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PFAPA Sendromu Tanılı Hastaların Klinik ve Laboratuvar Özelliklerinin Değerlendirilmesi

Evaluation of Clinical and Laboratory Characteristics of Patients with PFAPA Syndrome

Vildan Güngörer(0000-0002-9838-2603)[1], Alaaddin Yorulmaz(0000-0001-5478-1197)[2], Şükrü Arslan (0000-0001-5632-8273)[1]

[1]Selçuk Üniversitesi Tıp Fakültesi, Çocuk Romatoloji Bilim Dalı, Konya

[2]Selçuk Üniversitesi Tıp Fakültesi, Çocuk Sağlığı Ve Hastalıkları Bilim Dalı, Konya

Sorumlu yazar yazışma adresi:

Vildan GÜNGÖRER: [1]Selçuk Üniversitesi Tıp Fakültesi, Çocuk Romatoloji Bilim Dalı, Konya, Türkiye

E-mail:
vildan_61183@hotmail.com

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ÖZ

GİRİŞ ve AMAÇ: Giriş-Amaç: Periyodik ateş, aftöz stomatit, farenjit, adenit (PFAPA) sendromu en yaygın görülen periyodik ateş sendromudur. Bu çalışmanın amacı, PFAPA sendromu tanısı olan hastaların atak sırasında klinik ve laboratuvar bulgularını ve tedavilere verilen yanıtı değerlendirmektir.

YÖNTEM ve GEREÇLER: Bu çalışmaya tekrarlayan ateş ve boğaz enfeksiyonu nedeniyle çocuk romatoloji polikliniği tarafından PFAPA tanısı konulmuş 63 hasta dahil edildi. Hastaların demografik, klinik ve labaratuvar verileri hasta dosyalarından retrospektif olarak değerlendirildi.

BULGULAR: 42 (%66,7) hasta erkek, 21 (%33,3) hasta kızdı. Şikayetlerin başlama yaşı ortalama 2,72±1,59 yaş idi. Tanı koyulana kadar geçen süre ortalama 1,71 ± 1,28 yaştı. Bütün hastalarda dikkat çekici bulgu olarak ateş düşürücüye yanıt vermeyen dirençli yüksek ateş mevcuttu. Hastaların 59' unda (%93,7) lenfadenit, 56' sında (%88,9) aftöz stomatit mevcuttu. Tetkiklerinde lökositoz, artmış C-reaktif protein ve sedimantasyon gözlendi. Steroid tedavisi ile ateşin ortalama 2.24 ± 1.13 saatte düştüğü gözlendi. Bir diğer dikkat çekici bulgu ise steroid tedavisi ile 24 saatin sonunda exudatif tonsillit bulgularının gerilediği idi.

TARTIŞMA ve SONUÇ: PFAPA sendromuna ait semptom ve bulgular pediatrik yaş grubunda en sık görülen semptom ve bulgulardandır. PFAPA sendromu farkındalığı klinisyenlerde arttıkça hastalar gereksiz laboratuvar tetkikleri ve tedavilerden korunmuş olacaktır.

Anahtar Kelimeler: PFAPA syndrome, steroid, tedavi

ABSTRACT

INTRODUCTION: Periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA) syndrome is the most common periodic fever syndrome. The aim of this study was to evaluate the clinical and laboratory findings of patients with PFAPA syndrome at the time of the attack and the response to the given treatments.

MATERIALS and METHODS: Sixty-three individuals that applied to the pediatric rheumatology policlinic due to recurrent fever and throat infection and diagnosed with PFAPA syndrome were enrolled in this study. Patients' folders were evaluated retrospectively concerning demographic, clinical and laboratory data.

