

Review article

Periodic fever syndromes: a diagnostic challenge for the allergist

The objective was to present a case of periodic fever with aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA), summarize the medical literature on PFAPA, review the differential diagnosis and suggest a diagnostic approach to periodic fevers in children. A PubMed search was conducted for all case reports and series of patients with PFAPA. The references of these papers yielded further case reports. Review articles or large case series were used for sources of information regarding the other periodic fever and autoinflammatory syndromes. All cases reported as PFAPA were included in the review, even though a few of the cases may not have been accurately diagnosed. The periodic fever and autoinflammatory syndromes of childhood are a group of diseases that cause repeated febrile illnesses with various associated symptoms. Except for PFAPA, each of these diseases is caused by a known genetic mutation. Effective treatment options and long-term prognosis varies among these syndromes. Children with periodic fever or autoinflammatory syndromes sometimes present to an Allergy/Immunology clinic for immunologic evaluation. It is important for the Allergy/Immunology specialist to be familiar with the clinical presentation, diagnostic approach and treatment of these conditions.

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The pediatric Allergy/Immunology specialist is often called upon to evaluate a child with the chief complaint of recurrent febrile illnesses. These children often have been diagnosed with otitis media, sinusitis, pharyngitis, and other common childhood infections. In many cases, they are otherwise healthy children with frequent viral exposures in their daycare setting or through school-aged siblings. Allergic rhinitis can be an underlying cause of frequent sinusitis and otitis media because of obstruction of the Eustachian tubes and sinus ostia by mucosal edema. Less often, a child with recurrent febrile illnesses is found to have an immunodeficiency syndrome.

Occasionally, however, a child presents with fevers that occur in the absence of apparent infection and recur in a regular cyclic pattern. This situation is referred to as 'periodic fever syndrome', and is caused by several conditions of differing pathophysiology, clinical manifestations, and prognosis.

This paper will present the case of a toddler who presented with a periodic fever syndrome, review the medical literature regarding periodic fever with aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA), and discuss the differential diagnosis, treatment, and prognosis of PFAPA.

Case report

This 18-month-old boy presented to the Allergy/Immunology Clinic for evaluation of recurrent episodes of fever

to 39–40°C since 10 months of age. The episodes typically occurred every 2–3 weeks, with no systemic symptoms except pharyngitis and drooling. On one occasion, he was diagnosed with mastitis after 2 days of fever, but otherwise no infectious etiology was identified. Typically, the fevers lasted for 4–5 days and then spontaneously resolved. The child generally remained cheerful and active with good oral intake during the episodes, except for malaise, when his fever rose above 39°C. His parents had found that his fever and malaise responded better to treatment with ibuprofen than with acetaminophen. He required doses of ibuprofen every 4 h, to keep his temperature below 39°C. He had not been treated with antibiotics except for the episode of mastitis.

On review of systems, the patient had no history of arthritis, arthralgias, lymphadenopathy, gastrointestinal symptoms, abdominal pain, skin rashes, aphthous ulcers, or respiratory symptoms. He had been breastfed for the first 4 months. He was developmentally normal and was growing well. Immunizations were up to date. He had a past history of recurrent otitis media, which was successfully treated with tympanostomy tubes at 7 months of age.

Family history was positive for allergic rhinitis and asthma in the patient's father and second-degree relatives on both sides. The patient's mother was healthy. There was no family history of periodic fevers. The parents were of North and Central European descent (England, France, and Germany) and there was no consanguinity. The patient had no siblings. He did not attend daycare.

Physical examination revealed a happy, well developed, well nourished 18-month old, who was afebrile. The tonsils were slightly enlarged. There were no oral mucosal lesions. The nasal mucosa was normal with no rhinorrhea. Tympanic membranes were not inflamed; the tympanostomy tube was present in the right tympanic membrane, and in the external auditory canal on the left. Conjunctivae were normal. Neck was supple without adenopathy or thyromegaly. Lung, cardiovascular, and abdominal examinations were normal. There was no splenomegaly. Joints had full range of motion with no inflammation. Skin showed no rash. Laboratory evaluation revealed a normal complete blood count (CBC) and differential; immunoglobulin (Ig) A, IgG, IgM, and IgE; complement proteins C3, C4, and CH50 (hemolytic complement), C-reactive protein, and erythrocyte sedimentation rate. The IgD level was 3 mg/dl (normal range: 0–14).

