The First International Conference on Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis Syndrome

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In the last 20 years, autoinflammatory syndromes, a new category of immune-mediated diseases, have been described. These diseases are defined as attacks of inflammation, often multisystem, that are unprovoked (or triggered by a minor event) and primarily are related to dysregulation of the innate immune system.[1] Many of the syndromes are monogenically inherited. Unlike autoimmune diseases, there is a relative deficiency of both autoantibodies and autoreactive T lymphocytes. The inflammatory response is usually mediated by proinflammatory cytokines, especially interleukin (IL)-1 secreted by granulocytes and monocytes. These syndromes are often classified by the major mechanism of the immune dysfunction (**Table I**).

Autoinflammatory diseases should be suspected in patients with recurrent fever and increased acute phase reactants not explained by infections and/or when episodes are accompanied by stereotypic episodic symptoms in various body systems. Often a suggestive family history is elicited in monogenically inherited conditions including features of early-onset hearing loss, amyloidosis and/or renal failure.

Periodic/recurrent fever syndromes were the former name for these diseases. However, fever is neither necessary nor recurrent in some of the syndromes. Only in the periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA)—perhaps the most common autoinflammatory condition in children—are febrile episodes truly periodic. This report summarizes information presented at the First International Symposium on PFAPA, which took place at Schneider Children's Medical Center of Israel on June 2, 2016. The symposium focused on our current understanding of the clinical, diagnostic, pathogenic, and treatment aspects of PFAPA and the challenges and future research necessary to increase our knowledge of this unique syndrome.

Table I. The major autoinflammatory syndromes

FMF
Mevalonate kinase deficiency, formerly hyperimmunoglobulinemia D and periodic fever syndrome
Tumor necrosis factor associated periodic syndrome
Cryopyrin-associated periodic syndromes
Familial cold autoinflammatory syndrome
Muckle–Well syndrome
Neonatal onset multisystem inflammatory disease or
Chronic infantile neurological cutaneous and articular syndrome
Deficiencies in receptor antagonists
Deficiency in IL-1 receptor antagonist
Deficiency in IL-36 receptor antagonist
Interferonopathies
Nakajo-Nishimura syndrome
Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome
Joint contractures, muscular atrophy, microcytic anemia, and panniculitis-induced lipodystrophy syndrome
Stimulator of interferon genes associated vasculopathy with onset in infancy
Aicardi Goutières syndrome
Others
PFAPA
Chronic recurrent multifocal osteomyelitis
Pyogenic arthritis, pyoderma gangrenosum, acne syndrome
Blau syndrome/early-onset sarcoidosis
Deficiency of IL-10 or IL-10 receptor
Deficiency of adenosine deaminase 2

PFAPA Syndrome in the Context of Unexplained Fevers in Children

Fever is the endogenous elevation of core body temperature.[2] The classic papers addressing fever of unknown origin in children used minimum temperatures ranging from 38.1°C to 38.9°C (100.5°F to 102.1°F) to define "fever," with no uniformity in method or site of measurement.[2-7] Operationally, it seems reasonable to consider a core body temperature of ≥38.0°C (100.4°F) as abnormal. The most accurate measurements are obtained using liquid-in-glass or thermistor-based electronic thermometers that come into direct contact with the patient.[8] From birth through 3 years of age, the device is usually placed in the rectum; at ≥5 years of age, it is usually placed in the sublingual space. Between 3 and 5 years of age, placement in the axilla is more feasible, and the addition of 0.6°C

FMF	Familial Mediterranean fever
IL	Interleukin
PFAPA	Periodic fever, aphthous stomatitis, pharyngitis, adenitis

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(1.0°F) to the reading can be used to approximate core temperature.[9]