RESULTS: Forty-two (66.7%) of the patients were male, 21 (33.3%) were female. The age of onset of complaints was 2.72±1.59 years. The average delay in diagnosis was 1.71 ± 1.28 years. The remarkable finding which was seen all of our patients was the high fever. Lymphadenitis was detected in 59 (93.7%) of the patients and aphthous stomatitis was found in 56 (88.9%) of the patients. As a laboratory finding, leukocytosis, the increase in C-reactive protein and sedimentation was observed in patients. Fever decreased within a mean of 2.24 ± 1.13 hours after steroid treatment. Another remarkable finding after the first steroid treatment was the resolution of exudative tonsillitis 24 hours after the treatment.

CONCLUSIONS: Signs and symptoms of PFAPA syndrome are among the most common signs and symptoms in pediatric outpatient clinics. With increased awareness of PFAPA syndrome in clinicians, patients will be prevented from unnecessary laboratory procedures and medical treatments.

Key words: PFAPA syndrome, steroid, treatment

INTRODUCTION

Fever is one of the most frequent clinical findings among children and it is one of the most common causes of admission to the hospital. While fever is primarily caused by viral infections; the recurrence of fever without infection may originate due to many hereditary or non-hereditary causes (1,2). Furthermore, various diseases with non-infectious causes, recurrent fever attacks and healthy periods between attacks have been identified and grouped under the name of periodic fever syndromes. The physicians encounter recurrent high fever conditions quite frequently, and despite all the tests and treatments, rare cases without any response to the treatment can be observed. The most important characteristic of this condition is that the fever has regular intervals, the fever is non-responsive to antibiotherapy, and child does not exhibit any symptoms between the attacks.

Periodic fever syndromes are a group of diseases with spontaneous autoinflammation that presents without any microorganism stimulation. There are autoinflammation attacks that tend to relapse and cause localized inflammation on the serosal and synovial surfaces, as well as on the skin. In these diseases, apart from the fever, respiratory system, gastrointestinal system, musculoskeletal system, and dermatological findings are seen (3).

The most common recurrent fever syndromes in childhood are PFAPA (Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis) syndrome, Familial Mediterranean Fever (FMF), hyper IgD syndrome, systemic onset juvenile idiopathic arthritis, Behçet's disease, and cyclic neutropenia. PFAPA syndrome is an idiopathic disease that is characterized by sudden onset of high fever, aphthous stomatitis, pharyngitis, and cervical lymphadenopathy attacks and the periodic recurrence of these symptoms. The characteristic feature of the syndrome is sudden onset of fever, with fever temperatures that can reach 41°C, and which lasts for 3–6 days, while occurring at regular intervals every 3–6 weeks (4). This syndrome is more common in males younger than five years and it follows a benign course. Recurrent fever episodes may last for many years; however, as the child grows, the time between these episodes increases. This syndrome usually heals spontaneously within few years, without causing any sequalae in the long term (5). Additional manifestations have occasionally been reported including malaise, nausea, vomiting, headache, arthralgia, abdominal pain, eruption, cough, diarrhea, and hepatosplenomegaly (6,7). The patients are observed to be healthy between the episodes and exhibit normal growth (8,9).

PFAPA syndrome was first described by Marshall et al. on 12 children patients in 1987 (7). PFAPA syndrome is diagnosed clinically and by the exclusion of the other diseases. Thomas et al. suggested the first proposed diagnostic criterion for easier diagnosis in 1989 (10). According to this criterion, the association of one or more of the symptoms of aphthous stomatitis, pharyngitis and cervical adenitis with regularly recurring fevers in children less than 5 years of age suggests PFAPA syndrome (10,11). The dramatic response to single-dose oral steroid administration is unique to PFAPA syndrome and may be used as a diagnostic criterion (11). This syndrome should be well known to pediatricians due to the lack

of disease-specific laboratory results and furthermore the findings that are observed in the disease are the general symptoms of the common diseases seen in children.

The aim of this study was to evaluate the clinical and laboratory findings of patients with PFAPA syndrome at the time of the attack and the response to the given treatments. In addition, it was presented in order to draw attention to PFAPA syndrome; since it is not recognized clearly as a syndrome, it still causes unnecessary antibiotic use, even though the incidence of the disease is not rare in patients who had recurrent tonsillopharyngitis attacks accompanied by fever.