The patient was seen 1 week later for evaluation during a typical fever episode. He had abruptly developed fever to 39°C the night before. He had been drooling, with somewhat decreased appetite and loose stools, but no other symptoms. On physical examination, the child was alert and pleasant. Temperature was 38.8°C, 1 h after a dose of ibuprofen. His tonsils were erythematous and enlarged, with no exudate. There was no cervical adenopathy, no oral ulceration, and no other change from his previous examination. A throat swab for Group A *Streptococcus* was negative. Urinalysis was normal and urine culture negative. The CBC and differential were within normal limits, although the absolute neutrophil count had increased. The erythrocyte sedimentation rate was elevated at 50 mm/h (upper limit of normal is 10) and the C-reactive protein was 21.9 mg/dl (upper limit of normal: <1.0).

A tentative diagnosis of PFAPA was made. As a diagnostic trial, the patient was given a prescription for prednisone, 20 mg (2 mg/kg) to be given at the onset of the next febrile episode. The next episode began 18 days later. The patient was given the prednisone, and within 4 h his fever resolved and he felt well. He remained well for 36 h, then woke up in the middle of the night with malaise and a fever of 39°C. A second dose of prednisone was given the following morning; the fever resolved and did not recur. The next episode of fever occurred 27 days later. This time, the parents gave prednisone, 20 mg once daily for two doses. The fever resolved 4 h after the first dose and did not recur at all. The following three episodes again responded to the two doses of prednisone. The child continues to be well between fevers.

Discussion

This case illustrates the typical presentation of a child with a periodic fever syndrome. In this case, the patient's pediatrician had refrained from prescribing antibiotics for

his febrile episodes as there were no apparent bacterial infections. However, the tympanic membranes can appear erythematous in a febrile child, and pharyngitis is noted in most children with PFAPA; thus, it is undoubtedly common for these children to be repeatedly diagnosed with otitis media, streptococcal pharyngitis, or other infectious etiologies. After repeated episodes of these 'infections,' the primary care physician may decide to refer the patient to a specialist for further evaluation. Thus, the allergist should be alert for the occasional child with a periodic fever syndrome, among the many children referred for allergy and immunology evaluation because of recurrent febrile illnesses. The following discussion will summarize the medical literature regarding PFAPA, review the differential diagnosis of periodic fevers in children, and present an approach to diagnosis and treatment of these disorders.

PFAPA

This syndrome, described by Marshall et al. in 1987 and 1989 (1, 2) is a clinically diagnosed condition of unknown cause. It can be recognized by the typical presentation, dramatic response to oral corticosteroid treatment, and by the exclusion of other causes of periodic fever. The characteristic pattern of PFAPA is the sudden onset of fever in the range of 38.5–41°C, which persists for 4–5 days. The fever then spontaneously resolves, and the child remains well for 3–5 weeks after which the cycle repeats. No infectious cause is apparent and the fevers do not respond to antibiotics.

A search of the medical literature found a total of 254 cases of PFAPA reported as of November 2006 (1–19). Review of the reported cases (Tables 1 and 2) reveals the mean age of onset of fevers was 2.8 years (range: 6 weeks to 14 years), and the most common symptoms occurring during the fevers were pharyngitis (78%), cervical lymphadenopathy (69%), and aphthous stomatitis (51%). Arthralgias were present in 33% of patients reported by a rheumatology group (3), most likely due to selective referral patterns; arthralgia was rarely mentioned as a complaint in other papers. Some patients complained of gastrointestinal symptoms, and a few had a rash associated with the fever. Laboratory testing during febrile episodes reveals a mild leukocytosis and elevated erythrocyte sedimentation rate, with normalization of these test results during the symptom-free intervals. Mild elevations in IgA, IgG, and IgM are noted in some patients. Most authors report normal IgD levels in all patients in whom they were checked, but one group found significantly elevated IgD in 12 of 18 patients (4). These may represent cases of Hyper-IgD syndrome (HIDS), which has considerable clinical overlap with PFAPA (see below).

The pathogenesis of PFAPA is unknown. None of the 146 children for whom family history was reported had siblings with periodic fever syndrome. Thus, unlike the

