

Periodic Fever Syndromes

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Abstract The periodic syndromes represent a heterogeneous group of disorders that can be very difficult for practicing physicians to diagnosis and treat. This article presents an orderly approach to hyperimmunoglobulin D syndrome; tumor necrosis factor receptor-1 periodic syndrome; familial Mediterranean fever; periodic fever with aphthous stomatitis, pharyngitis, and adenitis syndrome; and cryopyrin-associated periodic syndromes by highlighting the disease presentation, diagnosis, pathogenesis, and treatment. Recent advances are also discussed.

Keywords Periodic fever syndrome · Periodic fever · Inflammasome · Autoinflammatory disorder · Hyper-IgD syndrome · HIDS · Tumor necrosis factor receptor-1 periodic syndrome · TRAPS · Familial Mediterranean fever · FMF · Periodic fever with aphthous stomatitis, pharyngitis, and adenitis syndrome · PFAPA · Cryopyrin-associated periodic syndromes · CAPS · NALP3 · NLRP3 · Cryopyrin · NOMID · Neonatal-onset multisystem inflammatory disease · Familial cold autoinflammatory syndrome · FCAS · Familial cold urticaria · MWS · Muckle-Wells syndrome

Introduction

The periodic fever syndromes represent a wide array of complex manifestations that can present diagnostic challenges to even the most seasoned clinicians. Patients often experience symptoms for years before the diagnosis is made. Many of the syndromes have been linked to mutations within a single gene, although the periodic fever with aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome is a notable exception. As the molecular mechanisms driving the pathogenesis of these diseases become elucidated, targeted therapies have emerged, with promising results. This article highlights the periodic fever syndromes in a practical manner for clinicians, with emphasis on the classical presentation for each disorder, diagnosis, and management (Table 1). Recent advances are also outlined. It is important to note that although the periodic fever syndromes are generally included in the field of autoinflammatory disease, not every monogenic autoinflammatory disease can be regarded as a periodic fever syndrome. Majeed syndrome, Blau syndrome, pyogenic arthritis, pyoderma gangrenosum and acne syndrome, and deficiency of the interleukin-1–receptor antagonist are all autoinflammatory syndromes that are typically not associated with fever.

Hyperimmunoglobulin D Syndrome

Clinical Presentation

The hyperimmunoglobulin D syndrome (HIDS) is characterized by episodic attacks of fever characterized by rigors, gastrointestinal symptoms (including vomiting and diarrhea), and lymphadenopathy, with an average age at onset within the

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Table 1 Summary of periodic fever syndromes

Disorder	Average age at onset	Length of fever	Fever-free interval	Clinical features	Laboratory features	Gene	Treatment
Hyper-IgD	1–2 y	3–7 d	1–2 mo	Lymphadenopathy, vomiting, rash, arthritis, splenomegaly	↑IgD, ↑IgA, ↑CRP, ↑ESR	<i>MVK</i>	NSAIDs, glucocorticoids, controversial role for statin drugs
TRAPS	Early childhood	5 d–2 wk	5–6 wk	Focal myalgias, rash, conjunctivitis, periorbital edema	↑CRP, ↑ESR	<i>TNFRSF1A</i>	Etanercept
FMF	Early childhood	3 d	Variable	Peritonitis, arthritis, pleuritis (all evidence of serositis), response to colchicine	↑CRP, ↑ESR, neutrophilia	<i>MEFV</i>	Colchicine, potential role for anakinra in true colchicine nonresponders
PFAPA	2–5 y	3–4 d	3–6 wk	Aphthous stomatitis, pharyngitis, lymphadenopathy	↑CRP, ↑ESR during episode, then return to normal; response to prednisone	Unknown	Prednisone during episode, NSAIDs generally ineffective, cimetidine if warranted for prophylaxis, controversial role for tonsillectomy as potential cure
NOMID	Neonatal	Continuous with flares	Variable	Rash, uveitis, mental retardation, impaired growth	Elevated inflammatory markers	<i>NALP3</i>	IL-1 blockade (anakinra, canakinumab, rilonacept)
FCAS	Infancy/early childhood	12–48 h	Variable, triggered by cold exposure	Urticarial rash, conjunctivitis, arthralgias	Elevated inflammatory markers	<i>NALP3</i>	IL-1 blockade (anakinra, canakinumab, rilonacept)
MWS	Early childhood/adolescence	12–36 h	Variable, not provoked by cold	Urticarial rash, arthralgia, progressive sensorineural hearing loss	Elevated inflammatory markers	<i>NALP3</i>	IL-1 blockade (anakinra, canakinumab, rilonacept)