MATERIALS and METHODS

Sixty-three individuals that applied to the pediatric rheumatology policlinic due to recurrent fever and throat infection and who were diagnosed with PFAPA syndrome were enrolled in this study. The study was approved by the Clinical Research Ethics Committee of Selçuk University (protocol no: 2019/208). Diagnosis of the PFAPA syndrome with the initial proposed diagnostic criteria included the following features: (1) recurring fever episodes (>38.3°C); (2) regular timing of episodes; (3) early age of onset (<5 years); (4) constitutional symptoms in the absence of upper respiratory infection with at least one symptom being aphthous stomatitis, cervical adenitis, or pharyngitis; (5) asymptomatic intervals between episodes; (6) normal growth and development; and (7) exclusion of cyclic neutropenia and other periodic fever syndromes on the basis of history or laboratory test results (5, 12). Variations of these diagnostic criteria have been utilized allowing for onset at older ages (11).

Patients' folders were evaluated retrospectively concerning demographic, clinical and laboratory data. The obtained data was collected digitally and the information of the patients was not used for any other purposes.

The patients with chronic infection, immune deficiency syndromes, malignity, autoimmune diseases, and periodic fever syndromes (Familial Mediterranean Fever and cyclic neutropenia, etc.) were excluded from the study. Moreover, the patients that had bacterial reproduction on their throat culture were also not included in the study. Lower neutrophil count than 1500 C/uL was accepted as neutropenia for the complete blood cell count analyses from patients.

Gender, age of the diagnosis, clinical findings, characteristics of the attacks, the response to corticosteroid treatment during attacks, the presence of other findings accompanying during attacks, demographic data such as family history, clinical data and the laboratory findings of the patients were investigated. The clinical and hematologic values of the patients were recorded during the attack. The patients were observed at least four times during the attack to monitor the clinical features and their response to steroid treatment. The fever of patients was recorded with an electronic thermometer as centigrade degrees.

The laboratory test results were obtained from the blood drawn during the attack period from the patients with PFAPA syndrome. Complete blood count test was performed in one hour after collecting the blood

to the tubes with EDTA using the hemogram device Sysmex XE-2100 following the manufacturer's instructions. Number of white blood cell counts (C/uL), neutrophil count (C/uL), lymphocyte count (C/uL), hemoglobin (gr / dL) (Hb), platelet count (C/uL), mean platelet volume (MPV) (fL), platelet distribution width (PDW) (fL), platelet (PCT) (µg/L), C-reactive protein (CRP) (mg/ dL) and erythrocyte sedimentation rate (ESR) values were recorded.

Statistical analyse: SPSS 21.0 (IBM SPSS Statistics 21) statistical software package was used to analyze data that was obtained from the study. The distribution of the variables was checked by means of histograms and Kolmogorov-Smirnov and Shapiro-Wilk tests to explore the normality and adequate transformations were performed in case of skewness. Meta-data statistical methods were displayed as Mean±Standard Deviation (SD). When the comparison of two independent numerical variables had a normal distribution, then Student's T-test was used, and the Mann-Whitney U test was utilized if the comparison did not show normal distribution. The statistical significance level was set at $p < 0.05$ (bilateral).

RESULTS

Forty-five (66.7%) of the patients were male, 21 (33.3%) were female. The female-male ratio was 0.50. The ages of the patients were between 10-126 months. The demographic characteristics of the participants are shown in Table 1.

