PFAPA syndrome: a rare cause of periodic fever

Hanifi Kurtaran[1], Ahmet Karadağ[2], Ferhat Çatal[2], Davut Aktaş[1]

Departments of [1]Otorhinolaryngology and [2]Pediatrics, Fatih University Faculty of Medicine, Ankara, Turkey

SUMMARY: Kurtaran H, Karadağ A, Çatal F, Aktaş D. PFAPA syndrome: A rare cause of periodic fever. Turk J Pediatr 2004; 46: 354-356.

PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, adenopathy) is characterized by abrupt onset of fever, malaise, aphthous stomatitis, tonsillitis, pharyngitis and cervical adenopathy. The age of onset of the disease is four years, with a range of 6 months to 7 years. The syndrome is sporadic and nonhereditary. Long-term sequelae do not develop. A nine- year-old boy presented with sore throat, fever and oral aphthae. After taking a throat culture, he was prescribed oral antipyretic and was called for a follow-up visit the next day. As the culture result was negative, he was given a single dose prednisolone with the suspected diagnosis of PFAPA. Twenty-four hours later his temperature was 36.8° C, with all his complaints regressed. Twenty-two days later the patient was again admitted to our hospital with the same complaints. Again, single dose oral prednisolone was given after a throat culture. On the next day the patient was free of all symptoms and the culture was again normal. To our knowledge this is the first PFAPA case report from Turkey in the literature.

Key words: PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, adenopathy), child, tonsillectomy, Turkey

In 1987, Marshall et al.[1] described a childhood disease comprising the following features: periodic fever, aphthous stomatitis, pharyngitis and cervical lymphadenopathy. Thereafter the disease has been referred to as PFAPA (periodic fever, aphthous stomatitis, pharyngitis and adenopathy syndrome)[2]. The syndrome usually begins around the 4th year of age, and is characterized by one episode per 3-8 weeks, lasting 3-6 days, with fever exceeding 39°C.[3-5] Padeh et al.[4] reported that exudative tonsillitis also accompanies the pharyngitis. Besides its yet to be determined etiology and epidemiology, symptoms usually do not improve with antipyretic or antibiotic treatment[3,4]. However, prednisone or prednisolone (1-2 mg/kg) regimens given one or two times dramatically cure the symptoms in a few hours.[3,4] To the authors' best knowledge, this is the first PFAPA case report from Turkey.

Case Report

A nine-year-old boy the only child of second-degree consanguineous parents admitted to our Ear Nose and Throat (ENT) Department with the complaints of malaise, sore throat, fever and oral aphthae. The history disclosed similar recurrent episodes every 20-25 days for the last five years, despite several oral antibiotic attempts and penicillin G benzathine prophylaxis in the preceeding two years. The family history was unremarkable except for his nephew who had suffered from similar episodes and had undergone tonsillectomy.

His weight, height and body temperature were 23 kg (3-10 percentile), 135 cm (25 percentile), and 39.8°C, respectively. The tonsils were hyperemic and hypertrophic with white exudative crypts (Fig. 1). There were multiple aphthous lesions on the buccal mucosa and the palate accompanying the multiple lymphadenopathies –smaller than 0.5x0.5 cm- residing in the cervical region. No organomegaly was detected. The laboratory analysis yielded Hb: 12.3 g/dl, Htc: 36.2%, MCV: 74 fl, WBC: 14400/µl, Plt: 276000/µl. The peripheral blood smear was consistent with 68% granulocytes, 26% lymphocytes, 4% band and 2% monocytes. Serum Epstein-Barr virus (EBV), cytomegalovirus (CMV) and immunoglobulin (Ig) M were negative. Serum levels of Ig D were normal (18 mg/L).