Table 1. Review of literature on PFAPA: fever patterns and outcomes

Reference	Number of patients	Age of onset (mean)	Duration of fever (mean; days)	Symptom-free interval (mean; weeks)	Tonsillectomy successful*	Cimetidine successful*	Resolution of PFAPA†
Thomas et al. (5)	94	2.8 years	4.8	4	7/11	8/28	34/83
Tasher et al. (6)	54	1.9 years	5.3	4	6/6		0/54
Miller et al. (3)	29	3 years	4.6	3			23/29
Padeh et al. (4)	28	4.2 years	4.3	5			9/28
Galanakis et al. (8)	15	3.1 years	n.a.	4	15/15		15/15
Stojanov et al. (19)	6	2.2 years	4	5			0/6
Dahn et al. (7)	5	1.8 years	n.a.	n.a.	5/5		5/5
Berlucci et al. (9)	5	2.8 years	4.5	5	5/5		5/5
Ciambra et al. (11)	5	19–60 months	n.a.	3.5	2/2		3/5
Abramson et al. (10)	4	<2 years	n.a.	n.a.	4/4		4/4
Pillet et al. (12)	3	5.7 years	4.3	3.5		3/3	3/3
Parikh et al. (16)	2	10 years	5	4	0/2		0/2
Frye (14)	1	'Preschool'	5	4–7			0/1
Lee et al. (17)	1	4.5 years	7	8.6			1/1
Scimeca et al. (15)	1	7 years	n.a.	3		0/1	0/1
Rubin and Kamani (18)	1	6 weeks	5	3			0/1
Total/mean	254	2.8 years	5	3.8	86%	33%	42%

References (1), (2), and (13) are not included in this literature summary, as it appears that the patients reported in these papers were also included in ref. (5).

*Number of patients reported to have resolution of febrile episodes/number of patients subjected to the intervention. Note that there were no control groups in any of these studies.

†Number of patients reported to have resolution of febrile episodes/number of patients reported. The duration of follow-up after resolution of symptoms was variable, from a few months to several years.

Table 2. Review of literature on PFAPA: associated symptoms

Number of patients	Pharyngitis	Cervical adenitis	Aphthous ulcer	Abdominal pain	Nausea/vomiting	Diarrhea	Rash	Arthralgia
254	78%	69%	51%	35%	21%	8%	6%	4%

The mean percentage of patients manifesting each of the above symptoms in association with febrile episodes was calculated by adding the number of patients reported with each symptom, from refs (1–19), and dividing by the total number of reported patients (254). In cases where the authors did not mention the presence or absence of a particular symptom, the symptom was considered to be absent for purposes of this calculation.

other syndromes described below, PFAPA does not have an apparent genetic basis. In the only published study looking for a genetic basis of PFAPA, six children with PFAPA were tested for mutations in the MEFV gene [associated with familial Mediterranean fever (FMF), see below]; an exhaustive analysis revealed no mutations (20).

One study has examined cytokine profiles in six children with PFAPA compared with age-matched healthy controls (19). The children with PFAPA were found to have elevated levels of the proinflammatory mediators interleukin (IL)-1 β , IL-6, tumor necrosis factor (TNF)- α , and IL-12p70 between attacks, with significant increases in IL-6 and interferon- γ during fever episodes. These findings are consistent with a T-helper 1 (TH-1)-mediated inflammatory process. Levels of the TH-2 mediator IL-4 were lower in the PFAPA patients than controls, both between and during fever episodes; IL-10 levels were comparable between the PFAPA and control groups and did not change significantly during fevers. In normal individuals, anti-inflammatory mediators such as IL-4 and IL-10 are produced in response to fevers. The authors suggest that the elevated levels of interferon- γ might be responsible for suppressing the production of

IL-4 and IL-10. Thus, PFAPA is characterized by immunologic dysregulation with a continuous proinflammatory cytokine activation and suppression of the anti-inflammatory response.

The long-term course of PFAPA is variable. Eighty-three of Marshall's initial 94 patients were contacted for follow-up, 1 month to 9.4 years after the initial diagnosis of PFAPA (5). Febrile episodes had resolved in 34 children (41%). In contrast, the second largest series (6) found no patients who had fully recovered from PFAPA, although the duration of follow-up was shorter. In general, the interval between fevers tends to be longer in patients with a longer duration of disease (5, 6) although there are exceptions. The longest persistence of PFAPA reported so far was more than 17 years in two patients, both of whom were experiencing milder and much less frequent febrile episodes than they had at the onset (5).

Significant medical complications are rare in patients with PFAPA. Unlike some of the other periodic fever syndromes, amyloidosis has not been reported in patients with PFAPA. An 11-year-old boy with otherwise typical PFAPA developed aseptic encephalitis and seizures

during two of his febrile episodes, 6 years apart (14). Developmental delays (two of 29 patients), petit mal epilepsy and progressive mitochondrial encephalopathy (one each of 29 patients) were noted to occur after resolution of periodic fevers, in one series of PFAPA patients (3). As central nervous system (CNS) disorders can be associated with recurrent fevers because of autonomic dysfunction, the diagnosis of PFAPA might be questioned in these cases. Significant CNS disease has not been associated with PFAPA in other reports.

A 4.5-year-old boy who had the onset of periodic fevers at 1 year of age developed increasingly prominent abdominal pain and biopsies revealed inflammatory bowel disease (3); his fevers resolved with treatment of the inflammatory bowel disease. In retrospect, this was a case of inflammatory bowel disease rather than PFAPA, but the presentation was reportedly typical of PFAPA for the first 3 years, highlighting the importance of careful re-evaluation of these patients at regular intervals.

