



CASE REPORT

A RARE CAUSE OF HIGH FEVER—PFAPA SYNDROME

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SUMMARY

* High fevers of unknown origin are common in infants and children. Recurrent fever is also common. A clinical entity of periodic fever associated with aphthous stomatitis, pharyngitis, and cervical adenitis, termed PFAPA syndrome, was first described by Marshall and coworkers in 1985. The etiology of PFAPA syndrome remains unknown, and treatment so far is not definitive. However, glucocorticoids are highly effective in controlling symptoms. Anecdotally, cimetidine and steroids have decreased illness duration. Several reports of complete resolution of symptoms after tonsillectomy have been published. We describe a patient with recurrent pharyngitis, fever, and cervical adenitis who is refractory to antibiotic therapy and antipyretics. The syndrome complex lasted for 4-6 days, with complete resolution of symptoms with corticosteroid use. A physical examination including bacterial cultures, chest radiographs, and blood analyses to determine the syndrome's etiology was inconclusive. The patient was diagnosed with PFAPA syndrome and following tonsillectomy, has remained symptom free.

Keywords: Fever; tonsillectomy

YÜKSEK ATEŞİN NADİR BİR NEDENİ-PFAPA SENDROMU: VAKA SUNUMU

ÖZET

İnfanlarda ve çocuklarda nedeni bilinmeyen yüksek ateş yaygın olarak görülmektedir. Bununla beraber tekrarlayan ateş de sık olarak görülmektedir. PFAPA sendromu olarak kısaltılan aftöz stomatit, farenjit, servikal adenit ile beraber periyodik ateş ile karakterize klinik antite ilk defa 1985'te Marshall ve arkadaşları tarafından tanımlanmıştır. PFAPA sendromunun etyolojisi ve tedavisi hala kesin olarak bilinmemektedir. Bununla beraber glukokortikoidler semptomların kontrolünde oldukça etkilidir. Anekdotal olarak simetidin ve steroidler hastalık süresini azalttığı bilinmektedir. Tonsillektomi sonrası semptomların tamamen düzeldiğine dair birçok yayın vardır. Bu yazıda antibiyotik tedavisine ve antipiretiklere refrakter rekürren farenjit öyküsü, ateşi ve servikal adeniti olan bir çocuk hasta sunulmuştur. Sendrom kompleksinin 4-6 gün sürdüğü, kortikosteroid kullanımı ile semptomların tamamen düzeldiği görülmüştür. Sendromun etyolojisini belirlemeye yönelik olarak yapılan fizik muayene, bakteriyel kültürler, göğüs röntgeni, kan analizleri sonuç vermemiş olup tonsillektomi sonrası hasta PFAPA olarak tanı almış ve semptomları düzelmiştir.

Anahtar Sözcükler: Ateş, tonsillektomi

INTRODUCTION

Periodic fever is defined as a series of febrile episodes that occur predictably at fixed intervals.^{1,2} These episodes last a few days and regress spontaneously.¹ In 1948, Raimann used the term periodic diseases to identify a group of disorders of unknown origin.³ These disorders are characterized by short episodes of illness that recur for several years regularly. Many periodic diseases have been described.³ A new periodic fever syndrome was described by Marshall in 1987.^{1,2,3} The acronym, PFAPA (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis), was coined in 1989.⁴ This disease is characterized by recurrent episodes of fever associated with head and neck symptoms.³ PFAPA is a clinical entity because specific laboratory abnormalities have not yet been found.^{2,4}

The disease's etiology remains unknown, and no ethnic or geographic factors have been found.^{1,4} PFAPA syndrome is defined clinically, and the diagnosis is one of exclusion.⁴

The syndrome is rare. We present a child with recurrent pharyngitis, fever, and cervical adenitis who was refractory to antibiotic therapy. After tonsillectomy, the patient was diagnosed as having PFAPA syndrome.

