

Periodic fever, aphthous stomatitis, pharyngitis, adenitis: a clinical review of a new syndrome

Henry M. Feder, Jr., MD

Periodic fevers (fevers that occur predictably at fixed intervals) are unusual in infants and children. The classic periodic fever syndrome is cyclic neutropenia (neutropenia followed by infections and fever that recur every 21 days). A new periodic fever syndrome PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis) has been characterized over the past decade. PFAPA is defined clinically, because specific laboratory abnormalities have not been found. The clinical characteristic of PFAPA is high fevers (usually 40.0°C to 40.6°C) recurring at fixed intervals every 2 to 8 weeks. The fevers last for about 4 days, then resolve spontaneously. Associated with the fevers are aphthous stomatitis in 70% of patients, pharyngitis in 72% of patients, and cervical adenitis in 88% of patients. PFAPA is not familial and begins before the age of 5 years. An episode of PFAPA can be aborted with one or two small doses of prednisone. The episodes of PFAPA may last for years and the patient is well between episodes. The cause of PFAPA is unknown and there are no reported sequelae. *Curr Opin Pediatr* 2000, 12:253–256 © 2000 Lippincott Williams & Wilkins, Inc.

Department of Family Medicine and Pediatrics, University of Connecticut Health Center and Connecticut Children's Medical Center.

Correspondence to Henry M. Feder, Jr., MD, Department of Family Medicine, University of Connecticut Health Center, Farmington, CT 06030.

Current Opinion in Pediatrics 2000, 12:253–256

Abbreviations

FMF familial Mediterranean fever
PFAPA periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis

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Clinical review

In 1987 Marshall *et al.* [1] described a new periodic fever syndrome in 12 children. The fevers in these children would recur predictably every 2 to 12 weeks, would reach a maximum of 40°C to 41°C, and would last for about 5 days. The children came from Tennessee, Alabama, and North Carolina. Their ancestries were diverse. Five were girls. For all patients the fevers began at less than 5 years of age. Between febrile episodes the patients were well. Associated with the fevers, nine of the 12 had aphthous stomatitis, nine of 12 had pharyngitis (cultures for group A β -hemolytic *Streptococcus* were negative), and eight of 12 had cervical adenitis. Other symptoms associated with the fevers included headache, nausea, vomiting, and abdominal pain. No immunologic abnormalities were found. The episodes were frequently associated with leukocytosis (with a left shift) and elevation of the erythrocyte sedimentation rate. The fevers were unresponsive to antibiotics or nonsteroidal anti-inflammatory drugs; however, the episodes would dramatically resolve with oral prednisone, but the next cycle was not prevented.

Following the report by Marshall *et al.* [1], children with a similar syndrome of periodic fever were reported from New York [2], Connecticut [3], and Guatemala [4]. Some of these patients reported a resolution of their periodic fever syndrome with cimetidine [3,4]. Cimetidine has many immunomodulating properties including suppressing suppressor T cells (T8), increasing interferon, and increasing chemotaxis of neutrophils and eosinophils [5,6]. The cause of this periodic fever syndrome was unknown and how cimetidine helped some patients was a mystery.

In 1989, the euphonious acronym FAPA (fever, aphthous stomatitis, pharyngitis, and cervical adenitis) was coined for this syndrome [3]. Later, it was changed to PFAPA to emphasize the periodic fever characteristic [7].

As a follow-up of these initial PFAPA reports, two of the original authors [1,3] established a registry for PFAPA patients. In 1999, they published a review of 94 patients with PFAPA [8••]. Of 99 patients initially thought to have PFAPA, five patients were excluded because cyclic neutropenia (three patients), Behçet syndrome (one patient), or familial Mediterranean fever (FMF) (one patient) was diagnosed. The 94 PFAPA patients resided

in 22 different states and three other countries (Sweden, Italy, and Saudi Arabia). They had diverse ethnic backgrounds. No two patients were from the same family.

The fevers began for these 94 patients [8••] at a mean of 2.8 years of age (all began at less than 5 years of age). The mean duration of each episode of fever was 4.8 days, and the mean period between episodes was 28 days. Associated with the fever were aphthous stomatitis (70%), pharyngitis (72%), or cervical adenitis (88%). The mean maximum temperature was 40°C. Laboratory findings were normal (including normal IgA, IgM, IgG, and IgD levels, lymphocyte subsets, and liver function tests) except during episodes, when patients sometimes had a leukocytosis or elevated erythrocyte sedimentation rate. Antibodies to herpes simplex virus, Epstein-Barr virus, and cytomegalovirus were sometimes present.

