Autoinflammatory Diseases in Pediatrics

Q2 Q3 Q4 Jonathan S. Hausmann, MD*, Fatma Dedeoglu, MD

KEYWORDS

• Autoinflammatory diseases • Periodic fever • Pediatrics • Familial Mediterranean fever • PFAPA • HIDS • TRAPS • CAPS

KEY POINTS

- Viral infections are the most common cause of recurrent fevers in children.
- Autoinflammatory diseases (AIDs) should be considered in a child with recurrent or persistent fever, when infectious and malignant causes have been excluded.
- AIDs are characterized by recurrent episodes of systemic and organ-specific inflammation, and are caused by defects in the innate immune system.
- Periodic fevers with aphthous stomatitis, pharyngitis, and cervical adenitis is the most common AID in children and occurs at regular intervals.
- Familial Mediterranean fever is the most common monogenic AID and presents with recurrent attacks of fever, abdominal pain, arthritis, and rash that last for 1 to 3 days.

Q6 INTRODUCTION

Repeated febrile illnesses are common in young children, especially in those attending daycare and school. Most often, these febrile episodes are caused by repeated viral infections. However, if there is continued recurrence of fever and other associated symptoms, it is important to maintain a broad differential that includes primary immunodeficiencies, anatomic and metabolic abnormalities, malignancies, and autoinflammatory diseases (AIDs). The diagnosis of an AID may be challenging, because there are numerous diseases, overlapping signs and symptoms, and lack of specific laboratory testing.

AIDs are characterized by recurrent episodes of systemic and organ-specific inflammation. Unlike patients with autoimmune disorders such as systemic lupus erythematosus, patients with AIDs do not have the presence of autoantibodies or antigen-specific T cells. Instead, AIDs result from inborn errors of the innate immune system.[1] They involve disorders of neutrophils, macrophages, and molecules of innate immunity that evolved to protect against external pathogens. These innate immune cells are activated by endogenous or exogenous stimuli, so-called pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), which lead to inflammation.

In contrast with most autoimmune diseases, AIDs usually present during childhood. Many are characterized by recurrent or persistent fever, and they are an important part of the differential diagnosis of the febrile child. It is essential for physicians who care for children to recognize these disorders, and to refer these children to specialists who can initiate treatment, improve quality of life, and avoid long-term complications.

Research over the last 10 years has identified many of the genes that cause AIDs. Most of these diseases are monogenic and inherited in an

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autosomal dominant or recessive pattern. However, understanding of these diseases continues to evolve. Most children with periodic fevers (greater than 80% in some studies) do not have mutations in known periodic fever syndrome genes.[2] This article presents the differential diagnosis of recurrent fever in children. It discusses periodic fevers with aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA), the most common AID in children. It then focuses on the clinical presentation of monogenic AIDs that present with fevers in children, including familial Mediterranean fever (FMF), tumor necrosis factor (TNF) receptor–associated periodic syndrome (TRAPS), cryopyrin-associated periodic syndromes (CAPS), deficiency of interleukin-36 receptor antagonist (DITRA), Majeed syndrome, and chronic atypical neutrophilic dermatosis with lipodystrophy and increased temperature syndrome (CANDLE). Two granulomatous disorders, pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome and Blau syndrome, are also discussed.

RECURRENT FEVERS

Fever is one of the most common reasons for children to visit their pediatrician.[3] Some children present with recurrent or periodic fevers, defined as 3 or more episodes of fever in a 6-month period without a known illness to explain the fevers, and with at least 7 days between febrile episodes.[4] The approach to children with recurrent fevers should be different than that for children presenting with fever of unknown origin, because their causes may differ.

To better create a differential diagnosis, the pattern of the fevers should be characterized precisely, especially whether there is a regularity to the intervals of fever. Episodes of fever occurring at regular intervals suggest a diagnosis of PFAPA or cyclic neutropenia. Other characteristics that should be noted include the age of fever onset, height of the fever, and pattern during the day. It is important to monitor for associated symptoms during an episode, including rashes, and involvement of the mucosa, joints, eyes, lung, or abdomen.

Viral infections are the most common causes of fevers occurring at irregular intervals in children.[4] Although most viral infections cause obvious symptoms, such as those of upper or lower respiratory tract infections, many viruses can also cause fevers without any other defining signs or symptoms.

Most children with occult bacterial infections present with prolonged rather than recurrent fevers. However, children with repeated bacterial infections should be evaluated for immunodeficiencies, cystic fibrosis, or anatomic abnormalities. Parasitic infections with *Plasmodium* may occur in children who have traveled to endemic areas.

Inflammatory bowel disease is a common cause of recurrent fevers, and the fevers may precede other signs of inflammatory bowel disease, such as abdominal pain, bloody stools, poor growth, and anemia, by weeks or months.