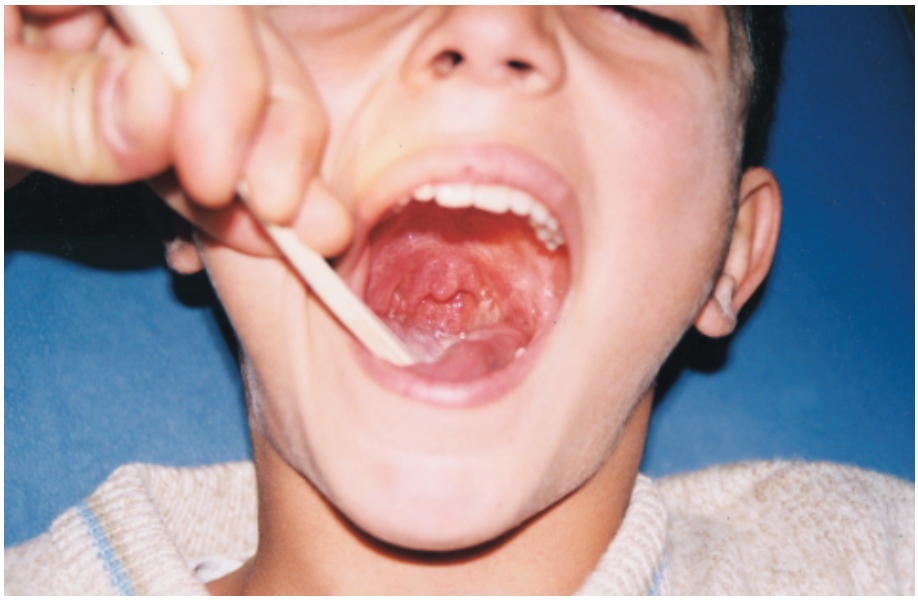

Fig. 1. White exudative crypts and hyperemia on the tonsils.

Mediterranean fever gene (MEFV) analysis was made, and familial Mediterranean fever (FMF) was not present. After performing a throat culture, he was prescribed oral ibuprofen and was called for a follow-up visit the next day. His temperature was 40°C with sustained symptoms of the disease at that visit. As the culture result was unremarkable, he was given a single dose of prednisolone (2 mg/kg) with suspected diagnosis of PFAPA. Twenty-four hours later his body temperature was 36.8°C with all complaints regressed. His mother declared that the fever had declined in the following first six hours and had not increased since then. Considering that a spontaneous remission could well ensue in these patients on the 4th or 5th day, the parent was alerted to bring the child immediately in case of another attack.

Twenty-two days later, the patient was again admitted to our hospital with the complaints of fever and sore throat for the previous 6-7 hours. The physical examination revealed hyperemic and hypertrophic tonsils with exudative crypts, multiple oral aphthae and bilateral cervical lymphadenopathy. Likewise, single dose oral prednisolone (2 mg/kg) was given after a throat culture. On the next day the patient was free of all former symptoms and the culture result was again normal. The patient was told to take 45 mg oral prednisolone when a new attack occurs, and in case of failure of this attempt within 24 hours, to call or come to the hospital for a follow-up visit.

Similarly, two, further episodes responded to prednisolone and the patient was eventually diagnosed as PFAPA.

Discussion

First becoming conspicuous in 1987 and having not drawn much concern thereafter, this new and mysterious disease, PFAPA, is probably the least known amongst the periodic fever syndromes. After being mentioned in the pediatric literature, it has also gained attention in the otorhinolaryngology literature; however, it is still not a widely known disease for either group of specialists. Thus, erroneously –due to the lack of awareness among physicians- most of the PFAPA patients are still being treated with penicillin G benzathine or oral antibiotics despite normal throat cultures.

The two most common periodic fever syndromes of childhood are PFAPA and cyclic neutropenia[3]. The latter is distinguished from PFAPA by its characteristic of neutropenia. On the other hand, there are also some diseases with irregular periodicity: FMF, hyper IgD syndrome, systemic onset juvenile rheumatoid arthritis (soJRA) and tumor necrosis factor

receptor associated periodic syndrome (TNFAPS). In FMF, painful pleuritis, peritonitis, arthritis and erythematous macular rash; in hyper IgD syndrome arthralgia, cervical lymphadenopathy, abdominal pain, erythematous macular rash and elevated IgD level during the attacks; in soJRA generalized lymphadenopathy, arthritis, hepatosplenomegaly and rash; in TNFAPS conjunctivitis, localized myalgia, arthralgia, erythematous skin lesions and abdominal pain are, by far, the leading clinical findings[3,6]. In PFAPA, on the other hand, periodic fever, pharyngitis, aphthous stomatitis and cervical lymphadenopathy are observed – without any –neutropenia or increased IgD levels during the attack[3,5].