The defining characteristic of PFAPA [8••] was a dramatic resolution of fever with one or two doses of prednisone (1 mg/kg/dose). However, following prednisone treatment the next episode of fever may occur earlier than expected. Aspirin, acyclovir, colchicine, and antibiotics were not effective. Acetaminophen or ibuprofen usually reduced the temperature. The PFAPA syndrome resolved in eight of 28 patients (29%) treated for 6 months with cimetidine. Also, 11 patients had tonsillectomies, or tonsillectomy plus adenoidectomy, and PFAPA resolved in nine of these 11 patients (82%). Of the 94 patients with PFAPA, disease resolved in 17 of 94 (18%) with cimetidine or tonsillectomy; disease resolved spontaneously in 49 of 94 (52%) (usually <5 years); and 28 of 94 patients (30%) continued to have febrile episodes after a mean of 4.5 years. Because PFAPA resolves spontaneously, we cannot be sure of the therapeutic impact of cimetidine or tonsillectomy.

In a study from Israel, Padeh *et al.* [9•] found 28 patients with PFAPA among hundreds of patients with FMF. Some FMF patients presented in childhood with intermittent fevers without polyserositis; thus in this group it was

difficult to diagnose FMF versus PFAPA. The patients with PFAPA had periodic fevers that responded to low-dose prednisone, whereas FMF patients had fevers that were not affected by steroids. Patients with FMF had the FMF gene [9•,10] whereas those with PFAPA did not. Also, for some patients with PFAPA illness resolved following tonsillectomy. During febrile episodes, patients with PFAPA frequently have leukocytosis (with a left shift) and an elevated erythrocyte sedimentation rate. In addition, α -interferon, tumor necrosis factor, and interleukin-6 were elevated [8••]. During episodes of fever, helper and suppressor T-cell ratios may be normal [4]. We also have performed flow cytometry on tonsils removed from patients with PFAPA and found nothing unusual. Careful studies of patients with PFAPA examining cytokines and lymphocyte markers, before, during, and after febrile episodes are greatly needed.

Differential diagnosis

Periodic fever syndromes are defined by febrile episodes that recur at regular intervals over years [11,12]. Between episodes of fever the patient is well. Biorhythms that recur at intervals longer than every 24 hours are unusual. The obvious exception is the menstrual cycle. The periodic fever syndromes include FMF, familial Hibernian fever, familial hyper-IgD syndrome, cyclic neutropenia, and occasionally juvenile rheumatoid arthritis (Table 1).

Familial Mediterranean fever is characterized by brief fevers associated with sterile peritonitis, pleuritis, or arthritis. About half of patients with FMF develop skin involvement with erysipelas-like erythema or Henoch-Schönlein purpura. The febrile episodes in FMF usually last 2 days, occur unpredictably, and are separated by months. FMF occurs predominantly in Sephardic Jews, Armenians, Arabs, and Turks. Patients with FMF can be treated with colchicine, which reduces the frequency of attacks. Lastly, patients with FMF do not respond to prednisone [9•,12,13].

Table 1. Periodic fever syndromes

	PFAPA*	Familial Mediterranean fever	Familial Hibernian fever	Hyper-IgD	Cyclic neutropenia	Juvenile rheumatoid arthritis
Age at onset, <i>y</i>	Usually < 5	Usually > 5	Usually > 5	Usually < 1	Usually < 1	Usually > 5
Response to prednisone	Dramatic (single dose)	None	Dramatic (single dose)	None	Rarely	Yes (multiple doses)
Aphthous stomatitis	Usually	No	No	No	Mucositis	No
Pharyngitis	Usually	No	No	No	Yes	No
Adenitis	Cervical	None	None	Generalized	Cervical	Generalized
Length of fever, <i>d</i>	5	2	2	5	3	> 7
Interval between fevers	21–42 <i>d</i>	Weeks to months	Weeks to months	Weeks to months	21 <i>d</i>	Variable
Periodic fevers	Yes	No	No	No	Yes	No
Familial	No	Autosomal recessive	Autosomal recessive	Autosomal recessive	Autosomal recessive (in 30% of patients)	Unusual
Laboratory diagnosis	No	Gene analysis	Gene analysis	IgD (> 100 U/mL)	Neutropenia	No

PFAPA, periodic fever, aphthous, pharyngitis, adenitis.

Hyper-IgD syndrome was first described in 1984 in six patients from the Netherlands [14]. Since then more than 50 patients with hyper-IgD syndrome have been described [15,16]. The febrile episodes of hyper-IgD syndrome last about 4 days and recur unpredictably separated by weeks or months. Associated findings include macular rash, arthritis, generalized lymphadenopathy, and splenomegaly. Episodes begin in infancy and frequently follow routine immunizations (the result of antigenic stimulation). Patients have markedly elevated IgD levels and usually have elevated IgA levels. Recently, the gene for hyper-IgD syndrome has been identified [17,18]. The gene that encodes for IgD also encodes for mevalonate kinase. During episodes of fever, patients with hyper-IgD syndrome have elevated levels of mevalonic acid in their urine. In a few PFAPA patients tested, we have not found increased urinary mevalonic acid during febrile episodes (samples sent to Richard I. Kelley, MD, PhD, Kennedy Krieger Institute, and John Hopkins University).