In Behçet disease, children also present with recurrent oral and genital ulcers, uveitis, or skin rashes such as erythema nodosum. Systemic juvenile idiopathic arthritis presents with at least 2 weeks of daily fevers, along with a rash, lymphadenopathy, hepatosplenomegaly, or serositis. These two syndromes share many of the features of AIDs but no clear genetic causes have been identified.

After the diagnoses mentioned earlier have been evaluated, AIDs should be considered, especially if there is a family history of recurrent fevers or if the child is of certain ethnic groups. One of the characteristics of AIDs is that the fever pattern and associated features are similar between episodes. In most of these diseases, children are well between episodes, although some of them follow a more chronic course and cause significant morbidity and mortality unless treated. Fever is not a part of all of the AIDs, although this article focuses on the ones in which fever is present, and briefly touch on several without fevers.

Clinical scoring systems have been created to determine the likelihood that a child will have an AID with a known genetic cause, and may help guide genetic testing (http://www.printo.it/periodicfever), although this needs to be validated in a diverse patient population.

PFAPA

The syndrome of PFAPA is the most common cause of periodic fevers in childhood. First described in 1987,[5] it is characterized by recurrent febrile episodes lasting 3 to 6 days, occurring every 3 to 6 weeks, in addition to the presence of the features that make up the name of this syndrome. Regular intervals (with almost clockwork regularity) between episodes are the cardinal feature of PFAPA, whereas the presence of associated symptoms is more varied. The disease is common in most ethnic groups.[6]

Cause

The cause of PFAPA is unknown. Genetic studies have failed to find a common genetic abnormality in patients with this syndrome. However, 17% to

45% of children with PFAPA have a family history of recurrent fevers, and 12% have a family history of PFAPA,[7,8] suggesting a genetic susceptibility. Some of these patients have been shown to have heterozygous mutations in various genes known to be involved in other monogenic AIDs such as NRLP3, Mediterranean fever (MEFV), TNFRSF1a, or mevalonate kinase (MVK).[9]

The resolution of PFAPA with tonsillectomy suggests that the tonsils may provide a reservoir for a pathogen that causes an augmented innate immune response.[10,11] These patients show increase in molecules of the innate immune system including complement and interleukin (IL)-1β.

Clinical Presentation

PFAPA usually presents in children less than 5 years of age,[6] although cases have been reported to occur during adolescence[10] and adulthood.[12] Several studies have noted a slight male predominance of 1.2:1 to 2.3:1.[6,8,10,13] Characteristics of patients with PFAPA are shown in **Table 1**.

The interval between febrile episodes varies from 21 to 42 days between patients.[6,10] However, for a particular patient, fevers recur at regular intervals. Many families state that they can predict the onset of fever with remarkable accuracy. Over a period of years, the cycles may shorten or lengthen, and may even stop for several months before restarting again with their usual regularity.

Most patients have a prodrome before the episode of fever begins. This prodrome may include fatigue, headache, abdominal pain, or irritability.[6] Pharyngitis and cervical adenitis are the most common features. When aphthous stomatitis is present, it is usually limited to 1 to 4 superficial aphthae (<1 cm or less) or less frequently by a crop of small aphthae.

Associated symptoms may include chills, headache, nausea, diarrhea, abdominal pain, lethargy, poor appetite, myalgias, and arthralgias.[10,13] Patients are completely well between episodes and have normal growth and development.

Long-term outcome for patients with PFAPA is excellent. Most patients have resolution of episodes after 4 to 6 years.[8,13,14] Those patients who are still symptomatic after several years typically have a shortening of febrile days and a decrease in the frequency of the episodes.[10,14] Follow-up studies have shown good long-term outcomes in children diagnosed with PFAPA without increased risk for malignancy, autoimmune disorders, or chronic infectious diseases.[13,14]

Diagnosis

There are no laboratory or genetic tests to confirm the diagnosis of PFAPA. As such, it is a diagnosis of exclusion made clinically. However, monogenetic AIDs can often overlap with PFAPA. A recent study showed that patients with monogenic AIDs such as hyper- immunoglobulin (Ig) D and periodic fever syndrome (HIDS) or TRAPS, also met criteria for PFAPA.[2,15]

During attacks, children have leukocytosis with increased monocytes and neutrophils, and an increase in inflammatory markers including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum amyloid A protein (SAA).[9] ESR may be normal at the onset of fever, but it increases within a few days.[6] Between attacks, all inflammatory markers normalize. Neutropenia during episodes should prompt evaluation for cyclic neutropenia. Diagnostic criteria are shown in **Box 1**.