Treatment of PFAPA is empirical, as the underlying cause is not known. Ibuprofen works better than acetaminophen for temporary relief of fever (5). The most effective treatment reported to date is prednisone or prednisolone, 1–2 mg/kg/day for one or two doses at the onset of fever. Most patients have a dramatic resolution of fever and associated symptoms with corticosteroid treatment (4–6). Some patients develop a shortened cycle, with fevers occurring more frequently, after treatment of previous episodes with corticosteroids (4, 5).

Cimetidine, given in a dose of 150 mg twice daily for 6 months, was associated with resolution of the febrile episodes for 11 of 32 patients (5, 12, 13). The mechanism of action of cimetidine in PFAPA has not been determined, although cimetidine is known to inhibit suppressor T-cell function by blocking the histamine type 2 receptors on the T cells.

Forty-four of 50 patients who had tonsillectomies performed because of pharyngitis associated with their periodic fevers had resolution of the fevers postoperatively (5–11, 16). However, Tasher et al. (6) noted that 26% of their 54 patients had remissions lasting 4–36 months, followed by a relapse. This observation should lead to caution in interpreting the apparently successful treatment of PFAPA by tonsillectomy or cimetidine; some of the reported cases had been followed for only a few months after treatment.

The patient presented in this paper fits the clinical picture of PFAPA in that he has the typical periodic fever pattern, elevated acute phase reactants during febrile episodes with normalization between episodes, normal IgD level, and the associated symptom of pharyngitis during fevers. As noted above, only about half the reported patients have aphthous stomatitis, and about two-thirds have cervical adenitis with their fevers; thus the absence of these findings does not rule out the diagnosis of PFAPA. In the setting of this clinical picture, the rapid resolution of the fever and pharyngitis after a

dose of prednisone further supports the diagnosis of PFAPA. As noted below, none of the other periodic fever syndromes show such a dramatic response to corticosteroid treatment. However, in the absence of a positive diagnostic test, the diagnosis of PFAPA is impossible to confirm. The patient must be followed closely for the development of specific signs suggestive of a different diagnosis (see below).

Hyper-IgD syndrome

Hyper-IgD syndrome, another cause of cyclic fevers in young children, is associated with mutations in the gene for mevalonate kinase (MVK), located on chromosome 12q24, and follows an autosomal recessive inheritance pattern (21). It is classified as one of the familial autoinflammatory syndromes, which are characterized by episodic inflammation not mediated by autoantibodies or antigen-specific T cells. Unlike PFAPA, which has been reported in all ethnic groups and in populations worldwide, HIDS is most often seen in Caucasians of western European origin; about 60% of reported patients are either Dutch or French (22). There is overlap in the presentations of HIDS and PFAPA, especially in the youngest children, but over time distinct differences emerge between the two syndromes (Table 3). Like PFAPA, HIDS is characterized by the sudden onset of high fever, persistence for 4–6 days, and spontaneous defervescence. The fevers most often occur about every 3–6 weeks but the intervals are quite variable, ranging from once weekly to twice a year. The fever cycles are also variable for individual patients and often do not have the regular periodicity that is typical of PFAPA. Some episodes are triggered by immunizations, stress, infection, or minor trauma. After defervescence, the rash and joint symptoms gradually resolve, and the patient then remains entirely well until the onset of the next fever. Some patients with frequent attacks, however, do not entirely clear their symptoms between episodes (22).

Cervical adenopathy is a common finding during febrile episodes but in contrast to PFAPA, HIDS patients usually do not have pharyngitis or aphthous ulcers associated with their fevers. Arthralgias occur in 80% of patients; arthritis eventually becomes evident, but destructive joint changes have not been described. Abdominal pain occurs during most febrile episodes in HIDS and can be severe enough to result in appendectomy or laparotomy, with findings of mesenteric lymphadenitis and/or peritoneal adhesions. Hepatosplenomegaly is frequently present. Diarrhea, watery or bloody, is also a common symptom, occurring in 82% of patients, and vomiting occurs in 56% (22). The skin rashes, seen in 82% of HIDS patients, are most commonly characterized by erythematous macules or papules, although urticaria, erythematous nodules, annular erythema with central clearing, purpura and petechiae

Table 3. Characteristic findings in PFAPA, cyclic neutropenia, and the autoinflammatory syndromes

