

EDITORIALS

Syndrome of Periodic Fever, Aphthous stomatitis, Pharyngitis, and Adenitis (PFAPA)—What it isn't. What is it?

Thomas et al¹ and Padeh et al² have done a great service in describing a collective experience of 122 children with the PFAPA (Periodic Fever, Aphthous stomatitis, Pharyngitis, and cervical Adenitis) syndrome. Most pediatricians and all subspecialists in infectious diseases and rheumatology will have had experience with such cases. Without a known cause or a confirmatory test, diagnosis is appropriately restricted to typical cases. In my experience such cases are both dramatic and unique in a sea of children evaluated in primary and referral care because of "recurrent fevers" or because they are "sick all the time." Two cardinal features are both required and discriminatory. The first is that episodes have clockwork periodicity (usual interval <4 weeks), unheralded onset (except when a keenly observant parent notes a few hours of lassitude), and brisk rise to high fever (>39°C) that is sustained over 3 to 6 days and is unaccompanied by remarkable respiratory tract or other symptomatology. Chills are common; but rigors, drenching sweats, and

myalgia or arthralgia are not features. The child's preserved sense of well-being at 40°C is notable. The second feature is the child's complete wellness between episodes. Appetite and energy are normal, lost weight is regained, and growth and development progress. Children with PFAPA are *not* "sick all the time," and their parents usually do not see them as such. When fever abates, they declare themselves well and are at the top of their game. They are quite different from that larger group evaluated because of chronic or recurring low-grade fever and nonspecific "dwindles," who tend to be older and have respiratory tract symptomatology (sometimes with frank allergic signs or symptoms), chronic absenteeism from school, and a persistent "down" feeling and whose family dynamics are frequently unusual. Seemingly, children with PFAPA *and* their parents are uncommonly cheerful, focused on wellness and as struck by the mystery of the episodes as are we.

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Periodic fever without other systemic manifestations or sites of disease has a short list of differential diagnoses. Thomas et al¹ discuss other pos-

sible diagnoses, each eliminated by careful attention to patient's ethnicity, family history, associated symptomatology, and results of *simple* laboratory tests (eg, complete blood counts). An infectious disease or malignancy is rarely diagnosed in an individual with

HIDS	Hyperimmunoglobulinemia D syndrome
PFAPA	Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis
RAS	Recurrent aphthous stomatitis

predictable periodic fever.^{3,4} Recognizable autoimmune diseases invariably have organ-specific symptoms or signs over time and rarely have predictable periodic fever as the *cardinal* feature. Unexplained episodic fever can be the singular feature 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 primary or acquired immunodeficiency disorders,^{5,6} such as deficiency of total immunoglobulins, IgG, or its subclasses; hyperimmunoglobulinemia M (mutations of CD40 ligand)⁷ and E⁸; dysfunction/de-

Table. Speculated cause of PFAPA syndrome by weight of its features

	Infection		Immune dysregulation	
	Pro	Con	Pro	Con
Age of onset <5 y	2			2
Predominance of male subjects	1			2
Sporadic familial occurrence		1		1
Sporadic season/geography		1	1	
Underrepresentation of African American and Hispanic subjects		2	1	
Ethnic diversity of cases	2			2
Periodicity of fever and wellness		3	2	
Aphthous stomatitis			3	
Duration of syndrome >4 y		3	3	
Lengthening intervals: wellness to spontaneous cure	2			3
Absence of sequelae				2
Responsiveness to corticosteroid but not to antimicrobial agents		3	3	
Increased episodes after corticosteroid therapy	3			1
Cure after tonsillectomy	3			
Totals	13	13	13	13

1 = light weight; 2 = middle weight; 3 = heavy weight.

iciency of T lymphocytes, phagocytic cells, or complement; cyclic neutropenia⁹; and human immunodeficiency virus infection. A constant feature of these disorders, however, is recurrent, unusual, or severe infections. In contrast, children with PFAPA seem to be spared from their siblings' and peers' common infections (eg, otitis media, colds, and bronchiolitis) and do not have unusual infections.

Aphthous stomatitis, present in 67% and 68% of US and Middle Eastern children reported with PFAPA, respectively, is frequently overlooked by parents or physicians at the time of referral for recurring fevers. Almost invariably, when an examination is requested during the next episodes, aphthous ulcers are seen. The number, size, sites, and pattern of healing of intraoral ulcers are not described in the current PFAPA case series, but in my experience, with notable exceptions, children have had few to several, non-clustered, small (<5 mm), shallow ulcers that were present in the pre-ulcerative phase on the day fever began and then ulcerated and healed over 5 to 10 days without scarring. Oral lesions are not distinctively

different from the common recurrent aphthous ulcers seen in older individuals without systemic illness, although those ulcers tend to be singular to few, large, deep, and painful; and they frequently follow an identifiable insult. PFAPA syndrome ulcers are distinguishable from the diffusely ulcerated, denuded, pseudomembranous lesions of Stevens-Johnson syndrome, as well as from the perigingival, diffusely denuded, erythematous, and swollen lesions of oral mucositis after cytotoxic chemotherapy and neutropenia in children with cancer. In children with PFAPA, periodic fever rather than stomatitis is the primary complaint. If ulcers are the cardinal feature of the child's problem or are debilitating, recur in crops of 3- to 15-mm ulcers with a red rim, involve multiple oral sites (palate, tongue, posterior pharynx, lips), and heal slowly over weeks, other manifestations of Behçet's disease should be diligently sought. These include arthritis, genital ulcers, uveitis, erythema nodosum-like skin lesions, evidence of systemic vasculitis, and pathergy. Aphthous stomatitis is usually the initial symptom of Behçet's dis-

ease and can predate other manifestations by years; periodic fever is not usual.^{10,11}