Table 1: Demographic characteristics of the study population

	Patients
Gender	**N %**
Male	42 66.7
Female	21 33.3
	Mean±SD (min-max)
Age (month)	53.33±24.46 (10-126)
The onset of the attacks (month)	32.71±19.17
The delay in diagnosis (month)	20.71±15.40 (3-60)
The duration of the attacks (day)	4.35±1.71 (1-10)
The frequency of the attacks (week)	4.04±2.48 (1-12)
Degree of fever (°C)	39.53 ± 0.60 (38.5- 41.2)

The mean age of onset of the attacks was 2.72±1.59 years. Onset time of the attacks according to gender was 1.78 ±0.38 years for females and 1.48±0.22 years for males, respectively. The average delay in diagnosis was 1.71 ± 1.28 years. Moreover, in 7 (11.1%) patients, the onset of the first attack was over 5 years old. The mean duration of attacks was 4.35 ± 1.71 days and the mean time between attacks was 4.04 ± 2.48 weeks. There was no statistically significant difference observed between female and male patients on the onset of the attacks, the time until diagnosis, the duration of the attacks, the frequency of the attacks, the duration of fever during attacks and the level of fever during their attacks ($p>0.05$) (Table 2).

Table 2: Clinical characteristics of patients follwed with PFAPA syndrome

	N	%
Periodic Fever	63	100
Adenitis	59	93.7
Aphthous Stomatitis	56	88.9
Weakness	48	76.2
Pharyngitis	42	66.7
Tonsillitis	40	63.5
Nausea-vomiting	27	42.8
Abdominal Pain	26	41.3
Headache	21	33.3
Joint Pain	19	30.2
Myalgia	11	17.5
Diarrhea	7	11.1
Rash	3	4.8

The remarkable finding which was observed in all of our patients was the high fever that was resistant to antipyretics that were used to mitigate the attacks. Lymphadenitis was detected in 59 (93.7%) patients and aphthous stomatitis was found in 56 (88.9%) patients. Tonsillitis was observed in 40 (%63.5) patients, and it was divided into exudative and non-exudative (at least grade 2 tonsillar hypertropia and hyperemia) groups. The clinical characteristics of the patients followed up with PFAPA syndrome are summarized in Table 3. Fifty-four patients (85.7%) used antibiotics and antipyretics together each time during fever attacks and they were nonresponsive to treatment. One (1.6%) of our patients had undergone tonsillectomy operation. The families of 10 (15.9%) patients, mentioned that they had similar complaints when they were in a similar age.

Table 3: Laboratory characteristics of patients with PFAPA syndrome

	Mean±SD	(Min-Max)
White Blood Cell (K/uL)	11784.13±3990.89	(4800-22500)
Neutrophil count (K/uL)	7332.51±4104.17	(950-19500)
Lymphocyte count (K/uL)	3257.35±1708.90	(610-9260)
NLR	3.42±3.85	(0.04-22.00)
Hemoglobin (g/dL)	11.79±0.98	(8.20-14.00)
MCV (fL)	76.52±4.91	(54.20-83.50)
Platelets count (K/uL)	344698.41±116872.36	(187000-937000)
Mean Platelet Volume	7.37±0.62	(6.22-8.70)
Platelet Distrubution Width	16.29±0.47	(15.17-18.20)
Sedimentation (mm/h)	25.36±18.01	(2-84)
CRP (mg/L)	45.83±48.20	(0.23-226.00)

TARTIŞMA

PFAPA syndrome, together with Familial Mediterranean Fever, is an important recurrent fever condition in our country. FMF often causes irregular intermittent recurrent fever and polyserositis attacks and does not respond to steroid treatment (13). Cyclic neutropenia is a disease characterized by regular intermittent recurrent fever and its clinical findings are very similar to PFAPA syndrome. In cyclic neutropenia, neutropenia attacks that recur for an average of 21 days and last for 3-6 days and spontaneously remittance of the attacks are seen (14). Neutropenia was not detected in the laboratory tests during the attacks and in the previous blood counts. Fever in Behçet's disease, which is characterized by aphthous ulcers on the oral mucosa, ulcers in the genital region, iridocyclitis and synovitis; in contrast to the fever in PFAPA syndrome, has irregular intervals between attacks and usually lasts more than one week. Moreover, the differential diagnosis between the various diseases that cause irregular high fever such as hyper IgD syndrome and systemic onset of juvenile rheumatoid arthritis should be taken into account. PFAPA syndrome, which does not cause any sequelae in the long term, is diagnosed clinically after the other causes of periodic fever have been excluded.