Syndrome	Genetic mutation/inheritance	Age at onset of symptoms (years)	Regular fever cycles?/duration of fever	Acute phase reactants during/between episodes	Skin rash	Other associated symptoms	Treatment
PFAPA	None known	0–14	Yes/4–5 days	High/normal	Rare, variable	Pharyngitis, cervical adenopathy, aphthous ulcers	Corticosteroids, cimetidine, tonsillectomy
HIDS	MVK/autosomal recessive	0.5–3	Sometimes/4–6 days	High/normal	Maculopapular or other	Abdominal pain, arthralgias, cervical adenitis	Colchicine, IVIG, cyclosporine, simvastatin, etanercept, anakinra
Cyclic neutropenia	ELA-2/autosomal dominant or sporadic	0–5	Yes/3–5 days	High/normal	Bacterial cellulitis	Deep oral ulcers, gingivitis/periodontitis, bacterial infections	G-CSF
FMF	MEFV/autosomal recessive	1–20	No/1–3 days	High/mildly elevated	Erysipeloid erythema	Abdominal pain, arthritis, pleuritis, amyloidosis	Colchicine
TRAPS	TNFR1A/autosomal dominant	0–53	No/days to weeks	High/high	Migrating erythema	Myalgia, periorbital edema, conjunctivitis, abdominal pain, arthritis, pleuritis, amyloidosis	Corticosteroids, etanercept
FCAS	CIAS1/autosomal dominant	Any	No (triggered by cold)/12 h	High/normal	Urticaria	Arthritis, conjunctivitis (amyloidosis rare)	Cold avoidance, anti-inflammatories
MWS	CIAS1/autosomal dominant	Infancy	No/variable	High/normal	Urticaria	Arthritis, myalgias, abdominal pain, aphthous ulcers, deafness, amyloidosis	Anti-inflammatories, anakinra
NOMID/CINCA	CIAS1/autosomal dominant	Neonatal	No/continuous, fluctuating in severity	High/high	Urticaria	Chronic meningitis, CNS damage, deafness, blindness, deforming arthropathy, eosinophilia, coagulopathy	Anakinra

IVIG, intravenous immunoglobulin; CNS, central nervous system; PFAPA, periodic fever with aphthous stomatitis, pharyngitis, and cervical adenopathy; HIDS, hyper-IgD syndrome; FMF, familial Mediterranean fever; TRAPS, tumor necrosis factor receptor-associated periodic syndrome; FCAS, familial cold autoinflammatory syndrome; MWS, Muckle-Wells syndrome; NOMID/CINCA, neonatal-onset multisystem inflammatory disease/chronic infantile neurologic cutaneous, and articular syndrome; MVK, mevalonate kinase; TNFR1A, tumor necrosis factor receptor 1A; CIAS1, cold-induced autoinflammatory syndrome gene; G-CSF, granulocyte colony-stimulating factor.

have also occurred in some patients. Biopsies of the rashes have shown variable findings (23).

The laboratory findings in HIDS are also distinctive. Typically the IgD level is > 100 U/ml. However, young children sometimes have normal IgD levels, which rise to abnormally high levels after 2–3.5 years. Immunoglobulin A levels are also markedly elevated in most patients with HIDS (22–24). As in PFAPA, acute phase reactants are elevated during febrile episodes, and leukocytosis with a predominance of immature neutrophils is seen. Urinalysis reveals mild erythrocyturia in some patients during attacks; renal function remains normal. Laboratory values return to normal between attacks. Tests of cellular and humoral immunity and serum complement levels are normal in HIDS patients. Autoantibodies are not detected. In contrast to FMF (see below), amyloidosis has very rarely been reported in HIDS patients. During attacks, urinary excretion of mevalonic acid is slightly elevated. If the urinary excretion of mevalonic acid is markedly elevated, this suggests the diagnosis of mevalonic aciduria, a metabolic disease characterized by hypotonia, ataxia, developmental delay, failure to thrive and cataracts as well

as periodic fevers with typical systemic symptoms. Interestingly, some families with HIDS have the same genetic mutation responsible for mevalonic aciduria (25). On the other hand, the incidence of the V3771 MVK gene variant, the mutation most commonly found in HIDS patients, in the Dutch population is significantly higher than would be anticipated based on the number of diagnosed cases of HIDS in Holland (about 2 : 100 000 live births), implying that some individuals who are homozygous for this mutation do not develop HIDS (26). The reason for the differing phenotypes produced by this genetic variant has not been determined. The relationship between mevalonic acid, IgD, and the periodic fever syndrome is not as yet understood.

Approximately one-fourth of patients who have the clinical picture of HIDS, including elevated IgD levels, do not have mutations in the MVK gene (27). This condition is referred to as ‘variant HIDS’ and tends to have a milder course than classical type HIDS.