Cyclic neutropenia usually begins during the 1st year of life, and like clockwork the neutrophil count goes to zero every 21 days [19]. The neutropenia is preceded by malaise. During the neutropenia episodes, patients develop mucositis (with aphthous stomatitis), otitis, and skin infections. Fever is the result of these infections. The fevers in PFAPA are not as exact in their cycles as those of cyclic neutropenia, and the interval between fevers in PFAPA is unusually longer than 21 days.

Systemic-onset juvenile rheumatoid arthritis is usually manifested by fever, generalized lymphadenopathy, and hepatosplenomegaly [20]. The length of the febrile episodes is weeks. After spontaneous remission the onset of the next febrile episode is not predictable. Ultimately, the patient develops arthritis, which establishes the diagnosis. In addition, patients may have morning stiffness, rash with fever spikes, serositis, and uveitis. Patients may also have a positive rheumatoid factor or positive antinuclear antibodies.

Infectious causes of recurrent fevers

A few infectious diseases involve febrile episodes alternating with afebrile periods. Classically, malaria was characterized by its fever pattern into quartan and tertian malaria. Fever spikes in patients with malaria follow the rupture of malaria-infected erythrocytes with the release of merozoites. The merozoites infect other erythrocytes and the cycle begins anew. This cycle takes 72 hours for *Plasmodium malariae* versus 48 hours for *Plasmodium falciparum*, *Plasmodium vivax*, and *Plasmodium ovale*. Therefore, the fever pattern may be used to distinguish *P. malariae* infection from the others. Malaria fever patterns are not always quartan or tertian because the parasites mature asynchronously [21].

Relapsing fever is either louse-borne (*Borrelia recurrentis*) or tick-borne (*Borrelia hermsii*). The episodes of fever last 3 to 6 days followed by approximately 7 days without fever. Episodes resolve spontaneously after a few weeks or months [22].

Labial, genital, or cutaneous herpes simplex virus infections can recur at regular intervals. Outbreaks may recur with menstruation or stressors that decreases helper T cells [23]. Recurrent outbreaks of herpes simplex virus do not cause high fevers.

Lastly, a patient has been reported with periodic illness due to Epstein-Barr virus [24]. A 15-year-old boy had fevers (maximum 40°C) recurring every 2 to 3 weeks, lasting 2 to 3 days, and associated with generalized adenopathy. Repeated Epstein-Barr serologic tests showed persistently positive antibodies to viral capsid antigen-IgM, -IgG, and -IgA; early antigen restricted; and Epstein-Barr nuclear antigen. Febrile episodes in this patient persisted despite tonsillectomy and cimetidine and prednisone treatment [24].

Aphthous stomatitis

Approximately 70% of patients with PFAPA have aphthous stomatitis associated with their fevers [8••]. Recurrent aphthous stomatitis without fever has been reported to occur in 5% to 25% of the general population [25]. Episodes of recurrent aphthous stomatitis are usually unpredictable and are not associated with fever. The most common presentation of recurrent aphthous is small (<5 mm), painful ulcers of nonkeratinized, nonfixed oral mucosa, which include labial mucosa, buccal mucosa, the soft palate, and under the tongue. These are called *aphthae minor* and they heal without scarring in 10 to 14 days. *Aphthae major* are greater than 5 mm, usually heal with scarring, and last 2 to 4 weeks. An uncommon type of aphthae are herpetiform aphthae, which are clusters of pinpoint ulcers that heal in 7 to 10 days. Herpetiform aphthous ulcers are not due to herpes simplex virus. Treatments for recurrent aphthous ulcers include local and systemic steroids or local and systemic antibiotics. Also, aphthous ulcers may be effectively treated with immune-modulating agents such as colchicine, cyclosporin, pentoxifylline, thalidomide, and cimetidine [4,25]. The cause of recurrent aphthous ulcers is unknown. The aphthous ulcers in PFAPA are *aphthae minor*.

Behçet's disease is easily distinguishable from PFAPA because fever and periodicity are not characteristic of Behçet's [26]. The aphthous ulcers of Behçet's are usually 1 to 3 cm and heal with scarring (*aphthae major*). In addition, patients with Behçet's have genital ulcerations, uveitis, pustular skin rashes, synovitis, and meningoenzephalitis.

Conclusions

High fevers without an obvious cause are common in infants and children. Recurrent episodes of fever are also common. However, when the fevers follow a cyclic pattern and parents are able to predict the next episode, then the diagnosis of PFAPA should be considered. If the individual febrile episodes resolve with one or two doses of prednisone, then the diagnosis of PFAPA is likely. PFAPA episodes may recur for years. A plan should be developed between the physician and family, defining when PFAPA patients need to be seen and how to empirically treat each episode. Families of PFAPA patients should be reassured that sequelae of PFAPA have not been reported and that ultimately the periodic fevers will resolve.

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