Although viral and autoimmune mechanisms have been proposed in the etiology, the exact cause is not known (7,14,15). The hereditary transition has not been reported (5). The dramatical response to prednisone suggests that fever is caused by dysregulation in cytokine production (16). Increased levels of CRP with the presence of increased IL-1 beta and IL-6 indicate that the etiology is based on an immunological mechanism (17). During febrile episodes, the elevated levels of cytokines of TNF-α, interferon Ɣ, interleukin-6 ve interleukin-1 β have been detected (18). In PFAPA syndrome, it has been

suggested that there may be an unexpected excessive response in the immunological response to the antigens or epitopes of infectious agents (15). In the conducted studies, IFN-γ and IL-2 production were significantly higher than healthy children.

It is known that PFAPA syndrome is more common in males (20,21). In our study 42 (66.7%) patients were male (female / male ratio: 0.50). Most cases with PFAPA are under the age of five (16,19,21). The onset of PFAPA syndrome in adulthood is extremely rare. In our study, in 7 (11.1%) of the patients, the onset of the first attack was over 5 years of age. This suggests that PFAPA Syndrome should be considered in the differential diagnosis in children over 5 years of age in the presence of periodic fever.

Growth and development are not affected in children with PFAPA (10,22). This parameter is one of the diagnostic criteria of the syndrome (5,11,16,23). In our study, all patients whose body weight was measured were between found to be between 3-97 percentile. The body weight of the majority of our patients (80.9%) was observed to be between 10-90 percentile. Our findings supported the literature.

Another important data regarding children with PFAPA is the absence of familial transmission. Although sibling cases have been reported in the literature, a genetic transmission has not been demonstrated (24). Femiano et al. in their study of 2008, reported that there is no genetic basis unlike the other periodic fever syndromes (19). A history of frequent throat infections, tonsillectomy/adenoidectomy and recurrent episodes of fever were questioned for the relatives of the participants. 15.9% of the patients had a positive family history. This high positive family history made us think that there might be a genetic transmission. FMF mutation analysis may be required for differential diagnosis in areas where FMF is common. In the literature, no positive mutation was detected in any PFAPA cases where FMF genetic mutation analysis was performed (19). Only in a study conducted in Israel, it was reported that heterozygous mutations in the MEFV gene were high (27%) in patients with PFAPA (25). MEFV gene mutation was detected in 5 (7.9%) of our patients with FMF gene mutation. We didn't include the results in this study, because we examined FMF gene mutation in a limited number of patients.

Disease symptoms occur irregularly with a mean interval of one month, if not intervened, for 3-5 days (10,22). The age of onset in infancy can go down to six months (26). Fever persists for 3-7 days (average of 5 days) and then decreases abruptly (20). In this syndrome, unlike other periodic fever syndromes, as the age increases, it is observed that the interval between attacks are getting longer and the spontaneous recovery is seen in 4-8 years (21). In our study, the interval between attacks was calculated as 4.04 ± 2.48 weeks. Also, the mean duration of fever during the attack was found at 4.35 ± 1.71 days.

In children with PFAPA, the population is unresponsive to antibiotic and antipyretic (paracetamol, ibuprofen) therapies administered in high fever and other clinical findings during the 3-4-day attack period (11,16). 85.7% of our patients used antibiotics and/or antipyretic drugs during their febrile periods and all of these treatments were unresponsive in reducing fever. Early diagnosis of PFAPA is based on the prevention of unnecessary antibiotic and antipyretic medication use.