Pharyngitis and cervical adenitis are the least distinctive or specifically described manifestations in the case series of PFAPA published to date. Pediatricians have been taught to hang hats (and scarves in the '90s) on these specifics, which help separate infectious causes in acute cases. In my experience, the pharynx and tonsils are erythematous, without exudate. Tonsils are only modestly enlarged (not asymmetrically) and do not have crypts with exudate; they regress between episodes. It is troublesome in this regard that all of the patients with PFAPA in the study by Padeh et al² had "exudative tonsillitis." Are differences related to inattention to semantics, evaluation, or recording; are there different findings on subsequent days of illness or in different children; are differences unimportant; or does the case series of Padeh et al represent a different disease? Cervical adenitis in PFAPA syndrome is described vaguely. Termed *lymphadenitis* and *lymphadenopathy* by the same authors, findings share

features of both. Enlarged nodes are moderately tender, rapidly appearing and regressing, but are bilateral, not exceeding 5 cm in diameter, not red or warm, and never fluctuant. Generalized lymphadenopathy or noteworthy hepatosplenomegaly suggests a diagnosis other than PFAPA syndrome. Again troublesome is the notation of "mild hepatosplenomegaly" in 21% of the cases described by Padeh et al.²

If we are convinced that PFAPA syndrome is a medical entity, distinguishable from others that it is not, then what is it? Infectious disease or immune dysregulation? The answer is easy: no one knows. The speculation is harder: clues abound. Interpretation, however, leads to oxymorons, palindromes, and endlessly circling carts and horses. The table is a scorecard of "pros" and "cons" for infective versus immunologic pathophysiology, based on superficial walks-like-a-duck, talks-like-a-duck comparisons of features of PFAPA syndrome with classic infectious and immunologic diseases (Table). The rare occurrence of PFAPA in older children and adults, as well as the predominance in boys, is "pro" infectious disease and "con" immune-mediated or autoimmune disease. Lack of second cases in siblings or other close contacts and lack of clustering in season or geographic areas make infection unlikely *unless* exposure to a vector or an unusual environmental factor is required. In the multiregional report of PFAPA cases by Thomas et al¹ and my Philadelphia experience (where primary populations served are Hispanic and African American yet no cases of PFAPA occurred in these groups), Hispanic and African American subjects are underrepresented. Potential explanations of bias of observation and referral aside, there are no infectious diseases from which urban, disadvantaged racial minorities would likely be protected except if a critical vector or environmental exposure or both were more associated with suburbs or affluence.

Speculation about a hereditary predisposition to immune dysregulation in PFAPA does not hold up well with multiple ethnicities of patients described. Persistence of identical episodes of PFAPA, over years, favors a mechanism of immunologic dysregulation. Cyclic neutropenia may be a relevant example in which the defect is in regulation of committed stem cells; explanation for its clockwork periodicity is lacking. Although familial periodic fever syndromes share features of PFAPA, paroxysmal serosal or synovial inflammation is their dominant feature, with fever less consistent or cyclic. Hereditary periodic fever genes on chromosomes 16p and 12p have been characterized recently in individuals with familial Mediterranean fever and familial Hibernian fever.¹² The familial Mediterranean fever gene encodes a protein that is speculated to serve as a regulator of inflammation in granulocytes. A new hyperimmunoglobulinemia D syndrome was described by van der Meer in 1984, and an international group of investigators published features of 50 cases in 1994.¹³ Children, predominantly but not exclusively of Dutch ancestry, had 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. In some children fevers predated elevated serum levels of IgD (>140 mg/mL); 82% also had elevated levels of IgA. Grose et al¹⁴ described possible cases in siblings of Northern European extraction in Iowa. The role of HIDS in symptomatology is unclear. IgD stimulates inflammatory cytokines; unstimulated peripheral blood mononuclear cells in patients with HIDS have been shown to release excessive proinflammatory cytokines.¹⁵ Is PFAPA HIDS? Padeh et al² report modestly elevated serum concentrations (mean, 140 mg/mL) in 12 of 18 Middle Eastern children with

PFAPA. Thomas et al¹ found no elevated IgD level in 15 US children with PFAPA tested but minimally to modestly elevated IgE levels in 8 of 16 tested. 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.