CRP C-reactive protein; ESR erythrocyte sedimentation rate; FCAS familial cold autoinflammatory syndrome; FMF familial Mediterranean fever; hyper-IgD hyperimmunoglobulin D syndrome; IL interleukin; MWS Muckle-Wells syndrome; NOMID neonatal-onset multisystem inflammatory disease; PFAPA periodic fever with aphthous stomatitis, pharyngitis, and adenitis; TRAPS tumor necrosis factor receptor-1 periodic syndrome

first year of life. It is not unusual for the symptoms also to include rash, arthralgias or frank arthritis, headache, and an examination finding of splenomegaly. These attacks generally last 3 to 7 days. As the fever declines, the symptoms improve, and when the patient becomes afebrile, the symptoms tend to remit. The interval between attacks lasts from 1 to 2 months, but this can vary as well. The attacks have been noted by patients to have a multitude of triggers, including surgery, vaccinations, and trauma [1].

Pathophysiology

HIDS can be genetically linked to a mutation of the *MVK* gene. It is inherited in an autosomal recessive manner. The protein encoded by the gene, mevalonate kinase, is involved in cholesterol synthesis [2]. Several

theories have been proposed, but none have yet been validated concretely for the disease's pathophysiology. A possible explanation is that a triggering event leads to a transient elevation of the core body temperature. Mutations in *MVK* may cause instability and decreased function of the encoded protein with elevated body temperature [3]. As some products downstream of mevalonate may have an anti-inflammatory effect, inactivation of the enzyme has a proinflammatory response.

Diagnosis

Patients with HIDS have elevated levels of quantitative IgD and IgA for their age [4]. These levels remain elevated when the patient is asymptomatic. Acute-phase reactants such as C-reactive protein (CRP), erythrocyte

sedimentation rate (ESR), ferritin, and serum amyloid A are also elevated. Whereas the IgD elevation is nearly universal in affected patients, the IgA level is elevated in about 80% of patients [1]. Mutations in the *MVK* gene have been identified in most patients with HIDS [5].

Treatment

NSAIDs are a cornerstone of treatment and may lessen the febrile spike as well as the duration of fever in patients. Some patients also respond well to oral glucocorticoids, but these are generally reserved for those who do not respond to NSAIDs. Colchicine does not seem to be effective in the treatment of HIDS [1]. As mevalonate kinase is one enzymatic step downstream of HMG-CoA reductase, some have tried HMG-CoA reductase inhibition through the use of statins in treatment of HIDS. The results of this type of intervention have been mixed, with one study showing a small but not statistically significant benefit in terms of number of febrile days [6]. However, there has been one report of a patient with HIDS responding exquisitely well to simvastatin [7]. Likewise, at this time, no evidence supports the use of etanercept in HIDS patients, except in the rare case in which there is an overlap syndrome with tumor necrosis factor receptor-1 periodic syndrome (TRAPS) [8]. Anakinra has been used successfully in two cases of HIDS, but further study is warranted [9].

Recent Advances

Within the past 2 years, novel mutations in *MVK* that result in the same clinical phenotype have continued to be discovered, including the first homozygous mutation in an Asian patient [10]. Interestingly, two brothers in Europe with compound heterozygous mutations for HIDS also had significant B-cell cytopenia and hypogammaglobulinemia thought to be due to the *MVK* mutations [11]. Case reports of patients with HIDS responding favorably to treatment with simvastatin also continue [7].