In PFAPA syndrome, fever is present in every episode, but the other three findings, pharyngitis, aphthous stomatitis, and cervical lymphadenopathy, may not be seen in the same episode. In studies, cervical lymphadenopathy (88%) was the most common finding except fever, followed by pharyngitis (72%) and aphthous stomatitis (70%) (10). In the study performed by Thomas et al., in addition to fever, aphthous stomatitis in 70%, pharyngitis in 72%, cervical lymphadenopathy in 88%, headache in 60% and abdominal pain were observed in 49% of the cases (5). When two large series of PFAPA syndrome studies were examined, it was seen that in addition to the fever seen in all patients, tonsillitis in 65% to 100%, aphthous stomatitis in 67% to 68%, and cervical LAP in 77% to 100%, were detected, respectively (5,10). In our country, Hızarcıoğlu et al. in their study evaluating 12 patients with PFAPA syndrome, found pharyngitis in all cases, LAP in 91%, aphthous stomatitis in 66%, and exudative tonsillitis in 58% (27) of the cases. In all of our patients, high fever (39 °C and above) was observed at regular intervals with 4-6 weeks intervals; in addition to this resistant fever, 93.7% had cervical LAP, 88.9% had aphthous stomatitis, 63.5% had exudative tonsillitis.

Fever attacks occur suddenly. It usually does not respond to antipyretic and antibiotic treatments. The fever is mostly above 39 °C (10,19,22). One of the most important findings of PFAPA syndrome is that the general condition of the child is good despite the high fever. This finding is very useful in the differential diagnosis of the disease with infections. Fever lasts for 3-5 days on average and then spontaneously decreases. Fever decreases rapidly and disappears within 3-4 hours following corticosteroid administration, which is the only temporary treatment of the disease. The fever remains at normal intervals until the next attack (10).

During an attack, patients usually have bilateral, mobile, painful and large lymphadenopathies, which are chain-shaped on both sides of the neck. Lymphadenopathies begin just below the jaw and spread along the anterior cervical chain. The presence of lymphadenopathy elsewhere in the body, outside the cervical region, is not a characteristic of this syndrome (28). Most patients have a typical clinical manifestation of tonsillitis. On the pharynx, there is a notable clinical presentation of pharyngitis. The throat culture and streptococcal tests are negative. Tonsillitis in patients is unresponsive to antibiotic treatments used, and crypts disappear rapidly after corticosteroid admission (28). Aphthous ulcer is the most frequently overlooked finding. They are usually in the form of superficial ulcers less than 5 mm in size without forming a group and they are mildly painful and heal without a scar (29). The aphthous lesion is seen as an oval, white or yellow oral ulcer with a red border with inflammation in the nonkeratinized mucosa (28). Headache, abdominal pain, nausea, vomiting, sweating, chills, cranial neuritis and rarely arthralgia are the other symptoms. While arthralgia or myalgia-like musculoskeletal complaints are observed in children with PFAPA, there is no clinical finding indicating arthritis (10). Hepatosplenomegaly may also be seen in some patients. The other main characteristic is that the patient is completely healthy between the attacks (25). Recurrent fever episodes may last for many years; however, as the child grows, the time between these episodes increases (10,24). Although PFAPA Syndrome is chronic in some children, long-

term sequelae of PFAPA syndrome have not been reported and the growth curves of these patients are consistent with their age (14,15).

There are no laboratory tests specific to the diagnosis of the syndrome. However, during episodes, leukocytosis, elevated erythrocyte sedimentation rate levels and elevated levels of acute phase reactants such as CRP may accompany (30,31). While a slightly increased leukocyte count and elevated levels of erythrocyte sedimentation rate are noted during the attack, these tests return to normal between the attacks (10). An increase in CRP levels during febrile episodes in children with PFAPA syndrome indicates that inflammatory mechanisms are involved in the process (32). Leukocytosis was found in 57.14%, high sedimentation rate was found in 76.19%, and CRP elevation was found in 84.12% of the patients.

