (U/L)	14,21±4,57	14	5-31	73/73
AST (U/L)	28,48±5,66	29	17-44	73/73
CRP (mg/dl)	69,17±48,60	73,05	14,51-247	72/73
ESR (mm/hour)	36,44±16,16	33	14-90	73/73

max: maximum, min: minimum, SD: standard deviation

Table 3. Laboratory findings of the patients after treatment

Mean±SD	Median	Min.-max.	Total number of patients	
Leukocytes (/mm3)	8,45±2,10	8,33	4,13-14,11	39/73
Neutrophils (/mm3)	4,41±1,81	4,38	1,64-8,95	39/73
Hemoglobin (g/dl)	12,81±0,87	12,7	11,2-15,8	39/73
Platelets (/mm3)	339,74±80,99	324	195-587	39/73
ALT (U/L)	17,04±5,25	16	17-40	52/73
AST (U/L)	26,30±6,19	25,50	10-30	50/73
CRP (mg/dl)	7,30±7,01	5,51	1,09-34,20	34/73
ESR (mm/hour)	11,33±4,10	11,50	5-19	24/73

max: maximum, min: minimum, SD: standard deviation

Discussion and Conclusion

Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis (PFAPA) syndrome is a disease characterized by recurrent fever attacks lasting 3-6 days, occurring every 3-6 weeks and associated with at least one of the three main symptoms [1,3]. In PFAPA syndrome, no gender-specific identification has been made, and in our study, the number of male patients with PFAPA syndrome was 39 (53.4%), which was higher. The majority of cases occur before the age of 5 [15]. In this study, the mean and median age of diagnosis for both girls and boys were 3.85 ± 1.47 years and 3.30 (1.1–7.5) years, respectively. PFAPA syndrome is the most common cause of recurrent fever in children [1]. In our study, the most common complaint was also fever. Fever was present in 64 out of 73 patients (87.6%). While the frequency of aphthous stomatitis in PFAPA syndrome cases is reported to range between 40% and 80% in the literature, aphthous stomatitis was present in 15 (20.6%) patients in our study [1,16]. This result may be related to the inability of young children to describe their condition and the less painful nature of the ulcers. In the literature, the attack interval is reported to recur every 3-6 weeks with an average interval of 30 days [1-3]. In our study, the duration of fever attacks was 30 days in 25 (34.2%) patients and between 15 and 30 days in 22 (30.1%) patients. Another notable finding in our study was that 17 patients (23.3%) had a history of frequent tonsil attacks in their first-degree relatives. It has been reported in studies that PFAPA cases are familial [17,18]. Leukocytosis and neutrophilia were present in our patients' laboratory findings.

Consistent with our study data, it has been reported that in PFAPA, inflammation occurs as a result of activation of the innate immune system, and neutrophil-leukocyte counts increase during febrile periods [1]. Inflammatory variables such as CRP and ESR increase during the attack period [19]. In our study, the CRP value of all patients before treatment (during the attack period) was found to be higher than the reference value of 8 mg/L. The ESR value before treatment (during the attack period) was higher than 20 mm/h in 63 patients (86.3%). Biochemical values, including liver and kidney function tests, were normal in patients during the attack period.

In the literature, it has been indicated that steroid treatment in PFAPA syndrome promptly stops flare-ups [20]. In our study, all of our patients (100%) had a dramatic response to methylprednisolone treatment. Tonsillectomy was performed in 10 of 73 patients (13.7%) in our study. Tonsillectomy and corticosteroids administered during attacks continue to be the most effective treatment [21]. The main limitations of our study are its retrospective design and the short duration of patient follow-up. The short follow-up period did not allow us to monitor the clinical response in patients who underwent tonsillectomy. In conclusion, the possibility of PFAPA syndrome should be considered in the differential diagnosis of patients younger than 5 years of age who present with recurrent fever attacks and whose fever does not decrease despite antibiotic treatment. When PFAPA syndrome is diagnosed, methylprednisolone treatment should be administered at the time of the attack. In this way, early diagnosis can be made, unnecessary antibiotic use can be avoided and unnecessary investigations, treatment and hospitalisations can be prevented.

Conflict of Interest and Financial Disclosure

The authors declare no conflicting interests. The authors also declare that they did not receive any financial support for this study.

References

1. Lazea C, Damian L, Vulturar R, Lazar C. PFAPA Syndrome: Clinical, Laboratory and Therapeutic Features in a Single-Centre Cohort. Int J Gen Med. 2022 Aug 29;15:6871-80.

2. Marshall GS, Edwards KM, Butler J, Lawton AR. Syndrome of periodic fever, pharyngitis, and aphthous stomatitis. J Pediatr. 1987;110:43–46.