Table 1
Characteristics of patients with PFAPA in various clinical studies

	Licamelli 2012 (n = 102)	Feder and Salazar 2009 (n = 105)	Thomas 1999 (n = 94)
Pharyngitis	79%	61%	72%
Cervical adenitis	84%	46%	88%
Aphthous stomatitis	44%	21%	70%
Steroids abort fever	96%	97%	76%
Age at disease onset	NA	3.3 y	2.8 y
Duration of episode	NA	4.1 d	4.8 d
Days between episodes	NA	29.8 d	28.8 d
Tonsillectomy aborts PFAPA	97%	100%	64%

Abbreviation: NA, not applicable.
Data from Refs.[6,10,13]

Box 1
Modified diagnostic criteria for PFAPA

- Regularly recurring fevers with an early age of onset (<5 years)
- Constitutional symptoms in the absence of upper respiratory infection with at least 1 of the following clinical signs:
    - Aphthous stomatitis
    - Cervical lymphadenitis
    - Pharyngitis
- Exclusion of cyclic neutropenia
- Completely asymptomatic intervals between episodes
- Normal growth and development

Data from Thomas KT, Feder HM, Lawton AR, et al. Periodic fever syndrome in children. J Pediatr 1999;135(1):15–21.

Treatment

Prednisone doses of 1 to 2 mg/kg at the beginning of an attack may be sufficient to halt an attack. If the fever does not resolve, a second dose 12 hours later may be attempted. A recent study found efficacy with a lower dose of prednisone of 0.5 mg/kg.[16] Other symptoms may take longer to resolve.[6,13] Although steroids have been effective in aborting episodes, they may paradoxically increase their frequency.[6,13]

Antipyretics are only partially effective in controlling the fevers.[10] Cimetidine has also been used for treatment, and seems to be effective in resolving fevers in 27% of patients.[6] Small case reports have shown good clinical responses with an IL-1 receptor antagonist (anakinra).[11]

Tonsillectomy has been shown to be successful in causing resolution of symptoms in several studies.[6,10,13] A recent report on 102 patients who underwent tonsillectomy showed excellent response in 97% of children without surgical complications.[10] However, tonsillectomy is still an invasive, expensive procedure, and may be considered unnecessary for an illness that is self-limiting and transient. However, the impact of monthly fevers on the daily lives of patients and families cannot be disregarded. As such, tonsillectomy can be an acceptable alternative for some patients.

FMF

FMF is the most common monogenic AID in the world. It presents as recurrent attacks of fever, serositis, arthritis, and rash, with completely asymptomatic episodes between attacks. The first case was described in 1908,[17] and the first series of patients was published in 1945.[18] It was initially thought to be a disease limited to certain populations living in the Mediterranean, including Sephardic Jews, Turks, Armenians, and Arabs. However, the discovery of the gene responsible for FMF in 1997[19,20] has allowed the identification of mutations in other ethnic groups including Europeans, Americans, Australians, Indians, Chinese, and Japanese.[21,22]

Carrier frequencies as high as 1:3 to 1:5 have been described in certain populations.[23] The high frequency of carriers of this mutation suggests that heterozygous individuals may have an evolutionary advantage, perhaps by conferring a more potent immune response against certain pathogens.[24,25]

Cause

FMF is an autosomal recessive disease caused by mutations in the MEFV gene located in chromosome 16. MEFV codes for the protein pyrin (marenostrin), which is expressed predominantly in neutrophils, although it is also found in eosinophils, monocytes, dendritic cells, and fibroblasts of the synovium, peritoneum, and skin. The distribution of expression of pyrin within the body accounts for the sites of inflammation that are affected during attacks.[22] Mutated pyrin leads to increased activation of caspase 1 and uncontrolled release of IL-1β from phagocytes.[1]

Although it is an autosomal recessive disorder, genetic sequencing of patients with FMF has revealed substantial numbers of patients with only 1 mutated MEFV allele but full phenotype of the disease,[26] suggesting that FMF could also result from MEFV haploinsufficiency.

Clinical Presentation

FMF is characterized by recurrent, self-limited, febrile episodes of sterile arthritis, peritonitis, pleuritis, and skin involvement. The episodes occur suddenly, typically last 12 to 72 hours, and resolve spontaneously. They can be triggered by a variety of factors including infections, stress, exercise, or menses.[27] The frequency of attacks varies, occurring several times per month to once yearly. Each attack is associated with leukocytosis and increased inflammatory markers including increased ESR, CPR, and fibrinogen.

The disease usually starts during childhood. Thirty percent of patients present at less than 2 years of age,[28] and 80% of cases present before 20 years of age.[29] Most young patients are homozygous for the M694V mutation. Younger children may present with recurrent fevers as the only manifestation of FMF, making the diagnosis a challenge and delaying the initiation of treatment.[28] The frequency of the initial presenting symptom for FMF is shown in **Box 2**.

