

# **Periodic Fever Accompanied by Aphthous Stomatitis, Pharyngitis and Cervical Adenitis Syndrome (PFAPA Syndrome) in Adults**

Shai Padeh MD, Nava Stoffman MD and Yackov Berkun MD

Department of Pediatrics A, Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, and Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

**Key words:** periodic fever, aphthous stomatitis, pharyngitis and adenopathy syndrome (PFAPA syndrome), familial Mediterranean fever

## **Abstract**

**Background:** The new syndrome, known as PFAPA, of periodic fever characterized by abrupt onset of fever, malaise, aphthous stomatitis, tonsillitis, pharyngitis and cervical adenopathy has been described only in pediatric patients. It usually begins before the age of 5 years and in most cases resolves spontaneously before age 10.

**Objectives:** To describe a series of adults with PFAPA syndrome.

**Methods:** This 6 year retrospective descriptive study includes all newly diagnosed incident adult cases aged 18 years and over referred to our center with symptomatology suggestive of PFAPA syndrome. Patients' medical records were reviewed for past history of the disease, demographic characteristics, symptoms and signs, course of the disease, laboratory findings, and outcome following corticosteroid therapy. The comparison group included our pediatric cohort children (N=320, age 0–18 years) followed for the last 14 years (1994–2008).

**Results:** Fifteen adult patients were diagnosed with PFAPA syndrome. Episodes of fever occurred at  $4.6 \pm 1.3$  week intervals, beginning at the age of  $20.9 \pm 7.5$ . All patients had monthly attacks at the peak of the disease, with attacks recurring at 4–8 week intervals over the years. Between episodes the patients were apparently healthy, without any accompanying diseases. Attacks were aborted by a single 60 mg dose of oral prednisone in all patients.

**Conclusions:** This study reports the presence of PFAPA syndrome in adult patients. Although the disease is rare, an increased awareness by both patients and family physicians of this clinical syndrome has resulted in more frequent diagnosis in adult patients.

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The PFAPA syndrome is a chronic disease of unknown etiology characterized by periodic episodes of high fever accompanied by aphthous stomatitis, pharyngitis, and cervical adenitis [1–4]. This syndrome has been well described in pediatric patients and belongs to the group of recurrent fever syndromes, which includes systemic onset juvenile idiopathic arthritis, cyclic neutropenia, and the expanding group of hereditary fevers [5]. PFAPA syndrome, however, differs from these autoinflammatory fevers in that it is a non-hereditary syndrome.

In the pediatric cohort of 320 cases with PFAPA followed in our center, only 10 patients continue to suffer from attacks after the age of 10, and 2 of them after the age of 20 [5]. PFAPA syndrome was previously reported in only two adult patients [6,7]. The present study reports the first series of 15 adult patients presenting typical PFAPA syndrome.

## **Patients and Methods**

This retrospective study included all patients aged 18 years old and over with periodic fever referred to our center for evaluation of periodic fever. The medical records were reviewed and analyzed for demographic, clinical and laboratory data. The diagnostic criteria for PFAPA syndrome are summarized in Table 1 [2]. Over the 6 year follow-up period (2000 to 2005), 17 patients met the criteria for PFAPA syndrome and were followed at the Safra Children's Hospital. The mean follow-up period was  $2.7 \pm 1.8$  years (range 0.5–6 years). Two patients previously diagnosed with other diseases that could mimic symptoms of PFAPA syndrome (one with familial Mediterranean fever and the other with Crohn's disease) were excluded from the study. The other 15 patients were otherwise healthy, with no underlying diseases.

## **Statistical analysis**

Data analysis was carried out using SAS 9.1 (Statistical Analysis Software). Descriptive statistics were reported as means  $\pm$  SD; ranges between extreme values were added to address skewness toward high values of distributions. The chi-square distribution was used to test homogeneity in proportions.

## **Results**

The patient group comprised 8 females and 7 males, with the first episode reported at the age of  $20.9 \pm 7.5$  years (range 8–37 years) [Table 2]. The average delay in diagnosis was  $6.3 \pm 5.4$  years (range 2–20 years). Two patients underwent tonsillectomy. Patient # 6 underwent tonsillectomy at the age of 3 and first presented with PFAPA syndrome at age 19. Patient # 15 underwent tonsillectomy at the age of 14, six years after disease onset, but subsequently continued with episodes of fever and severe pharyngitis. The clinical presentation of the patients is summarized in Table 3.