Treatment of HIDS is supportive and empirical. Only one patient has been reported to have complete resolution of attacks with corticosteroid treatment, and a few

additional patients had partial responses (22). Colchicine, which is effective treatment for FMF, diminished the frequency and intensity of attacks in only about 15% of HIDS patients. Cyclosporine and intravenous immunoglobulin have also been effective in some patients. Treatment with simvastatin, a coenzyme A reductase inhibitor, decreased the number of febrile days in five of six subjects (28). Etanercept, a TNF- α inhibitor, and anakinra, an IL-1 inhibitor, have each been effective in shortening the duration of the febrile episodes in a few patients, although ineffective in others (29–31).

The overall prognosis of HIDS is good. While the condition usually persists, there is a tendency for the attacks to become less frequent and less severe over time. No significant long-term morbidity or increased mortality has been described in patients with HIDS.

Cyclic neutropenia

The other cyclic fever condition that typically presents in children < 5 years of age is cyclic neutropenia. A mutation in the gene for neutrophil elastase (ELA2), on chromosome 19p13.3, is responsible for this rare, autosomal dominant disease (32). The syndrome is characterized by cyclic maturational arrest of the bone marrow myelocytes, leading to transient neutropenia with absolute neutrophil counts below 200 cells/ μ l. The fevers tend to be very regular, occurring at 21-day intervals and lasting 3–5 days. Fever often occurs during or just after the neutropenic episode and is typically associated with gingivitis, stomatitis, cervical adenopathy, and/or diarrhea. In contrast to the shallow aphthous ulcers seen in PFAPA, the mouth ulcers in cyclic neutropenia are deep, painful and last a week or longer; gingivitis and periodontal disease are common with cyclic neutropenia but are not seen with PFAPA (33). Fevers are typically more moderate than those seen in PFAPA and HIDS. Infectious complications such as cellulitis, bronchitis, sinusitis, pharyngitis, and otitis media frequently occur during the neutropenic cycles. Severe complications including bacterial peritonitis or septic shock occur rarely (34). The diagnosis is made by documenting the transient neutropenia; this requires checking absolute neutrophil counts two to three times weekly until a fever occurs. This testing was not performed in the patient reported here, as he had no mouth ulcers, gingivitis, bacterial infections, or other complications typical of cyclic neutropenia. The diagnosis can be confirmed by bone marrow examination during the neutropenic episode, and/or by genetic testing. Treatment by administration of recombinant granulocyte colony-stimulating factor is indicated for patients with significant infectious complications.

Familial Mediterranean fever

In addition to HIDS, several other familial autoinflammatory diseases can present with recurrent fevers in

children, although they are not characterized by regular fever cycles. The most common of these syndromes is FMF. Unlike PFAPA and HIDS, only about 50% of patients with FMF have onset of fever episodes before 4 years of age; 80% have symptoms by 10 years (35). Abdominal pain is usually the first symptom, followed by fever to 40°C, typically lasting 1–3 days and occurring at irregular intervals ranging from weekly to every 4 months or less. Associated symptoms can be severe, including acute abdominal pain, arthritis, pleuritis and hot, painful, swollen confluent erythematous rashes ('erysipeloid erythema'). However, some children have only brief fevers lasting a few hours, with no associated symptoms, for the first few years. Symptoms resolve between fevers. This condition is caused by mutations in the MEFV gene, located on chromosome 16p, and is recessively inherited. The disease is most prevalent among Arabs, Armenians, Druze, Turks, and North African Jews of non-Ashkenazi descent, who have the highest documented population incidence of 0.4% (36–38). Pyrin, the protein encoded by the MEFV gene, is found mainly in neutrophils and is thought to downregulate proinflammatory mediators. Neutrophilic infiltrates are found in peritoneal, pleural, or synovial fluid during episodes of inflammation in FMF (36, 39, 40). Acute phase reactants are elevated during fevers and often to a lesser extent between fevers. Autoantibodies are not present. Over time, systemic amyloidosis develops in some patients with FMF and can lead to early mortality. Treatment with colchicine is effective in reducing the fevers, associated symptoms, and risk of amyloidosis (41).