Abdominal attacks occur in 95% of patients.[30] Pain is usually severe, confining children to bed, and may be mistaken for appendicitis.[31] Radiologic examination may reveal air-fluid levels, leading to the suspicion of acute abdomen and the need for surgery.[32] In children, diarrhea is common, although constipation can also be seen.[30,32] Recurrent abdominal attacks may cause peritoneal adhesions.

Pleuritis, manifested as chest pain, is found in 23% to 62% of patients.[33] Pericarditis is only seen in a minority of patients.[34]

Arthritis is present in 37% to 77% of patients and may even be the presenting symptom.[30,33,35] The arthritis is of sudden onset, usually monoarticular, most often affecting the knees, ankles, and hips.[33,35] Joints may be red, swollen, warm, and tender, and may be mistaken for septic arthritis.[30] Although arthritis usually develops spontaneously, exertion and insignificant trauma can also precipitate an attack.[35] Short attacks of arthritis are most common and usually resolve within 1 week without sequelae. In a minority of patients, a chronic arthritis occurs, usually of the knee or hip. Sacroiliac involvement, presenting as inflammatory back pain, has also been described in several case series, and is thought to affect 0.4% to 7% of patients with FMF.[33,36–39] Sacroiliitis seems to be more common in patients with FMF and human leukocyte antigen (HLA)-B27.

Skin manifestation of FMF is limited to an erysipelaslike rash that occurs in 7% to 34% of children with FMF.[33] The rash mainly presents in the lower extremities, especially around the ankles or dorsum of the feet, and usually fades within 1 to 3 days.[31]

Exercise-induced myalgias are also common.[33] Up to 20% of patients develop lower extremity pain after physical exertion, mostly in the evening, which lasts from a few hours to 2 or 3 days, and resolves with rest.[40]

Protracted febrile myalgia syndrome is seen in a small percentage of patients with FMF and is characterized by high fever and severe, debilitating myalgias of the extremities.[41] It is occasionally accompanied by abdominal pain, diarrhea, arthritis, or a purpuric rash. Although there is extreme pain and tenderness on examination, laboratory work reveals normal creatine phosphokinase and nonspecific electromyogram changes.[42] Untreated, it typically lasts for 4 to 6 weeks, but resolves with steroids.

Other less-frequent features of FMF include orchitis and scrotal swelling, most commonly during childhood.[43] Splenomegaly may also occur.[31,33] Patients with FMF seem to be at increased risk of vasculitis including Henoch-Schonlein purpura, polyarteritis nodosa, and Behçet disease.[31,34]

Secondary amyloidosis is the most severe complication of FMF. It commonly affects the kidney, causing proteinuria or nephrotic syndrome. However, long-term use of colchicine in children prevents this potentially fatal complication.[44] Screening urinalyses are important to detect impaired renal function.

The clinical presentation of FMF may vary between individuals, and even among individuals through their lifetimes, which is likely related to the interplay between genes and the environment. For example, the most common mutation, M694V, is associated with earlier onset and more severe disease, including more frequent attacks, more joint disease, higher doses of colchicine required for control, and higher rates of amyloidosis among patients not adequately treated.[45]

The environment also plays a role. A recent study compared disease severity of Turkish children with FMF living in Turkey, with Turkish children living in Germany.[46] Although there was no difference between the increase of acute phase reactants during attacks, the severity of the attacks was significantly higher in children living in Turkey, suggesting that microbes or other aspects of the environment may affect the final disease expression.

Box 2
Presenting symptoms of FMF

Symptom	Percentage
Abdominal pain	55
Arthritis	26
Chest pain	5
Fever	3

Data from Sohar E, Gafni J, Pras M, et al. Familial Mediterranean fever. A survey of 470 cases and review of the literature. Am J Med 1967;43(2):227–53.

Diagnosis

Several clinical diagnostic criteria for FMF have been created; the Tel Hashomer criteria are the most widely used, and are shown in **Box 3**. There are efforts to create diagnostic criteria specifically for children, although these have yet to be validated in diverse populations.[47]

The use of genetic testing for the MEFV gene in countries with a low prevalence of FMF may be

Box 3
Simplified Tel Hashomer criteria for the diagnosis of FMF. Diagnosis requires 1 or more major criteria or 2 or more minor criteria. Typical attacks are defined as recurrent (≥3 of the same type), febrile (≥38°C), and short (lasting between 12 and 72 hours). Incomplete attacks differ from typical attacks in lack of fever, being of shorter or longer length, lack of abdominal attacks, localized abdominal attacks, or arthritis in joints other than those specified

Tel Hashomer criteria for the diagnosis of FMF

Major criteria:

- Typical attacks
  - Peritonitis (generalized)
  - Pleuritis (unilateral) or pericarditis
  - Monoarthritis (hip, knee, ankle)
  - Fever alone

Minor criteria

- Incomplete attacks involving 1 or more of the following sites:
  - Chest
  - Joint
- Exertional leg pain
- Favorable response to colchicines

Data from Livneh A, Langevitz P, Zemer D, et al. Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum 1997;40(10):1879–85.

helpful. However, even complete sequencing of the MEFV gene sometimes fails to identify any abnormalities in a small subset of patients who exhibit symptoms consistent with FMF and respond appropriately to colchicine, suggesting that other genes may be involved.