Undifferentiated fever occurs when fever is the main complaint and is unaccompanied by clinical features that suggest an etiology (this is not the same as fever without source, which refers to young febrile children who are at risk for acute serious bacterial infection).[10] Undifferentiated fevers in previously healthy children can be classified as follows: (1) prolonged—lasting longer than expected for a common illness, (2) intermittent—unpredictable, lasting for days to weeks and occurring more commonly than expected for a healthy child, or (3) periodic—stereotypical episodes lasting for several days recurring with clockwork periodicity over years. Although patients with prolonged fever may have infectious, inflammatory, neoplastic, or a host of miscellaneous conditions, the majority who are referred to infectious diseases specialists never receive a specific diagnosis and their fevers eventually resolve.[11] This may be due to the fact that the more ominous diagnoses are made in the periphery, and that referral occurs only after readily available diagnostic options have been exhausted. In evaluating the well-appearing child with prolonged fever, the cadence of the illness should dictate the pace of evaluation.[12] Steps include carefully cataloging symptoms, fever pattern, physical findings, and diagnostic studies; obtaining basic screening tests (eg, complete blood count, peripheral blood smear, chemistries, erythrocyte sedimentation rate, C-reactive protein, urinalysis, a chest radiograph); having the patient maintain a fever diary using an accurate thermometer; and returning to the healthcare provider weekly for serial examinations and laboratory studies.[13] This approach continues until a diagnosis is made or the fever resolves.

By far the most common cause of intermittent fevers is sequential viral illnesses. Some children can have as many as 1 illness a month,[14] prompting concern that a serious underlying condition exists. Reassurance can be gained by seeking information that separates the illnesses into distinct clinicopathologic entities—for example, if 1 illness included a sore throat, the next a slight cough, and another diarrhea, the case is made that these were likely unrelated uncomplicated infections. More serious or unusual illnesses should prompt consideration of evaluation for immune deficiency. Monogenic autoinflammatory diseases are rare, but should be considered if there is a strong family history or characteristic clinical features.

The hallmark feature of periodic fever is the recurrence of symptoms at regular intervals. In cyclic neutropenia, the periodicity is a remarkably consistent 21 days.[15] Episodes of illness are preceded by a decrease in neutrophil count and are accompanied by malaise, mouth ulcers, gingivitis, periodontitis, and bacterial infections. By the time medical attention is sought, the neutrophil count may have recovered. The syndrome is caused by mutations in the neutrophil elastase gene, but the mechanism by which the neutrophil count cycles so precisely is not known.

PFAPA is the only other truly periodic fever syndrome in children. Although diagnostic criteria differ (**Table II**) and there is no consensus research definition,[16-18] patients with classic PFAPA are not difficult to recognize. They typically are young and have been followed by primary care providers for months to years, being given serial diagnoses of viral illness and having had negative point-of-care diagnostic tests. Parents volunteer that each episode is identical, from the clingy, glassy-eyed, whiny prodrome to the abrupt onset of high fever and the sudden cessation of fever 3 or 4 days later. There is a distinct absence of other symptoms such as cough, vomiting, and diarrhea, and no other family members are ill at the same time. Aphthous stomatitis, pharyngitis, and/or (cervical) lymphadenitis, if present, support the diagnosis, and the absence of all 3 symptoms calls the diagnosis into question. Acute phase reactants are elevated during episodes and normal between episodes; if a corticosteroid is given—even a single dose of 1 mg/kg of prednisone—the episode resolves dramatically in a few hours. The child usually does not have a rash, joint complaints, or other symptoms that would suggest an alternative diagnosis, and although there is no family history of heritable periodic fever syndromes, the parents themselves may have

Table II. Diagnostic criteria for PFAPA syndrome

Criteria	Marshall et al, 1989[15]	Thomas et al, 1999[16]	Garavello et al, 2009[17]	Feder and Salazar, 2010[18]
Onset <5 years of age	✔	✔	✔	
Characteristics of fever	Abrupt onset	Not specified	Abrupt onset	>38.9°C
Frequency of episodes	Regular	Regular	Regular	≥6 every 2-8 weeks
Duration of episodes	~5 days		~5 days	≤10 days
Constitutional symptoms	✔	✔	✔	
Clinical findings (≥1 of the following:)				
Aphthous stomatitis	✔	✔	✔	✔
Pharyngitis	✔	✔	✔	✔
Cervical lymphadenitis		✔	✔	✔
Acute phase reaction	✔			
Asymptomatic intervals	✔	✔	✔	✔
Exclusion of URTI	✔	✔	✔	
Exclusion of CN	✔	✔	✔	✔
Other exclusions	✔		✔	✔
Benign long-term course	✔			
Response to corticosteroid			✔	
Normal growth and development	✔	✔	✔	

CN, Cyclic neutropenia; *URTI*, upper respiratory tract infection.

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