Tumor necrosis factor receptor-associated periodic syndrome

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) has a widely variable age of onset, ranging from 2 weeks to 53 years (42). This syndrome was initially called Familial Hibernian Fever, because it was first described in a Scotch-Irish family. It has now been described in many other populations (43). The autoinflammatory syndrome is caused by dominant mutations in the TNFR1A gene on chromosome 12p (44), leading to a decrease in the soluble TNF receptor and thus increased TNF activity (42). Regular fever cycles are not a feature of TRAPS; intervals between episodes vary from weeks to years, and the duration of each episode ranges from days to weeks, with a mean of about 21 days. Some patients do not have episodic attacks, but have daily symptoms of variable severity. The typical episode begins with deep muscle cramping in an extremity, which becomes more severe over a few days and is usually associated with fever of 38–41°C. A tender, raised erythematous rash resembling cellulitis often overlies the area of myalgia. The myalgia and rash tend to migrate distally over the course of the episode. The other symptom that distinguishes TRAPS from FMF and HIDS is the frequent occurrence of painful periorbital

edema and conjunctivitis. Other associated symptoms are similar to those of FMF, with severe abdominal and/or scrotal pain, arthritis, and pleuritis. Unlike HIDS, TRAPS is not characterized by splenomegaly. Serpiginous and plaque-like skin rashes are sometimes seen.

Biopsies of affected muscles reveal monocytic fasciitis, and skin biopsies show an interstitial infiltrate of monocytes and lymphocytes, without vasculitis (45). Laboratory evaluation demonstrates elevated acute phase reactants during and often between symptomatic periods. Levels of the soluble TNF receptor are low both during and between attacks (42). Systemic amyloidosis occurs in about 14% of patients and is the major cause of mortality, because of renal failure. Amyloidosis is much more likely to develop in patients with cysteine-substitution mutations (24%) *vs* noncysteine mutations (2%) (46). Unlike FMF, TRAPS does not respond to treatment with colchicine. A single dose of corticosteroid does not

cause dramatic resolution of fever and symptoms in patients with TRAPS as it does in PFAPA, but the symptoms of a TRAPS episode resolve gradually with a 7- to 10-day course of corticosteroid. Trials of other immunosuppressants have not shown efficacy for TRAPS (47). Etanercept has been shown to be effective in reducing symptoms and laboratory abnormalities in about two-thirds of patients (48).

CIAS1-related autoinflammatory syndromes (cryopyrinopathies)

Three distinct syndromes are caused by dominant mutations in the cold-induced autoinflammatory syndrome gene, located on chromosome 1p44 (CIAS1). The product of this gene is a complex protein known as cryopyrin that is known to play an important role in activation of IL-1 β . All of these syndromes are characterized by bouts of fever, arthralgias, and a rash that appears urticarial,

Table 4. Diagnostic approach to the child with periodic or recurrent fevers of unknown etiology

1. History
 - a. Fever pattern
 - (1) Regular cycles?
 - (2) Duration of fevers
 - (3) Interval between fevers
 - b. Associated symptoms including type of skin rash, if any; arthritis, edema, pain (abdominal, limb, chest), growth failure
 - c. Family history of similar syndrome?
 - d. Ethnic origin
 - e. Other comorbidity (see 5)
2. Physical examination
 - a. Normal between episodes?
 - b. Findings during fever episode: rash, oral ulcers, pharyngitis, lymphadenopathy, hepatosplenomegaly
3. Laboratory testing
 - a. CBC and differential, erythrocyte sedimentation rate, C-reactive protein: obtain during a febrile episode and between febrile episodes
 - b. IgG, IgM, IgA, IgD levels
 - (1) If IgD level is elevated, send urine for mevalonic acid and genetic testing for mutations in mevalonate kinase gene: rule out HIDS
 - c. Complement levels: C3, C4, CH50: if low, consider evaluation for autoimmune disease
4. Diagnostic trial of oral corticosteroid: if history, physical examination and laboratory findings are consistent with PFAPA (see tables and text), prescribe a single dose of prednisone, 2 mg/kg, or equivalent, to be given at the onset of the next fever
 - a. Resolution of fever and associated symptoms within a few hours of the dose of corticosteroid: supports diagnosis of PFAPA
 - b. No or partial response to corticosteroid: consider other diagnoses
5. Further testing for patients who do not have a definite response to oral steroid treatment, and/or characterized by:
 - a. Regular fever cycles, aphthous ulcers or gingivitis, diarrhea, bacterial infections: repeat CBC and differential three times per week beginning 1 week before next expected fever episode: rule out cyclic neutropenia
 - b. Regular fever cycles, no oral lesions, maculopapular rash, arthralgias, splenomegaly, and/or abdominal symptoms: genetic testing for mevalonate kinase gene mutations; rule out HIDS
 - c. Irregular fever cycles, 1- to 3-day fevers, prominent abdominal pain, erysipeloid erythema, and/or arthritis: genetic testing for MEFV mutations; rule out FMF
 - d. Irregular cycles, prolonged fevers, prominent myalgias, migrating erythema, periorbital edema, continuously elevated acute phase reactants: genetic testing for TNFR1A mutations: rule out TRAPS
 - e. Brief episodes of fever and hives triggered by chilling: genetic testing for CIAS1; rule out FCAS
 - f. Irregular fevers, hives, arthritis, abdominal pain, onset in infancy, deafness: genetic testing for CIAS1: rule out MWS
 - g. Continuous fevers and hives, onset in infancy, continuously elevated acute phase reactants, neurologic deterioration, arthropathy: genetic testing for CIAS1; rule out NOMID/CINCA
 - h. Crampy abdominal pain, diarrhea, growth failure, perianal lesions, and/or joint pain: endoscopy; rule out Crohn's disease
 - i. Evanescent macular rash during fevers, arthralgias and myalgias during fevers, pericarditis, myocarditis, pleuritis, lymphadenopathy, hepatosplenomegaly, and/or iritis: consider diagnosis of systemic-onset juvenile idiopathic arthritis