Treatment

The simultaneous discovery of the efficacy of colchicine for FMF by Dr Ozkan in Turkey and Dr Goldfinger[48] in the United States changed the landscape of the disease. Before colchicine, up to 75% of patients developed amyloidosis during adulthood. However, this has become a rare outcome. Early introduction of colchicine in children is helpful to prevent painful, febrile attacks, avoid unnecessary interventions (laparotomy, antibiotics), and prevent amyloidosis.[49] The exact mechanism of colchicine efficacy in FMF is unknown, although colchicine inhibits leukocyte chemotaxis and alters the expression of adhesion molecules.

Colchicine has been found to be safe and effective in children with FMF. Complete remission occurs in up to two-thirds of patients treated with colchicine; whereas a partial response, characterized as a significant decrease in frequency and severity of episodes, occurs in a third of patients.[50] Multiple studies have shown that amyloidosis can be prevented in children with regular use of colchicine, even if it does not completely prevent attacks.[33,51]

True colchicine resistance is rare (~5% of patients).[49,50] In patients who do not respond to colchicine, compliance should be evaluated, and alternative diagnoses should be sought. Newer biologics with anti–IL-1 activity (anakinra and canakinumab) have shown excellent responses in patients who do not tolerate, or are resistant to, colchicine.[52]

Treatment of acute attacks include nonsteroidal antiinflammatory drugs (NSAIDs) and opiates if pain is severe.[49] Increasing colchicine doses during attacks does not seem to have any beneficial effects.[29]

HIDS/MVK DEFICIENCY

HIDS is a rare, autosomal recessive AID characterized by recurrent episodes of systemic inflammation that includes fevers, abdominal pain, diarrhea, rash, arthralgias, aphthous ulcers, and lymphadenopathy. It is caused by mutations in the MVK gene, an enzyme involved in the synthesis of cholesterol and isoprenoids. Mutations of this gene cause a range of phenotypes, depending on the level of functioning enzyme. Reduced activity of the enzyme causes HIDS, whereas a complete deficiency results in mevalonic aciduria, a syndrome of severe fever episodes and neurologic complications including ataxia, mental retardation, and early death. The exact mechanism of how mutations in MVK lead to periodic fevers is still unknown, but shortage of a product of the MVK pathway seems to activate of the inflammasome and secrete IL-1β.[53]

Half of the documented cases of HIDS have been found in people of Dutch origin,[54] although cases have now been identified globally, with most patients being of European ancestry.[55] In the largest study of patients with HIDS, the average age of onset was 6 months, 78% of patients had their first attack within the first year, and all of them presented during childhood.[55] For most patients, childhood vaccinations precipitated their first attack. Emotional and physical stress can also precipitate attacks. The frequency of attacks decreased after age 20 years, although they still occurred at least every other month.

Attacks typically last 3 to 7 days and are characterized by lymphadenopathy, abdominal pain, vomiting or diarrhea, and arthralgia. Two-thirds of patients have a rash, usually maculopapular. Aphthous ulcers, sometimes with genital ulcers, occurred in about 50% of patients, mistaking this diagnosis with Behçet disease. Many features of HIDS are also seen in patients with PFAPA. However, HIDS can be differentiated by an earlier age of onset, with longer periods of fever, longer intervals between episodes, and more frequent vomiting and abdominal pain. **Box 4** shows criteria to help make the diagnosis of HIDS.

Leukocytosis and increases in inflammatory markers including ESR and CRP were seen during attacks. Urinary levels of mevalonic acid are increased during attacks, and are helpful in making the diagnosis.[56] IgD and IgA concentrations were increased in most patients, although 22% of patients with HIDS have normal IgD levels. IgD serum concentrations did not vary during acute episodes and are not correlated with severity of symptoms or frequency of attacks,[57] suggesting that the increased levels of IgD may be an epiphenomenon of the disease and, despite the name, not central to the pathogenesis of HIDS. Furthermore, 50% of patients with other periodic fever syndromes also have increased IgD levels.[58] Increases in IgD can also be seen in other conditions such as lymphoma and tuberculosis. Thus, genetic testing is probably the best way of diagnosing this disease.