Tumor Necrosis Factor Receptor-1 Periodic Syndrome

Clinical Presentation

TRAPS is a rare autoinflammatory disorder that usually presents in early childhood but can also have a wide range of presentation, from infancy into middle life. The hallmark clinical history is recurrent fevers in the absence of an infectious process. Patients generally experience a fever every 5 to 6 weeks with no identifiable trigger. The fever itself lasts from 5 days to 2 weeks [12]. About 80% of patients experience some

combination of other symptoms concurrent with the fever, including myalgias, rash, conjunctivitis, or periorbital swelling. About 15% of patients eventually develop secondary amyloidosis.

Pathophysiology

TRAPS can be linked to a genetic defect in the *TNFRSF1A* gene, which is inherited in an autosomal dominant fashion [13]. The exact pathogenic mechanism has not been elucidated, but most theories center on excess tumor necrosis factor receptor-1 (TNFR1) leading to enhanced action of tumor necrosis factor (TNF) and a greatly exaggerated inflammatory response [14].

Diagnosis

To diagnose TRAPS, other causes of the fever first must be excluded, including infectious and neoplastic etiologies. Elevated markers of inflammation such as ESR and CRP can be seen, especially during attacks. If patients have secondary amyloidosis, dysfunction of involved organs can be seen, such as proteinuria and renal insufficiency [12]. The diagnosis is confirmed by genetic testing of the *TNFR1* gene.

Treatment

NSAIDs can be used in the treatment of TRAPS, but glucocorticoids typically are first line in treatment of attacks [15]. Particularly promising is the role of TNF blockade in the treatment of this disorder. Etanercept, a soluble fusion protein of two copies of the TNFR2 receptor bound to the Fc portion of human IgG, reduces symptoms in many patients and may also have a role in reversing amyloidosis [16].

Recent Advances

In addition to etanercept being promising in the treatment of TRAPS, blockade of interleukin (IL)-1 with anakinra may be effective. In a series of four children and one adult with TRAPS and prolonged and frequent bouts of fever, all responded favorably and promptly to anakinra therapy. When anakinra was withdrawn, their symptoms returned, and inflammatory markers became elevated [17•]. Whereas etanercept has shown promise in the treatment of TRAPS, therapy with infliximab, another anti-TNF drug, has not been shown to be helpful and in some cases has caused patients to worsen clinically. To help explain this phenomenon, researchers in one study found that cells of patients with TRAPS failed to respond to infliximab through proapop-

otic induction of caspase-3 activity, as was seen in cells from controls. Instead, the TRAPS-affected cells showed increased antiapoptotic c-Rel subunit activity accompanied by a significant increase in secretion of proinflammatory cytokines [18].

Familial Mediterranean Fever

Clinical Presentation

Familial Mediterranean fever (FMF) typically presents with an onset in early childhood. The clinical hallmark of this disease is fever plus serosal inflammation. The most common sites of serosal inflammation are the peritoneum, chest (pleuritis), and joints (arthritis). The pain of peritonitis can be severe enough that patients may undergo exploratory laparotomy prior to diagnosis. The attacks typically last about 3 days and then resolve spontaneously. The frequency of attacks varies, and although some patients can describe a trigger, it is not consistently identifiable in most. As in TRAPS, these patients are prone to develop secondary amyloidosis. Although it has been traditionally linked to ethnic groups surrounding the Mediterranean, FMF has been encountered in several other ethnicities [19].

Pathophysiology

FMF is inherited in an autosomal recessive fashion and caused by a mutation in the *MEFV* gene. The encoded protein is a regulator of transcription for peptides involved in inflammation [20]. The neutrophil appears to be the primary cell involved in the pathogenesis of this disease, as neutrophilic predominance in serosal fluid is seen during acute attacks. In addition, patients with FMF respond well to colchicine therapy, the effect of which is suppression of neutrophil phagocytosis and chemotaxis [21].

