

Periodic Fever Syndromes

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FEVER ACCOMPANIED BY APHTHOUS STOMATITIS, PHARYNGITIS, AND CERVICAL ADENITIS SYNDROME (PFAPA SYNDROME)

The PFAPA syndrome is a chronic disease of unknown etiology characterized by **P**eriodic episodes of high **F**ever accompanied by **A**phthous stomatitis, **P**haryngitis, and cervical **A**denitis, often associated with headache and/or abdominal or joint pain. This syndrome belongs to the group of recurrent fever syndromes, which includes systemic onset juvenile rheumatoid arthritis, cyclic neutropenia, and the group of hereditary fevers. PFAPA however differs from these hereditary autoimmune fevers as it is a sporadic syndrome and second cases in siblings are not found.

CLINICAL FEATURES

The earliest report of the syndrome was by Miller et al. who described 29 patients with febrile episodes occurring every 21.6 days for an average of 4.6 days. In 1987 Marshall et al. described a syndrome of periodic fever in 12 children, lasting 3 to 6 days and recurring every 3 to 8 weeks, accompanied by aphthous stomatitis, pharyngitis, and cervical adenitis, and in 1989 coined the acronym PFAPA to describe this entity. They later described a larger series of 94 children identified with PFAPA

and provided the long-term follow-up on 83. Along with this report we have reported our experience with 28 cases. PFAPA episodes last 4-5 days and resolved spontaneously. Attacks recur every 4-6 weeks, with temperature up to 40.5° C. The affected children had no long-term sequelae. Episodes of fevers begin at the age of 4.2 ± 2.7 years. Fever, chills, sweats, headache, muscle and bone pain are common. General malaise, resembling streptococcal pharyngitis, tonsillitis with negative throat cultures, and cervical adenopathy are typical of the syndrome. Less common are aphthae, abdominal pain, and arthralgia. Mild hepatosplenomegaly was observed in some patients. There is complete resolution between episodes, appetite and energy return to normal and lost weight is regained. Affected children grew and developed normally, had no associated diseases, and no long-term sequelae. The clinical presentation of patients with PFAPA in two large series is summarized in Table 1.

Table 1. Clinical presentation of patients with PFAPA

	Thomas et al. [46] (%)	Padeh et al. [68] (%)
Fever	100	100
Exudative tonsillitis	72*	100
Malaise	NA	100
Cervical adenopathy	88	100
Aphthae	70	68
Headache	60	18
Abdominal pain	49	18
Arthralgia	79	11
Chills	80	NA [@]
Cough	13	NA
Nausea	32	NA
Diarrhea	16	NA
Rash	9	NA

The differences between the 2 series probably derive from the differences in the diagnostic criteria of the two centers (Table 2). With the exception of the prevalence of aphthae, these figures have not changed in the current series of 220 children with PFAPA followed in our center.

TABLE 2. PFAPA; Diagnostic CRITERIA	
<i>Thomas, Feder, Lawton & Edwards [68]</i>	<i>Padeh [46]</i>
I. Regularly recurring fevers with an early age of onset (<5 years of age)	I. Monthly fevers – cyclic fever at any age groups
II. Constitutional symptoms in the absence of upper respiratory infection with at least 1 of the following clinical signs: a) Aphthous stomatitis b) Cervical lymphadenitis c) Pharyngitis	II. Possibly aphthous stomatitis
	III. Cervical lymphadenitis
	IV. Exudative tonsillitis + negative throat culture
III. Exclusion of cyclic neutropenia	
IV. Completely asymptomatic interval between episodes	V. Completely asymptomatic interval between episodes
V. Normal growth and development	VI. Rapid response to a single dose of corticosteroids

LABORATORY INVESTIGATION

Laboratory investigation at onset of the fever showed a normal hemoglobin level, mild leukocytosis of $13 \times 10^9 / \text{mm}^3$, moderate elevation of the sedimentation rate 41-56 mm/1st h, and normal platelet count. Serum IgD levels were elevated in 12 of the 18 patients (66%) in whom we measured. The levels were >100 U/mL, which is the cutoff level for HIDS. The serum IgD levels (140.2 ± 62.4 U/mL) were

significantly higher than those found in healthy children in an age-matched control group (16.5 ± 15.8 U/mL) or children with juvenile rheumatoid arthritis (85.9 ± 47.4 U/mL). Serum IgD levels were normal in the European and US reports. Immunologic and serologic studies were uniformly nondiagnostic. Distributions of T-lymphocyte subsets were normal in all 12 patients studied. IgE levels were elevated in 8 of 16 patients. Imaging studies included chest films, sinus films, gastrointestinal series, computed tomography scans of the head and abdomen, gallium scans, and bone scans, all of which were negative.