Ig, immunoglobulin; HIDS, hyper-IgD syndrome; PFAPA, periodic fever with aphthous stomatitis, pharyngitis, and cervical adenopathy; FMF, familial Mediterranean fever; TNFR1A, tumor necrosis factor receptor 1A; TRAPS, tumor necrosis factor receptor-associated periodic syndrome; CIAS1, cold-induced autoinflammatory syndrome gene; FCAS, familial cold autoinflammatory syndrome; MWS, Muckle-Wells syndrome; NOMID/CINCA, neonatal-onset multisystem inflammatory disease/chronic infantile neurologic cutaneous, and articular syndrome.

although biopsies of the lesions reveal neutrophils and lymphocytes rather than degranulated mast cells.

Familial cold autoinflammatory syndrome, the mildest of the cryopyrinopathies, is rare, with only 20 affected families reported since the syndrome was described in 1940. Patients can present at any age with episodes of urticaria, chills, fever, and painful swollen joints triggered by chilling. Symptoms begin 30 min to 6 h after exposure to the cold, and last about 12 h (49, 50). Amyloidosis develops in some cases and leads to nephropathy. Treatment includes moving to a warm climate; several classes of medications have been found to have variable effectiveness including corticosteroids, colchicine, stanazolol, nonsteroidal anti-inflammatory medications, and anakinra, a recombinant human IL-1 antagonist.

Muckle-Wells syndrome usually presents in infancy with episodes of low-grade fever and urticarial rash, sometimes associated with arthritis, myalgias, abdominal pain, aphthous ulcers, and/or conjunctivitis. These episodes are not associated with exposure to cold. Sensorineural hearing loss begins during adolescence in about two-thirds of patients, with gradual progression to deafness. Amyloidosis develops in approximately one-third of patients (51).

The most severe of the cryopyrinopathy syndromes is the neonatal-onset multisystem inflammatory disease (NOMID), also known as chronic infantile neurologic cutaneous and articular syndrome (CINCA). As its names imply, this rare syndrome (about 100 cases have been reported worldwide) manifests in infancy with multisystem inflammatory disease (52). Fever and systemic symptoms are continuous, with recurrent exacerbations. In addition to the fever and persistent urticarial rash, which are present at birth in 75% of cases, infants with NOMID/CINCA have chronic meningitis with

progressive neurologic deterioration resulting in visual deficits, deafness, seizures, spasticity, and developmental impairment. Chronic arthritis and arthropathy, with overgrowth of joint cartilage leading to deformities of the knees, ankles, wrists, and elbows, occurs in about half of the patients. Long-term prognosis has been poor, with no reported cases of spontaneous remission and minimal response to corticosteroids and other anti-inflammatory drugs (52). Recently, however, there have been reports of a good response to daily injections of anakinra in NOMID/CINCA patients with and without identifiable CIAS1 mutations (53). Caspase-1 inhibitors are also being studied as potential therapeutic agents for CIAS1 (54).

Systemic-onset juvenile idiopathic arthritis and Crohn's disease must also be considered in the differential diagnosis of the young child with recurrent high fevers. In some cases, fevers occur for several months before the more pathognomic signs and symptoms of the underlying disease become evident. Crohn's disease can also be associated with aphthous stomatitis. Laboratory tests in these conditions reveal elevated acute phase reactants as in the periodic fever syndromes. Children with a working diagnosis of PFAPA should be followed carefully for the development of arthritis, suggesting rheumatoid arthritis, or gastrointestinal symptoms such as crampy abdominal pain, diarrhea, weight loss, or hematochezia suggesting the diagnosis of Crohn's disease.

In conclusion, the child presenting with recurrent febrile illnesses presents a diagnostic challenge. If a careful history, physical examination and screening laboratory testing do not reveal an infectious etiology for the fevers, the patient could have one of several fever syndromes. A stepwise approach, as shown in Table 4, can be useful in reaching an accurate diagnosis.

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