CASE REPORT

A 3-year-old boy presented to our clinic with a diagnosis of PFAPA syndrome. He had been followed for 7 months by the Department of Pediatrics, and he had a history of recurrent episodes of fever, sore throats, aphthous stomatitis and cervical lymphadenopathy. These episodes occurred every month. The patient's family history was unremarkable. At first visit, his weight, height, and body temperature were 12.3 kg (25th-50th percentile), 85.5 cm (10th-25th percentile), and 36.1°C. The tonsils were hyperemic and hypertrophic with multiple accompanying lymphadenopathies

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smaller than 1 cm. No organomegaly was detected. Results of standard laboratory analyses yielded the following values: Hb: 11.7 g/dL, Hct: 34.3%, MCV: 71.6 fl, WBC: 7540/ μ L, and platelets, 243000/ μ L. Serum levels of IgA (0.75 g/dL), IgG (7.9 g/dL), IgM (0.57 g/dL) were normal. Monospot test, EBV IgM and HSV type1 IgM were negative. Three months later, the patient was again admitted to our hospital with complaints of fever and sore throat. Physical examination revealed hyperemic and hypertrophic tonsils with exudate in the crypts and bilateral cervical adenopathy. After throat culture, a single dose of oral methylprednisolone (2 mg/kg) was given. After 8 hours, the patient was free of all symptoms. Similarly, 2 further episodes responded to prednisolone, and the patient was diagnosed as having PFAPA. The patient was referred to our ear, nose, and throat (ENT) department. ENT examination revealed hypertrophic tonsils and adenoid vegetation that obstructed the choanae. Tonsillectomy was performed owing to the beneficial outcome of tonsillectomy in PFAPA syndrome and to keep the patient free of corticosteroids. Adenoidectomy also was performed. Tonsillectomy and adenoidectomy materials were sent to pathology department for histopathological examination. The pathological diagnosis was chronic tonsillitis and adenoiditis. Tonsillectomy culture was not taken but throat cultures which were made several times were negative. The patient's febrile attacks stopped just after the operation, and he had no further attacks at 1 year's follow-up.

DISCUSSION

The PFAPA syndrome is a chronic disease of unknown etiology. The diagnosis of this disease is difficult because none of its clinical symptoms are pathognomonic, and there is no specific biologic abnormality. The symptoms may mimic other recurrent fevers.⁵

In the late 1980s, Marshall reported a periodic fever syndrome in 12 children. The patients presented febrile episodes that recurred every 2 to 12 weeks.⁵ The fevers in these children would reach 40° to 41°C and would last for about 5 days.² The onset of symptoms started before 5 years of age in all cases.⁵ Between febrile episodes, the patients were well. Associated with the fevers, 9 of 12 patients had aphthous stomatitis, 9 of the 12 patients had pharyngitis, and 8 of the 12 patients had cervical adenitis.² Other minor symptoms were headache, abdominal pain, nausea, vomiting, chills, and malaise.⁵ No immunologic abnormalities were found in these children. Results of bacterial viral, and fungal studies were all negative. Only 2 patients had

group A beta hemolytic streptococcus isolated from the pharynx.⁵ The episodes were frequently associated with leukocytosis and an elevation in the erythrocyte sedimentation rate.² The fevers were unresponsive to antibiotics and nonsteroidal antiinflammatory drugs.² The use of oral prednisone controlled the symptoms but did not prevent the next cycle.^{2,5}

To diagnose PFAPA syndrome, other known periodic diseases must be ruled out.⁶ Periodic fever syndromes include familial Mediterranean fever (FMF), familial Hibernian fever, familial hyper IgD syndrome, cyclic neutropenia, Behçet's disease, juvenile rheumatoid arthritis, and several infectious diseases.

FMF is an autosomal recessive disease, which can be easily differentiated from PFAPA syndrome by family history.³ FMF is characterized by brief fevers associated with sterile peritonitis, pleuritis, arthritis, and rash.^{2,3,6} It occurs predominantly in Sephardic Jews, Arabs, Turks, and Armenians.^{2,3} These patients do not respond to prednisone, they can be treated with colchicine.

Hibernian fever demonstrates autosomal dominant inheritance and is characterized by recurrent attacks of fever, abdominal pain, tender skin lesions, and muscular pain.⁶ If patient has a negative family history this disorder may be excluded.³ It is not periodic, and it responds to corticosteroids.⁶

Hyperimmunoglobulinemia D syndrome is characterized by self-limiting febrile episodes of variable frequency. These periods are accompanied by headache, cervical adenopathy, arthritis, chills, macular rash, and splenomegaly. In these patients, high serum IgD levels are present. During febrile attacks, high levels of mevalonic acid are found in the urine. All of these laboratory findings are not present in patients with PFAPA syndrome.^{3,6}