Dramatic clinical improvement in 2 to 4 hours after single dose prednisolone treatment (1-2 mg/kg/day) can be used as a diagnostic criterion. With this treatment, the interval between attacks often grows. In a study by Femiano et al., the most effective treatment was reported to be 1-2 mg/kg/day dose of prednisolone during the febrile attacks (1-2). In our study, all patients receiving methylprednisolone during their first episode benefited from lowering of their fever. Five (7.4%) patients required second dose steroid treatment.

Tonsillectomy and adenoidectomy are recommended in cases that cannot be controlled with prednisolone admission. In the study performed by Thomas et al., the response to steroid was 90%, 75% for tonsillectomy, and 86% for tonsillectomy and adenoidectomy together (5). In two studies, attacks were prevented in some children with tonsillectomy, but success was not achieved in all cases (14,32). In two studies conducted by Burton et al. in 2014, it was determined that PFAPA patients benefited from a tonsillectomy (33). One of our patients (1.58%) had a tonsillectomy, which resulted in successful treatment of the patient.

Conclusion: In conclusion, signs and symptoms of PFAPA syndrome are among the most common signs and symptoms in pediatric outpatient clinics. High fever is a worrying symptom for families. Numerous tests performed for diagnosis are depressing for the patients and their families. It is also mistaken for upper respiratory tract infection, causing unnecessary antibiotic use. The most important way to prevent this is to take a good medical history and to conduct the physical examination carefully. We should suggest the differential diagnosis of PFAPA syndrome when fever, pharyngitis, aphthous stomatitis, and lymphadenopathy are detected in case of the presence of recurrent attacks in children under five years of age.

The most important limitation of this article was that it was a retrospective study, hence some data were missing.

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REFERENCES

1. Keleş S, Özdemir C, Bahçeciler NN, Barlan IB. Periyodik Ateş Sendromları. Güncel Pediatri 2007;5: 57–61.

2. Trübenbach J, Wildhardt G, Niebel J, Hawle H, Steinberger D. A monoallelic double mutation as a cause for TNF receptor-associated periodic fever syndrome. Rheumatol Int 2010;30: 805-809.

3. Kastner DL, Janka G. Hereditary Periodic Fever Syndromes. Childhood and Adolescent Hematology 2005;45: 74-81.

4. Hofer M, Pillet P, Cochard M, 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.

5. Thomas KT, Feder HM, Lawton AR, Edwards KM. Peridic fever syndrome in children. J Pediatr 1999; 135: 15-21.

6. Vanoni F, Theodoropoulou K, Hofer M. PFAPA syndrome: a review on treatment and outcome Vanoni et al. Pediatric Rheumatology 2016 ;14: 38.

7. Marshall GS, Edwards KM, Butler J, Lawton AR. Syndrome of periodic fever, pharyngitis and aphthous stomatitis. J Pediatr 1987; 110: 43-6.

8. Mahamid M, Agbaria K, Mahamid A, Nseir W. Vitamin D linked to PFAPA syndrome. Int. J. Pediatr. Otorhinolaryngol 2013; 77: 362–4.

9. Aktas Ö, Aytuluk HG, Caliskan SK, Erdur Ö, Cirik AA. Long-term follow-up of tonsillectomy efficacyin children with PFAPA syndrome. Braz J Otorhinolaryngol 2019; 85: 78-82.

10. Padeh S, Brezniak N, Zemer D, Pras E, Livneh A, Langevitz P, et al. Periodic fever, aphthous stomatitis, pharyngitis, and adenopathy syndrome: clinical characteristics and outcome. JPediatr 1999;135: 98–101.

11. Padeh S. Periodic fever syndromes. Pediatr Clin North Am 2005; 52: 577-609.

12. Wurster VM, Carlucci JG, Feder HM, Edwards KM. Long-term follow-up of children with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome. J Pediatr 2011;159: 958–64.

13. Meyerhoff J. Familial Mediterranean fever: report of a large family, review of the literature, and discussion of the frequency of amyloidosis. Medicine (Baltimore) 1980; 59: 66-77.