3. Otar Yener G, Aktaş İ, Altıntaş Meşe C, Çakan M. Does having MEFV gene sequence variants affect the clinical course and colchicine response in children with PFAPA syndrome? Eur J Pediatr. 2022 Nov 15:1-7.

4. Cochard M, Clet J, Le L, et al. PFAPA syndrome is not a sporadic disease. Rheumatology. 2010;49:1984–87.

5. Dammeyer KL, Schneider A, April MM, Kahn PJ. Synchronous disease onset and flares in siblings with PFAPA. Pediatr Rheumatol Online J. 2022 Oct 5;20(1):87.

6. Rydenman K, Fjeld H, Hätting J, Berg S, Fasth A. Epidemiology and clinical features of PFAPA: a retrospective cohort study of 336 patients in western Sweden. Wekell P.Pediatr Rheumatol Online J. 2022 Sep 15;20(1):82.

7. Kanık A, Eliaçık K, Kanık ET, Demirçelik Y, Demir BK. A comparative study for the clinical features in children with PFAPA syndrome who were diagnosed before and after the age of five. Int J Pediatr Otorhinolaryngol. 2022 Jul;158:111153.

8. Banday AZ, Joshi V, Arora K,et al. Challenges in the diagnosis of periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome in developing countries-A decade of experience from North India. Front Immunol. 2022 Sep 20;13:958473.

9. Espin Diaz PC, Singh K, Kher P, et al. Periodic Fever in Children: Etiology and Diagnostic Challenges. Cureus. 2022 Jul 25;14(7):e27239.

10. Kaynak D, Yildiz M, Sahin S, et al. NLRP3 gene variants and serum NLRP3 levels in periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome. Clin Rheumatol. 2022 Sep 10. doi: 10.1007/s10067-022-06370-1. Online ahead of print.

11. Okamoto CT, Chaves HL, Schmitz MJ. Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome in children: a brief literature review. Rev Paul Pediatr. 2022 Jun 10;40:e2021087.

12. Førsvoll JA, Onymar K. C-reactive protein in the periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome. Acta Paediatr. 2007. PMID: 17937691.
13. Levinsky Y, Butbul Aviel Y, Ahmad SA, et al. PFAPA flares observed during COVID outbreak: can emotional stress trigger PFAPA attacks? A multicenter cohort study. Pediatr Rheumatol Online J. 2022 Jul 8;20(1):46.
14. Sopeña B, Araújo O, Freire M, Barrera-López L, José HR. Efficacy of Canakinumab in a Patient With Adult-Onset Glucocorticoid-Resistant Periodic Fever, Aphthous Stomatitis, Pharyngitis and Cervical Adenitis (PFAPA) Syndrome. Mod Rheumatol Case Rep. 2022 May 27:rxac043.
15. Wang A, Manthiram K, Dedeoglu F, Licameli GR. Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome: A review. World J Otorhinolaryngol Head Neck Surg 2021 Jun 27;7(3):166-73.

16. Yıldız M, Haslak F, Adrovic A, Ülkersoy İ, Gücüyener N, et all. Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis Syndrome: A Single-Center Experience. Turk Arch Pediatr 2022 Jan;57(1):46-52.doi: 10.5152/TurkArchPediatr.2021.21229.

17. Soriano A, Soriano M, Espinosa G, et al. Autoinflammatory Diseases and PFAPA Syndrome: Evidence-Based Approach and Proposal of a Practical Guide. Front Immunol 2020 Jun 3;11:865 doi: 10.3389/fimmu.2020.00865. eCollection 2020.

18. Wekell P, Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome PFAPA syndrome. Presse Med 2019 Feb;48(1 Pt 2):e77-e87.doi:10.1016/j.lpm.2018.08.016. Epub 2019 Jan 22.

19. Rydenman K, Berg S, Karlsson-Bengtsson A, Fasth A, Wekell P. PFAPA syndrome - An important differential diagnosis in children with recurrent fever. Lakartidningen 2019 Oct 29;116:FP9U.

20. Gaggiano C, Rigante D, Sota J, Grosso S, Cantarini L. Treatment options for periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome in children and adults: a narrative review. Clin Rheumatol 2019 Jan;38(1):11-17.doi: 10.1007/s10067-018-4361-2.

21. Batu ED, Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome: main features and an algorithm for clinical practice. Rheumatol Int 2019 Jun;39(6):957-970.doi: 10.1007/s00296-019-04257-0.

22. 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 Dec 30;12(12):CD008669.doi:10.1002/14651858.CD008669.pub3.