Treatment is not standardized, and can include trials of NSAIDs, prednisone, anakinra, or etanercept.[50,59–61]

Box 4
Clinical criteria for the consideration of a diagnosis of HIDS

When to consider HIDS

Recurrent episodes of fever lasting 3 to 7 days for more than 6 months

And 1 or more of the following:

Sibling with genetically confirmed HIDS

Increased serum IgD (>100 IU/L)

First attack after childhood vaccination

Three or more symptoms during attacks:

- Cervical lymphadenopathy
- Abdominal pain
- Vomiting or diarrhea
- Arthralgia or arthritis of large peripheral joints
- Aphthous ulcers
- Skin lesions

Data from van der Hilst JC, Bodar EJ, Barron KS, et al. Long-term follow-up, clinical features, and quality of life in a series of 103 patients with hyperimmunoglobulinemia D syndrome. Medicine 2008;87(6):301–10.

TRAPS

TRAPS is the most common autosomal dominant, inherited periodic fever syndrome.[62] It is characterized by prolonged, episodic fevers with systemic inflammation. Previously referred to as familial Hibernian fever because of its first description in an Irish family,[63] TRAPS has been found in other populations throughout the world.[64,65]

TRAPS is caused by mutations in the TNF receptor (TNFR1a), which is found mainly on monocytes and macrophages and responds to the inflammatory cytokine TNF. The pathogenic mechanism by which the mutation results in the phenotype of TRAPS is still not well understood.[66] Some mutations seem to result in impaired shedding of the soluble receptor.[62] Other mutations result in misfolding of the protein and retention of the receptor intracellularly.[64] The mutant receptor seems to accumulate within the cell and sensitizes the cell to produce inflammatory cytokines with little stimulation.[67]

Patients with TRAPS usually present at a median age of 3 years, although cases have been identified as early as 2 weeks and as late as 53 years.[65] Patients experience recurrent, prolonged episodes of fever, lasting an average of 3 weeks, but sometimes as long as 6 weeks.[26,65,68] Attacks may occur every 5 to 6 weeks and usually consist of myalgias, fever, and rash. The rash is usually a centrifugal, migratory, erythematous patch that overlies the area of myalgia. The rash is tender, warm, and blanchable. There is no increase of muscle enzymes.

Peritonitis causing abdominal pain is common, and may be mistaken for an acute abdomen. Patients may also have arthralgias, conjunctivitis, periorbital edema, uveitis, and iritis.[65]

Laboratory examinations show increases in acute phase reactants including ESR, CRP, haptoglobin, fibrinogen, and ferritin.[65] There may be leukocytosis, thrombocytosis, and anemia from the chronic inflammatory disease.[66] Patients may also have polyclonal hypergammaglobulinemia. Acute phase reactants may remain increased while asymptomatic, although at lower levels than during attacks.

Because of the persistent inflammatory state, children with TRAPS are at risk of developing amyloidosis, most commonly involving the kidneys.[65] Q9

Treatment of TRAPS seems to be more challenging than for other AIDs, possibly due the heterogeneity of genetic mutations and clinical phenotypes.[66] Treatment of acute attacks can be effective with NSAIDs and corticosteroids, especially if associated with certain mutations.[50,66] Etanercept has been shown to be beneficial in most patients, although a complete response is not always achieved.[50,69] Other anti-TNF agents seem to cause exacerbation of the disease.[66] Anakinra was shown to produce a complete response in most patients in one observational study.[50]

CAPS

The CAPS are a set of rare, autosomal dominant AIDs that encompass a spectrum of severity from mild to severe disease. They are caused by mutations in nucleotide-binding domain, leucine-rich repeat family, pyrin domain containing 3 (NLRP3), which codes for cryopyrin. NLRP3 is a key component of the inflammasome and is expressed in neutrophils, monocytes, and chondrocytes.[70] Most patients with CAPS have gain-of-function mutations that activate the inflammasome and cause release of IL-1β, in response to reduced or absent stimuli.[26] The discovery of NLRP3 in 2001[71] linked 3 diseases (familial cold autoinflammatory syndrome [FCAS], Muckle-Wells syndrome [MWS], and neonatal-onset multisystem inflammatory disease [NOMID]), previously thought to be unrelated. Most cases of NOMID are associated with de novo mutations, whereas the mutated gene is commonly inherited in FCAS and MWS.

CAPS is distinguished from other AIDs by the presence of an urticarial rash and cold exposure as a trigger for attacks. Unlike other some of the AIDs, a third of patients do not have fever accompanying the episodes.[72]

FCAS is characterized by recurrent episodes of fever, urticaria, and arthralgia brought about by cold exposure. The rash is seen in the trunk and limbs, and individual lesions migrate and last less than 24 hours.[73] The rash is minimal during the morning and increases in severity in the evening.[74] Amyloidosis is a rare complication of this disease.