14. John CC, Gilsdorf JR. Recurrent fever in children. Pediatr Infect Dis J 2002; 21: 1071-1077.

15. Scholl PR. Periodic fever syndromes. Curr Opin Pediatr 2000; 12: 563-6.

16. Kasapçopur Ö, Arısoy N. PFAPA Sendromu. Turk Arch Ped 2009; 44: 80-3.

17. 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 acti-vation responsive to IL-1 blockade. Proc Natl Acad Sci 2011; 108: 7148–53.

18. Stojanov S, Hoffmann F, Kéry A, Renner ED, Hartl D, Lohse P, et al. Cytokine profile in PFAPA syndrome suggests continuous inf-lammation and reduced anti- inflammatory response. Eur Cytokine Netw 2006; 17: 90-7.

19. Femiano F, Lanza A, Buonaiuto C, Gombos F, Cirillo N. Oral aphthous-like lesions, PFAPA syndrome: a review. J Oral Pathol Med 2008; 37: 319-23.

20. Vehapoglu Turkmen A, Uzuner S, Taşkın N. PFAPA sendromu ve herediter periyodik ateş sendromları. J Pediatr Inf 2012; 6: 24-9.

21. Long SS. Syndrome of Periodic Fever, Aphthous stomatitis, Pharyngitis, and Adenitis (PFAPA)--what it isn't. What is it? J Pediatr 1999;135: 1-5.

22. Padeh S, Berkun Y. Auto-inflammatory fever syndromes. Rheum Dis Clin North Am 2007; 33: 585-623.

23. Feder HM, Salazar JC. A clinical review of 105 patients with PFAPA (a periodic fever syndrome). Acta Paediatr 2010; 99: 178-84.

24. Sampaio IC, Rodrigo MJ, Monteiro Marques JG, Pereira JG. Two siblings with periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA) syndrome. Pediatr Infect Dis J 2009; 28: 254-5.

25. Dagan E, Gershoni-Baruch R, Khatib I, Mori A, Brik R MEFV, TNF1rA, CARD15 and NLRP3 mutation analysis in PFAPA. Rheumatol Int 2010; 30: 633-66.

26. Drenth JPH, van der Meer JWM. Hereditary periodic fever. N Engl J Med 2001; 345: 1748-57.

27. Hizarcıoğlu M, Asilsoy S, Demir Özek G, Ağın H, Kayserili E, Gülez P, et al. PFAPA Sendromlu Olgularımızın Klinik ve Laboratuvar Özellikleri. Bakırköy Tıp Dergisi 2008; 4: 107-10.

28. Feder HM. Periodic fever, aphthous stomatitis, pharyngitis, adenitis: a clinical review of a new syndrome. Curr Opin Pediatr. Jun 2000;12: 253-6.

29. Çiftçi E, Özdemir H, İncesoy S, İnce E, Doğru Ü. Periyodik ateş, aftöz stomatit, farenjit ve servikal adenit (PFAPA) sendromlu bir vaka. Türk Pediatri Arşivi 2004; 39: 36-40.

30. Bilici M, Kara S, Turkay S, Doğan G, Aydemir S. Periyodik Ateş, Aftoz Stomatit, Farenjit, Lenfadenit (PFAPA): Tekrarlayan Ateşin Önemli Bir Nedeni. Turkiye Klinikleri J Pediatr 2010; 19: 187-90.

31. Padeh S, Stoffman N, Berkun Y. Periodic fever accompanied by aphthous stomatitis, pharyngitis and cervical adenitis syndrome (PFAPA syndrome) in adults. Isr Med Assoc J 2008;10: 358-60.

32. Hernández-Bou S, Giner M, Plaza AM, Sierra JI, Martín Mateos MA. PFAPA syndrome: with regard to a case. Allergol Immunopathol (Madr) 2003; 31: 236-9.

33. 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 2014; 9: 1-30.