DIFFERENTIAL DIAGNOSIS

Periodic fever without other systemic manifestations or sites of disease has a short list of differential diagnoses. An infectious disease or malignancy is rarely diagnosed in an individual with predictable periodic fever. Unexplained episodic fever can be the early manifestation of Crohn's disease for months to years. Young age, normal growth, sustained sense of well-being, normal hemoglobin level, normal sedimentation rate between febrile episodes, and absence of recurring, even mild, pathologic signs or symptoms related to the bowel help distinguish those with the PFAPA syndrome. Recurrent fever can be associated with congenital or acquired immunodeficiency disorders, such as deficiency of total immunoglobulins, IgG, or its subclasses; hyperimmunoglobulinemia M (mutations of CD40 ligand) and E ; dysfunction/deficiency of T lymphocytes, phagocytic cells, or complement; cyclic neutropenia; and human immunodeficiency virus infection. However recurrent unusual, or severe infections do not follow in PFAPA syndrome. Oral lesions are not distinctively different from the common recurrent aphthous ulcers seen in individuals without systemic illness, although those ulcers tend to be singular to few, large, deep, and painful; and they frequently follow an identifiable insult. The prevalence of aphthae has dropped since our first report of 28 patients and is now only 22% among the 220 patients with PFAPA followed in our clinic. Other manifestations of Behçet's disease such as arthritis, genital ulcers, uveitis, erythema nodosum-like skin lesions, evidence of systemic vasculitis, and pathergy are not seen in PFAPA patients. Systemic onset juvenile idiopathic arthritis has hectic spiking fevers, generalized adenopathy, hepatosplenomegaly, and arthritis. Fever may persist for months without remission. Other than complicating infections and neutropenia, the clinical manifestations of cyclic neutropenia and PFAPA are remarkably similar. Although hereditary periodic fever syndromes share

features of PFAPA, paroxysmal serosal or synovial inflammation is their dominant feature, with fever less consistent or cyclic. In HIDS, patients are predominantly (but not exclusively) of Dutch ancestry and have onset of fevers with predictable periodicity in infancy. Unlike PFAPA, abdominal symptoms, especially vomiting (56%) and diarrhea (82%), were dominant features, and 80% had polyarthralgia; aphthous stomatitis was not a manifestation. Modestly elevated serum concentrations of IgD and minimally to modestly elevated IgE levels have been reported. Whether findings reflect normal variations in immunoglobulins, are results or markers of another abnormality, or represent one or more immunologic dysregulations, as the cause of PFAPA syndrome remains unclear.

TREATMENT

Glucocorticoids are highly effective in controlling symptoms. Most of the patients given one dose of corticosteroids (2 mg/kg/d prednisone or prednisolone, preferably 0.3 mg/kg of bethamethasone (which has a longer half life), report a dramatic resolution of fever within 2 to 4 hours after the ingestion of the corticosteroids. In many cases, lower doses of corticosteroids successfully aborted the attacks, and the parents individually adjusted the doses. In addition, most of the associated symptoms resolved, with aphthous stomatitis being the slowest manifestation to respond. Although corticosteroid therapy did not prevent subsequent attacks, patients continued to respond on subsequent cycles. In Thomas' report, some patients defervesced only after a longer course. They recommend a dose of 1 mg/kg prednisone or prednisolone at the beginning of an attack, the same dose on the next morning, and one half of that dose on days 3 and 4 as a starting point. Doses on days 3 and 4 may be omitted in some patients, as determined by trial during subsequent episodes. We usually instruct the patients to give the medication at the onset of the attack, and consult their pediatrician only if the attack does not abort. The cycles of fever became more closely spaced after initiation of glucocorticoids treatment in many patients, a phenomenon that is worrisome to the parents, but always abates with time. The syndrome completely resolves over a period of 8 ± 2.5 years. In our clinic, in most of the patients the attacks discontinued before the age of 10. Two therapies reported to be effective in some patients are cimetidine and tonsillectomy, with or without adenoidectomy. Tonsillectomy had been previously associated with

resolution of PFAPA recurrences. In our clinic, 12 patients underwent tonsillectomy. Histology and electron microscopy of the specimens were unrevealing, and deep cultures were negative. Attacks continued in 3 (25% failure rate), and therefore we do not currently recommend tonsillectomy.

PATHOPHYSIOLOGY

The cause of PFAPA is unknown. One potential clue is the remarkable similarity of uncomplicated episodes of cyclic neutropenia and febrile attacks in PFAPA.

Cyclic neutropenia is caused by an unidentified defect in hematopoietic precursor cells or by alterations in the regulation of cytokines. Mutations of the gene ELA2 encoding neutrophil elastase, cause a perturbed interaction between neutrophil elastase and serpins or other substrates which regulates the clock-like timing of haematopoiesis.

Perhaps PFAPA and cyclic neutropenia share common pathways of immune dysregulations. The ability of a single dose of corticosteroid to abort attacks of PFAPA 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 γ -interferon, tumor necrosis factor, and interleukin-6. It seems that an abnormal host immune response to as yet unidentified commensally microorganisms in the tonsils or the oral mucosae may account for the symptomatology. Long has hypothesized that the periodicity of the PFAPA syndrome derives from intermittent expression or suppression of antigens or epitopes of infectious agents or alteration in nature or kinetics of immunologic response. Lack of second cases in siblings or other close contacts, lack of clustering in season or geographic areas and duration of PFAPA for years, without progression, weigh heavily against an infectious disease.