In MWS, in addition to fever, urticarial rash, and arthralgias, the episodes often lead to progressive neurosensory hearing loss secondary to cochlear inflammation,[26] which was present in 50% of patients in one study.[72] The urticaria is present most days, and tends not to be pruritic, or only mildly pruritic. Other commonly occurring symptoms include conjunctivitis, uveitis, headache, abdominal pain, and diffuse aching of the extremities. Amyloidosis can be seen as a late complication in 25% of patients with MWS.

The most severe form of the disease, called NOMID or chronic infantile neurologic cutaneous and articular syndrome (CINCA), includes all of the symptoms of MWS but presents during the newborn period. Episodes are nearly continuous and also associated with dysmorphic features, chronic aseptic meningitis, blindness, mental retardation, and bone deformation.[75] Patients with NOMID have significant arthropathy affecting large joints, resulting in functional disability with endochondral ossification and calcified masses in the joints.[73]

Laboratory abnormalities include increases in CRP and SAA, which usually remain increased even without attacks.[73] Urine should be checked for protein, to screen for amyloidosis. Biopsy of the urticarial lesion shows a sparse interstitial neutrophilic infiltrate in the reticular dermis,[74] and can help in the diagnosis of this syndrome.

Anakinra has been shown to be effective in resolution of fever, rash, conjunctivitis, and joint symptoms, as well as normalization of inflammatory markers.[76] It may even be effective in reversing amyloid deposits.[72] Canakinumab[77] and rilonacept[78] also seem to be effective in controlling the disease, again highlighting the importance of IL-1β in the pathogenesis of this AID.

A similar phenotype to that seen in FCAS, with arthralgias and myalgias in response to cold exposure, has been found as a result of mutations of a different gene, NLRP12, which also seems to enhance secretion of IL-1β.[79]

DITRA

An autosomal recessive disease first described in 2011 in several Tunisian families, DITRA is characterized by generalized pustular psoriasis.[80] It is caused by mutations in IL36RN, the gene that encodes for interleukin-36 receptor antagonist. In the wild-type state, IL-36 receptor antagonist works to block several proinflammatory signaling pathways. Most patients present between birth and 11 years of age. Patients have repeated flares of sudden-onset, high-grade fever of more than 40°C, malaise, and weakness, in addition to a diffuse, erythematous rash associated with pustules, leukocytosis, and increased CRP.

MAJEED SYNDROME

Majeed syndrome, first described in 1989, is a rare, autosomal recessive condition that consists of 3 prominent features: chronic recurrent multifocal osteomyelitis (CRMO), congenital dyserythropoietic anemia, and an inflammatory dermatosis.[81] It has been identified in Kuwaiti,[81] Jordanian,[82] and

Turkish[83] families. The gene responsible for this syndrome is LPIN2, although its function is still unclear.[82]

Majeed syndrome presents in children less than 2 years of age. It is characterized by recurrent fevers, occurring every 2 to 4 weeks and lasting 3 to 4 days. CRMO has an early age of onset; as many as 1 to 3 relapses per month; and short, infrequent remissions.[81] It eventually leads to delayed growth, joint contractures, or both.[82] Anemia severity can range from mild to severe depending on the need for blood transfusions. The inflammatory dermatosis commonly presents as Sweet syndrome. Anakinra and canakinumab have been effective in 2 patients,[83] highlighting the important role of IL-1 in the pathogenesis of this disease.

CANDLE

CANDLE syndrome is characterized by recurrent fevers, purpuric skin lesions, violaceous swollen eyelids, arthralgias, progressive lipodystrophy, anemia, delayed physical development, and increase of acute phase reactants.[84] It is caused by mutations in PSMB8, which lead to immunoproteasome dysfunction. The immunoproteasome is critical for protein degradation and generation of antigenic peptides for major histocompatibility complex class I presentation. Mutations within this structure cause inability to maintain cell homeostasis and results in increased interferon signaling.

Previously identified diseases, including Nakajo-Nishimura syndrome, Japanese autoinflammatory syndrome with lipodystrophy, and joint contractures, muscular atrophy, microcytic anemia, and panniculitis-associated lipodystrophy (JMP) syndrome, have been shown to result from mutations within this same gene.

The onset of this disease usually occurs shortly after birth, and is uniformly present by 6 months of age.[84] Fevers occur daily or almost daily and have poor response to NSAIDs.[85] In addition, children develop erythematous and violaceous, annular cutaneous plaques that last days to weeks and leave residual purpura. During infancy, children develop persistent periorbital erythema and edema, finger or toe swelling, and hepatomegaly. During the first year of life, patients lose peripheral fat and develop failure to thrive, lymphadenopathy, and anemia. Use of high-dose steroids improved clinical symptoms, but the disease rebounded with their tapering. Methotrexate, calcineurin inhibitors, TNF inhibitors, anti–IL-1 and anti–IL-6 therapy have limited success in managing this disease.[84]