Diagnosis

Major diagnostic clues to FMF can be found within the framework of periodic fevers in conjunction with serositis. During the acute episode, a rise in inflammatory markers and neutrophilia can be seen. The patients symptomatically improve with colchicine administration, which aids in diagnosis. Patients may have secondary amyloidosis, a family history of the disorder, or be of Mediterranean descent. Detailed clinical criteria for this disorder's diagnosis have been proposed for adults and children [22]. Mutations of the FMF gene (*MEFV*) are associated with the disease, and assay testing for this is available commercially.

Treatment

Colchicine is effective for most patients with FMF. About 70% have a long-term, complete response to this therapy, with about 15% having a partial response [23]. For patients not responding to this therapy, important consideration should be given to patient nonadherence to medication as well as to other periodic fever syndromes [24]. Interferon- α may have a role in aborting attacks in FMF if started very early in the attack [25].

Recent Advances

In recent years, through a series of case reports, it appears there maybe a role for IL-1 blockade with anakinra in patients with FMF, particularly those with colchicine resistance or contraindications to colchicine [26, 27].

Periodic Fever with Aphthous Stomatitis, Pharyngitis, and Adenitis

Clinical Presentation

Whereas fevers associated with other periodic fever syndromes occur at variable intervals, those associated with PFAPA syndrome occur at strikingly regular intervals. The age at onset is usually between 2 and 5 years of age, with a slightly male predominance. The fevers start abruptly and are usually accompanied by tender cervical lymphadenopathy. Prior to the actual fever, patients experience a prodrome of malaise. Sore throat and aphthous ulcers begin the preceding day in about 70% of patients. The fever lasts 3 to 4 days, at which point body temperature returns to normal. Between episodes, patients are entirely asymptomatic [28]. The disorder's natural history is self-limited. Episodes usually last for a mean of about 4.5 years and then fade away slowly over time [28, 29].

Pathophysiology

The pathophysiologic mechanism of PFAPA is unknown at this time. It does not seem to be associated with any of the known monogenic autoinflammatory syndromes [30]. One hypothesis is that dysregulated cytokine production contributes to the clinical presentation, mainly with elevations of interferon- γ , TNF- α , and IL-6 [31].

Diagnosis

The diagnosis of PFAPA is made clinically. During episodes, leukocytosis is present with an elevated ESR and CRP, but in

the interval between episodes, the laboratory values return to normal. Diagnostic criteria have been established to aid the clinician. Patients should have at least three documented episodes of fever lasting no more than 5 days and recurring at regular intervals every 3 to 6 weeks. With each attack, the interval should be highly predictable and the symptoms identical. Along with fever, pharyngitis should be present with tender cervical lymphadenopathy and/or aphthous ulcers. Between episodes, patients should be healthy and growing well. The fever should resolve promptly with one dose of prednisone [29, 32]. Any patient with neutropenia, atypical symptomatology, or abnormal inflammatory markers in between episodes should prompt evaluation for a different etiology [33].

Treatment

Given the benign nature of this disorder, treatment is entirely optional. Commonly used antipyretic drugs in childhood, such as acetaminophen and ibuprofen, show little if any benefit [28]. Prednisone has been noted to alleviate symptoms totally in just a matter of hours, and if needed, this effect can help distinguish PFAPA from other periodic fever syndromes such as FMF [34]. In some patients, cimetidine has been noted to be beneficial as well, particularly with regard to prophylaxis of episodes [35]. Tonsillectomy has been shown to induce remission or decrease symptoms in affected patients [36].

Recent Advances

Much of the recent literature describes the potential role of tonsillectomy in abatement of symptoms or even its potential to be curative. Whether tonsillectomy should be recommended, however, is under debate given the benign, self-limited nature of the disease. Recently, PFAPA also has been recognized in adults, with a group of 15 patients in Israel having onset of the disease in their early- to mid-20 s [37].