Duration of PFAPA for years, without progression, weighs heavily against an infectious disease as causative. Just such curious cases have been documented, however. In 1996, Lekstrom-Himes et al¹⁶ documented recurrent-persistent Epstein-Barr virus proliferation and aberrant serologic response in a 15-year-old boy who had a 13-year history of episodes of fever, cervical adenopathy, mild splenomegaly, and neutrophilia recurring at regular intervals (average 2 to 4 weeks and never exceeding 12 weeks) with intervals of well-being. The authors postulated a complex interaction of oral epithelial cell turnover and B-cell kinetics to explain the striking periodicity. We¹⁷ reported a healthy, immunocompetent boy with episodes of periodic fever, beginning at 18 months of age and continuing through 5 years of age when his mother remarked that she had noted crops of tiny red painful lesions on his hands and feet over the previous 18 months.¹⁷ *Mycobacterium chelonae* was isolated from a biopsy specimen from a lesion. Clarithromycin therapy was associated with remission of syndrome, but episodic fevers and lesions recurred after cessation. *M chelonae* was isolated again. He was cured after removal of his tonsils. Other unusual bacterial infections can cause relapsing, repetitive disease (eg, *Plasmodium*, *Borrelia*, and *Brucella* species). Latent viruses can reactivate with inexplicable regularity; herpes simplex 1 and 2 and cytomegalovirus are examples. Clinical manifestations could be due to reactivated infection itself (eg, herpetic cold sores), or possibly, intermittent expression or suppression of antigens or epitopes of infectious agents or alteration in

nature or kinetics of immunologic response (eg, herpes-related recurrent erythema multiforme).

At first, the strong association of aphthous stomatitis with PFAPA stands, seemingly, as evidence for immune dysregulation. Recurrent aphthous stomatitis is the most common oral mucosal disease in North America. Immunologic and genetic factors, local trauma, smoking, stress, hormonal state, food hypersensitivity, and infection have been postulated as causes, and many have been investigated. Findings of heightened mucosal levels of messenger RNA for interleukin-2, interferon- γ , and tumor necrosis factor- α with reduced IL-10 mRNA levels in RAS-affected compared with RAS-unaffected individuals suggest that the cytokine set-point may be pro-inflammatory.¹⁸ Association of RAS with Behçet's disease, Reiter's syndrome, Crohn's disease, systemic lupus erythematosus, and cyclic neutropenia support an immunopathologic basis. Evaluation by a rheumatologist of 64 adults referred to an oral medicine clinic for treatment of RAS uncovered that almost two thirds had Reiter's syndrome, Behçet's disease, familial Mediterranean fever, or unclassifiable extraoral manifestations (primarily joint disease).¹⁹ Extensive and debilitating aphthous stomatitis in patients with acquired immune deficiency syndrome occurs with severe immune dysregulation; thalidomide (a potent immune modulator) is an effective treatment.²⁰ On the other hand, there is growing evidence of participation of infectious agents in RAS—from identification of human immunodeficiency virus in the base of ulcers in patients with acquired immune deficiency syndrome, to Epstein-Barr virus²¹ and cytomegalovirus DNA²² in biopsy specimens of pre-ulcerative oral lesions of patients with Behçet's disease, to human herpesvirus 6 or cytomegalovirus DNA or both in biopsy specimens from individuals with RAS.²³

This brings us to the question asked by my colleague, Dr Bennett Lorber,

in 1996, "Are All Diseases Infectious?"²⁴ Who ever would have thought that peptic ulcer disease, Whipple's disease, degenerative brain diseases, many cancers, and possibly atherosclerosis are infectious diseases gone awry? The exquisite responsiveness of fever in children with PFAPA to corticosteroid therapy does not dissuade this infectious diseases enthusiast. Would that autoimmune diseases responded so promptly to a single dose of prednisone! Clearly, the host inflammatory response is the cause of systemic symptoms of many infectious diseases, influenza and Epstein-Barr virus to name just two. The authors' experience^{1,2} and my own that corticosteroid-treated children with PFAPA experience shortened interval to the next febrile episode, that is, "worse" disease, favors the infection model and is unprecedented in immune-mediated diseases. Finally, the remarkable "cure" of some children with PFAPA on the day of tonsillectomy, after years of clockwork febrile episodes, is more compatible with having removed an infected organ than a tissue with localized aberrant immunologic behavior. I have annoyed microbiologists and pathologists throughout the Northeast with requests to "tell us everything" about the extirpated gland. Alas, tonsils are the cesspools of the oral swale.

In awe of the cleverness of microbes (to use us and not usually kill us) and bolstered by tallies of 13 across my scorecard, I conclude that PFAPA syndrome walks like dysregulation of cytokines and sounds like an infection. At last, a "kinecton"? Thomas et al¹ and Padeh et al² have led the way with good experiential information. Now, we need good experimental information. Meanwhile, upbeat parents and patients with PFAPA syndrome leave our offices with their disability, relieved that we recognize the constellation and predict ultimate good health, satisfied with the notion of an upregulated immune system, and armed with a prescription for prednisone should

an episode land on a birthday party or trip to Disney World.

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