Behçet's disease manifests with aphthous ulcers in the oral cavity, ulcerated genital lesions, iridocyclitis, and synovitis. Erythema nodosum, thrombophlebitis, and meningoencephalitis are also observed. Cyclic neutropenia usually begins during the first year of life, and the neutrophil count goes to zero at nearly exactly every 3 weeks.^{2,3} During these attacks, patients develop mucositis, otitis, and skin infections. The diagnosis of this disease is based on clinical features and international criteria for classification of Behçet's disease have been used since 1992. Behçet's disease is usually diagnosed in third decade of life and pediatric cases are uncommon (mostly seen in late childhood). In addition to this familial occurrence has been reported



in paediatric cases⁷. In the PFAPA syndrome, neutropenia is not seen, and the interval between fever is unusually longer than 21 days.^{2,3} Therewithal our case is 3-year-old and familial history is not known. The other symptoms except aphthous stomatitis is not seen in our case. But Behçet's disease must be in differential diagnoses of recurrent aphthous stomatitis⁷.

Juvenile rheumatoid arthritis presents with arthritis, fever, hepatosplenomegaly, and generalized lymphadenopathy. The fever lasts several weeks or months, and the next episode is not predictable. Patients may have morning stiffness, rashes, uveitis, and positive antinuclear antibodies or positive rheumatoid factor, unlike patients with PFAPA syndrome.^{2,3}

Several infectious diseases involve febrile episodes with afebrile periods (*Borrelia recurrentis*, *Streptobacillus moniliformis*, hepatitis B virus, *Rickettsia prowazekii*, *Entamoeba histolytica*, *Plasmodium malariae*, Herpes simplex virus, and Epstein-Barr virus). All of these diseases have identifying laboratory and/or physical features.³

Treatment of PFAPA syndrome is controversial. There is no specific treatment. Symptomatic treatment is reasonable in patients with PFAPA syndrome.⁶ Administration of antibiotics, NSAIDs, acyclovir, and colchicine all have been shown to be ineffective.³

In the treatment of PFAPA syndrome, glucocorticoids are highly effective in controlling symptoms.¹ Padeh and colleagues have reported that attacks were aborted with a single dose of oral prednisone (2 mg/kg) in 16 of 28 patients, and 9 patients showed complete resolution of the syndrome.⁸ A review of 94 cases by Thomas and coworkers reported that "glucocorticoids were highly effective in controlling symptoms."⁹ Use of corticosteroids has had variable results. The severity of the attack may be reduced by steroids, but steroids may have no impact on the frequency of future attacks.⁶

Other authors have described successful results with cimetidine.^{10,11} Cimetidine is an H₂ antagonist that inhibits suppressor T cells, increasing interferon production, eosinophil and neutrophil chemotaxis, neutrophil lysosomal enzymatic release, and migratory inhibitory factor production.³ If an underlying problem requires long-term immunosuppressive medication, cimetidine may be chosen rather than increasing the steroid dosage.¹ However, the action of cimetidine remains unclear.⁶

The value of tonsillectomy in treating PFAPA syndrome also remains unclear.⁶ Tonsillectomy is associated with remission in some patients.¹ Overall in the literature, tonsillectomy has been found to be successful in 86.7% of children and has improved symptoms in another 7.1%.^{3,8,9,12,13,14}

Abramson and coworkers first described 4 patients with PFAPA whose symptoms resolved after tonsillectomy and adenoidectomy.¹³ In a retrospective review of 6 cases of PFAPA syndrome treated with tonsillectomy, Dahn and colleagues reported that 4 patients showed improvement.¹² And in a review by Padeh and colleagues, 3 patients had complete resolution after tonsillectomy.⁸

It is not understood why PFAPA syndrome does not recur after tonsillectomy in most children. It is said that the syndrome can be elicited by an immunologic process beginning at the level of the tonsillar parenchyma.³ Also viral or bacterial infections that are currently unknown may be chronically located in the tonsillar tissue. It can be said that tonsillectomy is mostly beneficial as it also is in infectious mononucleosis indicating a special role of the tonsils also in similarity with IgA nephropathy so that one effect of tonsillectomy is reduction of number of plasma cells, i.e. antibody producing cells.

In conclusion, while the role of medical and surgical treatment for PFAPA syndrome is evolving, our patient obtained benefit from tonsillectomy. His febrile attacks stopped just after tonsillectomy and did not recur.

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