Though immune dysregulation is generally thought to take place in these patients, the etiology of PFAPA still remains unclear. Like with other cases of recurrent aphthous stomatitis, increased interferon-γ, tumor necrosis factor (TNF)-α interleukin (IL)-4, and IL-5 levels are thought to also exist in PFAPA; however, the studies in the relevant literature are quite limited[5,7]. No specific gene has been described pertaining to its etiopathogenesis.

In spite of the fact that no ethnic predisposition has been mentioned, Padeh et al.[4] reported a series of 28 patients, all of whom originated from Mediterranean or nearby countries. This might imply a geographical tendency similar to FMF. Another outstanding evidence that merits significant concern was the ratio of 28/94 in the series of patients reported by Thomas et al.[3], which represented the frequency of single parent amongst children with PFAPA. This was in accordance with our patient, whose parents divorced when he was one year of age, and somewhat justifies the probable psychosocial impact on disease causation. The possible role of the psychosocial factors in the etiology of PFAPA is pointed out in this report for the first time.

The symptoms of PFAPA usually do not regress with antibiotic and antipyretics[3-5]. Although spontaneous recovery may ensue on the 4th-5th day, the treatment entails single dose prednisolone (1-2 mg/kg) at any time during the illness attack, after which the entire symptomatology vanishes, even in a mother of hours[3,4]. According to some authors, this may also confirm the diagnosis and stands as one of the diagnostic criteria[4]. Cimetidine, an immunomodulator, has also been shown to exert a curative effect in PFAPA[8]. Tonsillectomy is definitely another method of treating these patients. Overall, the effectiveness of the treatment alternatives are as follows: steroids 90%, tonsillectomy 75% and tonsillectomy and adenoidectomy 86%[3]. In a retrospective study of 40 patients with recurrent pharyngitis who had tonsillectomy, 15 (37.5%) were detected to have PFAPA and in all of them the surgery was beneficial[9]. No sequela has been reported among PFAPA patients.

Besides drawing the attention of pediatricians and otorhinolaryngologists to the topic, we wish, in presenting this case report, to encourage their vigilance about PFAPA. Not only will such patients be treated promptly, but also utilization of unnecessary antibiotics will hopefully decline.

REFERENCES

1. Marshall GS, Edwards KM, Butler J, Lawton AR. Syndrome of periodic fever, pharyngitis, and aphthous stomatitis. J Pediatr 1987; 110: 43-46.
2. Marshall GS, Edwards KM. PFAPA syndrome (letter). Pediatr Infect Dis J 1989; 8: 658-659.
3. Thomas KT, Feder HM Jr, Lawton AR, Edwards KM. Periodic fever syndrome in children. J Pediatr 1999; 135: 15-21.
4. Padeh S, Brezniak N, Zemer D, et al. Periodic fever, apthous stomatitis, pharyngitis, and adenopathy syndrome: clinical characteristics and outcome. J Pediatr 1999; 135: 98-101.
5. Long SS. Syndrome of periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) – What isn't. What is it? J Pediatr 1999; 135: 1-5.
6. Drenth JP, van der Meer JW. Hereditary periodic fever. N Engl J Med 2001; 345: 1748-1757.
7. Buno IJ, Huff JC, Weston WL, Cook DT, Brice SL. Elevated levels of interferon gamma, tumor necrosis factor alpha, interleukins 2, 4 and 5, but not interleukin 10, are present in recurrent aphthous stomatitis. Arch Dermatol 1998; 134: 827-831.
8. Feder HM Jr. Cimetidine treatment for periodic fever associated with aphthous stomatitis, pharyngitis and cervical adenitis. Pediatr Infect Dis J 1992; 11: 318-321.
9. Galanakis E, Papadakis CE, Giannoussi E, Karatzanis AD, Bitsori M, Helidonis ES. PFAPA syndrome in children evaluated for tonsillectomy. Arch Dis Child 2002; 86: 434-435.