Cryopyrin-Associated Periodic Syndromes

The cryopyrin-associated periodic syndromes (CAPS) are three distinct entities in terms of age at onset, symptomatology, and organ involvement but share a common genetic cause. The affected protein in all three disorders appears to be NALP3, alternatively called NLRP3 or cryopyrin [38]. This protein belongs to the family of NOD-like receptors, which are integral to the formation of inflammasomes. Mutations result in increased processing and secretion of the proinflammatory cytokine IL-1 [39•]. The clinical features of the three related disorders are discussed subsequently.

Neonatal Onset Multisystem Inflammatory Disease

Clinical Presentation

Patients with neonatal-onset multisystem inflammatory disease (NOMID) present with symptoms at or near the time of birth, as the name implies. The first sign tends to be an urticarial rash with fever. Most will have concurrent uveitis, lymphadenopathy, and hepatomegaly. Impaired growth, mental retardation, frontal bossing, and saddle nose are commonly seen as well. As the patient ages, limb pain and arthralgias may develop, and cartilaginous proliferation around the growth plate can form protuberances. Premature death can occur [39•].

Familial Cold Autoinflammatory Syndrome

Clinical Presentation

The hallmark symptom in familial cold autoinflammatory syndrome (FCAS) is a systemic inflammatory response resulting from exposure to generalized cold. The response includes fever, urticarial rash, conjunctivitis, and arthralgias. This disorder was formerly called *familial cold urticaria* and is inherited in an autosomal dominant fashion, although de novo mutations are common. Symptoms usually are seen within the first year or 2 of life but have been known to present later as well. The attacks last about 12 to 48 h before subsiding [39•].

Muckle-Wells Syndrome

Clinical Presentation

Similar to patients with FCAS, those with Muckle-Wells syndrome (MWS) have episodes of fever, urticaria, and arthralgia that typically are not provoked by cold. They can have progressive sensorineural hearing loss in the second to fourth decade of life and can develop secondary amyloidosis. Episodes last 12 to 36 h and recur irregularly every few weeks [40].

Pathophysiology

NALP3 is a protein involved in innate immunity that belongs to a group of pattern-recognition receptors that recognize intracellular pathogens. As mentioned previously, NALP3 has an important role in the formation of the intracellular inflammasome complex, serving as a building block for the complex's assembly. Point mutations in the NALP3 protein lead to inappropriate production of IL-1 β [41]. Differences in the phenotypes seen in CAPS are reflective of the wide distribution of mutations within the protein and interaction with an individual's genetic background [42].

Treatment/Recent Advances

Therapeutic blockade of IL-1 in these disorders has been found to be effective in preventing attacks, alleviating symptoms, reducing baseline systemic inflammation, and preventing secondary amyloidosis [43•]. In patients with FCAS, treatment with anakinra, an IL-1 receptor antagonist, can prevent attacks and reduce baseline symptoms [44•]. Anakinra can also control inflammation in MWS and possibly even partially recover hearing loss [45, 46]. In NOMID, improvement in signs and symptoms related to the systemic inflammation can be seen in some cases, but not all [47]. Treatment by IL-1 blockade using other agents, such as rilonacept and canakinumab, also has been shown to be effective in CAPS [48, 49•]. Recent work in murine models highlights the potential role of NALP3 inflammasome activation in induction of a T-helper type 17-mediated immune response [50].

Conclusions

This article has highlighted the periodic fever syndromes, with emphasis on diagnosis, pathogenesis, and therapy. This article is also testament to the incredible progress that has been made in the periodic fever syndromes during the past 15 years. The recent work behind these disorders serves to exemplify one of the current buzz terms in our field: translational medicine. Researchers were able to identify causative genes in affected individuals, in turn elucidate the mechanism of disease on a molecular level, and in many cases treat the disease through blockade of the cytokine shown to be in dysregulation. Exciting work continues to appear on the horizon in this and many other fields using similar approaches, offering further relief to patients whose diseases were at one time difficult to diagnose and even more difficult to treat.

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