**Table 1. Diagnostic criteria of PFAPA syndrome [5]**

- Monthly fevers – cyclic fever at any age group
- Exudative tonsillitis + negative throat culture
- Cervical lymphadenitis
- Possibly aphthous stomatitis
- Completely asymptomatic interval between episodes
- Rapid response to a single dose of corticosteroids (60 mg prednisone)

**Table 2.** Age of onset and diagnosis of patients with PFAPA

Patient no.	Gender	Age at onset (yrs)	Age at diagnosis (yrs)	Delay in diagnosis (yrs)
1	M	37	38	1
2	M	24	25	1
3	F	18	20	2
4	F	20	22	2
5	M	24	27	3
6*	M	19	21	3
7	F	18	22	4
8	M	15	20	4.8
9	F	25	30	5
10	F	25	31	5
11	F	25	31	6
12	M	35	44	6
13	F	21	28	7
14	M	25	31	9
15*	F	8	28	20

\* Patients 6 and 15 underwent tonsillectomy at the age of 3 and 14 respectively.

**Table 3.** Comparison of clinical presentation in adults with PFAPA (n=15) and children with PFAPA (n=320)

	Adults with PFAPA % (n)	Children with PFAPA % (n)*
Fever	100 (15)	100 (320)
Exudative tonsillitis	100 (15)	100 (320)
Malaise	100 (15)	100 (320)
Cervical adenopathy	100 (15)	100 (320)
Aphthae	40 (6)	68 (217) **
Arthralgia or myalgia	40 (6)	11 (35) **
Abdominal pain	20 (3)	18 (57)
Headache	20 (3)	18 (57)
Chills	13 (2)	60 (192) **

\* Reviewed in Padeh et al. [5]

\*\* Significantly different by chi-square (< 0.05)

Compared to adults, children with PFAPA syndrome have significantly less arthralgia and myalgia ( $P < 0.05$  by chi-square) and a higher rate of aphthae and chills ( $P < 0.05$  by chi-square), but headache and abdominal pain were not significantly different in prevalence.

Symptoms of each episode resolved spontaneously in  $4.3 \pm 1.7$  days with a range of 3–10 days of fever before treatment. Symptoms resolved irrespective of treatment with antipyretics or antibiotics. Episodes of illness occurred at  $4.6 \pm 1.3$  week intervals (range 3–10 weeks). All patients had monthly attacks at the peak of the disease, with attacks recurring at 4–8 week intervals over the years. Ten patients reported two or three intervals of 2–6 months free of symptoms during the course of the disease. In 11 patients the attacks recurred at precise intervals, with a fixed time interval between episodes. Two patients had the first episode during childhood (8 and 15 years old) but were only diagnosed at age 28 and 20 respectively. The remaining 13 patients had no

attacks during their childhood and the medical histories of all 13 patients were unremarkable. All patients were free of symptoms between episodes and their physical examinations were normal. All patients were of Jewish ancestry, with no particular predilection of ethnicity, and no patient had affected siblings.

Laboratory investigation at onset of the fever showed normal hemoglobin level, mild leukocytosis of  $12.0 \pm 2.6 \times 10^9$  mm white blood cells/mm<sup>3</sup>, moderate elevation of the sedimentation rate to  $52 \pm 15$  mm/first hour, and normal platelet counts. All patients had repeated negative throat cultures for beta hemolytic streptococci. Test for anti-streptolysin antibody was negative and serum immunoglobulin levels, complement, liver and kidney functions tests were all within the normal range.

A single 60 mg dose of oral prednisone was prescribed for all patients at the onset of the attacks and resulted in abrogation of the episodes. All patients reported a dramatic improvement in their general well-being, return of body temperature to normal, and complete abortion of the attack within 2–4 hours following ingestion of the corticosteroids. The patients were reexamined on the following day and all had a normal physical examination with clearing of the tonsillar exudates and oral ulcers. Eight patients subsequently complained of increasing rate and incidence of the attacks, recurring at 3 week intervals, following initiation of the corticosteroid therapy.

## Discussion

We identified 15 adults who presented with PFAPA syndrome – the new syndrome of periodic fever characterized by abrupt onset of fever, malaise, aphthous stomatitis, tonsillitis, pharyngitis and cervical adenopathy. PFAPA syndrome is characterized by febrile episodes lasting 4–5 days accompanied by chills, sweats, headache and myalgia. Pharyngitis, resembling streptococcal tonsillitis with negative throat cultures, and cervical adenopathy typify the syndrome. Attacks recur every 4–6 weeks, with a complete resolution of all symptoms between episodes. All patients report a dramatic resolution of fever within 2–4 hours after one dose of corticosteroids at each episode.