DEFICIENCY OF THE INTERLEUKIN-1 RECEPTOR ANTAGONIST

First described in 2009 by Aksentjevich and colleagues,[86] deficiency of the interleukin-1 receptor antagonist (DIRA) is an inherited, recessive disease caused by mutations in IL1RN, the gene that codes for the interleukin-1 receptor antagonist. The endogenous IL-1 receptor antagonist normally inhibits the proinflammatory cytokines IL-1a and IL-1β. A mutation in IL1RN leads to overstimulation by proinflammatory cytokines. Although the mutation has been found in patients from Canada, the Netherlands, Lebanon,[86] Brazil,[87] and Turkey,[88] it seems to be particularly common in some areas of Puerto Rico as a result of a founder mutation, with an incidence as high as 1 in 6300 births.[86] DIRA usually presents within the first 2 weeks of birth with fetal distress, a pustular rash, arthritis, oral lesions, and pain with movement. Soon after birth, children develop cutaneous pustulosis, multifocal aseptic osteomyelitis, and periostitis. Fever is typically not present, but inflammatory markers, including ESR and CRP, are markedly increased. Neutrophilia is present in the blood and neutrophilic infiltrates can be found in skin and bones. DIRA is often confused with infections in the newborn period.[87] Untreated disease can lead to death from multiple organ failure[86]; however, treatment with anakinra has shown rapid and complete remission of the disease.[86,87,89]

PAPA

PAPA is a rare, autosomal dominant, inherited AID distinguished by painful flares of recurrent sterile arthritis with a prominent neutrophilic infiltrate.[90] The disease is caused by missense mutations in the proline-serine-threonine phosphatase-interacting progein 1 gene (PSTPIP1). PSTPIP1 is an adaptor protein that seems to interact with pyrin and the inflammasome. Mutations are thought to cause spontaneous activation of the inflammasome and release of IL-1β.[90]

The skin involvement is variable, and may present as ulcerations, pyoderma gangrenosum, cystic acne, or pathergy.[90,91] Arthritis usually presents during early childhood, and may begin after minor trauma or sporadically.[91] It is characterized by recurrent episodes that lead to accumulation of pyogenic, neutrophil-rich material within affected joints, which results in synovial and cartilage destruction. It typically affects 1 to 3 joints at a time. By puberty, joint symptoms tend to subside, and cutaneous symptoms become more prominent.

Laboratory findings reflect systemic inflammation. Treatment has been successful with anakinra[92,93] and infliximab.[94]

BLAU SYNDROME/EARLY-ONSET SARCOIDOSIS

The familial Blau syndrome is an autosomal dominant AID manifested as a triad of granulomatous dermatitis, arthritis, and uveitis. In 2001, mutations in NOD2 were found in Blau syndrome[95] and subsequently discovered in patients with early-onset sarcoidosis, now known to be the sporadic form of the same disease.[96] NOD2 acts as an intracellular sensor of bacterial cell wall components and activates nuclear factor kappa B (NF-κB) and enhanced autophagy. Gain-of-function mutations, as seen in Blau syndrome, lead to increased NF-κB activity and possibly to the release of inflammatory cytokines.

The average age of onset of the disease is between 2 and 3 years. Arthritis is polyarticular, often affecting the hands and feet, and produces a boggy synovitis and tenosynovitis as a result of granulomatous inflammation.[97,98]

The dermatitis is described as a tan, maculopapular rash with ichthyosiform desquamation and the presence of dermal granulomas.[99] Bilateral uveitis occurs in most patients between 7 and 12 years of age.[97] It presents as anterior uveitis with eye pain, photophobia, and blurred vision. Over time, eye inflammation can cause severe visual impairment and blindness. About one-third of patients also have other prominent features including fever, sialadenitis, lymphadenopathy, erythema nodosum, and vasculitis.

Diagnosis is made by finding noncaseating granulomas in skin, synovium, or conjunctiva.[99] Genetic testing for the NOD2 mutation has increasingly helped to make the diagnosis. There are no studies on the optimal treatment of the disease, but methotrexate, thalidomide, corticosteroids, TNF inhibitors, and IL-1 inhibitors have been tried with various levels of success.[98]

SUMMARY

Fever is one of the most common reasons for a child to present to a pediatrician. Repeated febrile episodes are most commonly caused by viral infections. However, in a child with recurrent fevers and other features of inflammation, AIDs should be considered. Although these diseases are rare, they have helped clinicians to understand the role of the innate immune system and inflammatory pathways that are ubiquitous in health and disease. Over the last decade, advances in genetics and molecular biology have focused attention on AIDs, and the pathways responsible for these rare syndromes have also been implicated to play a role in a variety of more common conditions such as gout, diabetes mellitus, and atherosclerosis. By continuing to study and improve the treatment of children with AIDs, treatments may be discovered for many of the diseases that affect people in the modern world.

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