The cause of PFAPA is unknown. The ability of a single dose of corticosteroid to abort PFAPA attacks suggests that the symptoms may be caused by inflammatory cytokines rather than by infection. Preliminary studies of cytokines in patients with PFAPA indicate that several cytokines are elevated during febrile episodes, most notably interferon-gamma, tumor necrosis factor, and interleukin-6 [1] and significantly higher levels of IL-1 $\gamma$ , TNF $\alpha$  and IL-12p70 [8]. It seems that an abnormal host immune response to yet unidentified commensal microorganisms in the tonsils or the oral mucosae may account for the symptomatology.

Long [9] hypothesized that the periodicity of the PFAPA syndrome derives from intermittent expression or suppression of antigens or epitopes of infectious agents or an alteration in the nature or kinetics of immunological response. Lack of additional cases in siblings or other close contacts, lack of seasonal or

IL = interleukin

TNF $\alpha$  = tumor necrosis factor-alpha

geographic clustering, and the progression-free duration of PFAPA for years weigh heavily against an infectious cause. The dramatic response to a single oral dose of corticosteroids is unique to this syndrome, therefore we have used it as a diagnostic criterion in patients suspected of having PFAPA syndrome. Still, the mechanism of action is speculative [5].

Two of the patients presented in their childhood but continue having attacks in their adult lives. The other 13 patients had adult onset of the syndrome and continue having episodes of the disease for several years. Early childhood is characterized by an increased susceptibility to infectious diseases, attributed to immaturity of the immune system and to the slow development of immune competence. This period is critical in the development of immune responsiveness, with implications for the development of both infectious and non-infectious disorders. A recently reported example for such delayed maturation was impaired Th1 responses in healthy children [10]. Normal healthy individuals demonstrated an impaired capacity of peripheral blood mononuclear cells to synthesize bioactive IL-12 p70 at birth, with a slow maturation to adult levels only after age 12. Similar to PFAPA syndrome, other childhood diseases sometimes present as similar syndromes in adults (e.g., adult-onset Still's disease, Henoch-Schönlein purpura and others). It has been suggested that alterations in cytokine production have an important pathophysiological role in adult-onset Still's disease [11]. A predominance of Th1 cytokines was shown in the peripheral blood and tissues of patients with active untreated adult-onset Still's disease. The Th1 immune response is characterized by increased production of IL-2, IFN $\gamma$  and TNF $\alpha$  cytokines that steer B cells toward immunoglobulin-G2a production, activate macrophages and natural killer cells, and promote cell-mediated immunity. Our hypothesis is that, similarly, children with the PFAPA syndrome present some form of delayed maturation of the immune system, and that symptoms disappear once the normal adult capacity of the immune system is regained. Adult patients with PFAPA syndrome are individuals whose immune system never reached maturation and are therefore prone to stimuli triggering PFAPA episodes. This hypothesis is exemplified by the two patients who presented in childhood and continue to experience febrile episodes as adults. We therefore elect not to exclude them from this series of adult PFAPA syndrome.

Tonsillectomy had previously been associated with resolution of PFAPA recurrences [12]. In our pediatric cohort of 320 patients, 15 children with PFAPA underwent tonsillectomy [5]. Histology and electron microscopy of the specimens were unrevealing and deep cultures were negative. Attacks continued in 5 (33% failure rate) and we therefore do not currently recommend tonsillectomy. Two of the 15 adult patients had their tonsils removed, but this did not affect the course of their disease. Successful prophylactic therapy with cimetidine has been reported in six patients with PFAPA syndrome [13]. We believe that the intermittent use of a single oral corticosteroid dose should be the preferred first line of treatment as it is safe, convenient and certainly cost effective.

IFN $\gamma$  = interferon-gamma

We have found that PFAPA syndrome is common in children, and an increasing number of adults with PFAPA have been diagnosed in recent years. Since PFAPA syndrome is generally not well recognized by family practitioners and otorhinolaryngologists, all our patients were self-referred or referred by pediatricians.

This is a preliminary study of adults with PFAPA syndrome. Our pediatric cohort (N=320) is based on 14 years of patient follow-up that describes over time the main characteristics of the disease course [5]. The relatively short follow-up period in the adult PFAPA patients and the small study sample (N=15) weaken the statistical power to reach any conclusion regarding the course of the disease in adult patients.

In conclusion, increased awareness of the PFAPA clinical syndrome has resulted in an increased number of adult PFAPA patients. Steroid therapy has proved successful. The diagnosis of PFAPA should be considered in any adult with recurrent unexplained episodes of fever.

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**Correspondence:** Dr. S. Padeh, Dept. of Pediatrics A, Safra Children's Hospital, Sheba Medical Center, Tel Hashomer 52621, Israel. Phone: (972-3) 530-4430; Fax: (972-3) 547-4429 email: shay.padeh@sheba.health.gov.il