Periodic Fever Disorders

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INTRODUCTION

The periodic fever disorders are a group of inflammatory diseases characterized by recurrent episodes of fever alternating with disease-free periods. Systemic inflammatory symptoms involving the joints, skin, eyes, or abdomen are also characteristic of episodes. Since the inflammation is not due to infection or autoantibodies, a new category called autoinflammatory diseases has emerged.[1] The main diseases in this group include Familial Mediterranean Fever (FMF), Hyper IgD Syndrome (HIDS), Tumor necrosis factor Receptor Associated Periodic Syndrome (TRAPS), and the Cryopyrin Associated Periodic Syndromes (CAPS). Each of these disorders has unique clinical features, pathophysiology, and treatment. In first part of this review, we will describe the clinical presentation and molecular basis of these disorders. The second part of the review will focus on diagnosis and treatment.

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PART 1 – CLINICAL FEATURES AND MOLECULAR BASIS OF DISEASES

CLINICAL FEATURES

Familial Mediterranean Fever (FMF)

Familial Mediterranean Fever (FMF; MIM#249100) is the most prevalent and well known of the hereditary autoinflammatory diseases. It affects more than 10,000 patients worldwide, mostly from the Mediterranean area, including Armenians, Arabs, Turks and Sephardic Jews. It is almost always inherited in an autosomal recessive fashion. Patients with FMF suffer from recurrent fever attacks, with acute monoarthritis, abdominal pain, and/ or serositis such as peritonitis, pleurtiis, or pericarditis. [2-5] Some patients have an erysipelas-like rash and a few develop chronic erosive arthritis.[2-6] Symptoms usually presents in childhood, with ~80% of patients having their first attack before the age of 20 years.[3,6-8] The attacks usually last 1 to 3 days, and between attacks patients are well with symptom-free intervals sometimes lasting many months or even years. Long-term prognosis depends on the development of amyloidosis, which can result in renal failure.

TNF-receptor associated periodic syndrome (TRAPS)

Familial Hibernian Fever was first reported in 1982 in a large family of Irish and Scottish descent[9] and in other countries, several patients with apparent autosomal dominant periodic fever were reported. This disease is now referred to as TNF-receptor associated periodic syndrome (TRAPS; MIM#142680) and has been described

in more than 20 families from a many ethnic groups.[10, 11] Most patients have their first symptoms in childhood, but the age of onset is between a few weeks and 53 years of age. TRAPS episodes include fever, conjunctivitis, periorbital swelling, migratory rash, abdominal pain, myalgias, and monoarthritis lasting several days to weeks and recurring a few times a year.[11] Attacks can be set off by emotional stress, minor infections or vigorous exercise, but often are unprovoked. The main determinant for prognosis is the development of amyloidosis.

Hyper IgD Syndrome (HIDS)

The Hyper IgD Syndrome (HIDS; MIM#260920) is an autosomal recessive disease, mostly affecting people from Caucasian origin.[12] HIDS affects approximately 200 patients worldwide, but the disease is relatively common in The Netherlands.[13] The recurrent fever attacks of HIDS last for 3 to 5 days and usually return with some periodicity every 3 to 6 weeks. Episodes are almost always characterized by painful cervical lymphadenopathy as well as abdominal pain, vomiting and diarrhea.[14-16] Other symptoms including skin rashes, mucosal ulcers, myalgia, arthralgia and headache may also occur. Ninety percent of HIDS patients will experience their first attack within the first year of life, but the fever episodes tend to become less frequent and less severe with age. Usually there is no obvious trigger, but episodes are occasionally provoked by infection, vaccinations, or minor trauma.[15] Although fever may disappear after a few days, malaise and arthritis may take longer to resolve. Between attacks, patients are well.

Cryopyrin Associated Periodic Syndromes

The Cryopyrin Associated Periodic Syndromes include Familial Cold Autoinflammatory Syndrome (FCAS; MIM#120100), Muckle Wells Syndrome (MWS; MIM#191900) and Neonatal Onset Multisystem Inflammatory Disease (NOMID; MIM#607115). These diseases were previously thought of as distinct disorders, but now they are considered a spectrum of one systemic inflammatory disease with varying severity. The exact prevalence of these rare autosomal dominant inherited diseases is unknown, however over 300 patients with FCAS, MWS and NOMID have been reported worldwide.

FCAS patients present with recurrent episodes of urticaria-like rash, fever, chills, and joint pain precipitated by generalized cold exposure. Attacks are also characterized by conjunctivitis, sweating, drowsiness, headache, extreme thirst, and nausea. Symptoms usually develop 1-2 hours after exposure, peak approximately 6-8 hours later, and resolve in less than 24 hours. While significant cold exposure can trigger attacks, air-conditioning is a common precipitant of episodes. Many patients have daily rash and fatigue that begin in the afternoon, peak at night, and resolve by morning, regardless of cold exposure during the day. Ninety-five percent of patients experience symptoms by 6 months of age, and the majority present with neonatal rash.[17]

Attacks associated with MWS are very similar to FCAS, except episodes often have no clear trigger. Occasionally, attacks may be precipitated by cold, heat, exercise and stress. Acute episodes last less than 24-48 hours, but there are often daily symptoms of rash, fatigue, and joint pain. Disease symptoms present in early childhood, but sensorineural deafness, one characteristic feature of MWS, develops in up to two-thirds of patients in later childhood and progresses through adulthood. Systemic amyloidosis develops in up to 25% of MWS patients and often leads to renal failure in adulthood.[18]

NOMID, also known as chronic infantile neurological cutaneous articular (CINCA) syndrome is the most severe of the cryopyrin associated phenotypes. Patients present in the neonatal period with urticaria-like rash, but also develop chronic multisystem inflammatory symptoms including persistent fever, chronic meningitis leading to neurologic impairment and complications, and progressive joint and cartilage abnormalities. One characterisitic finding is cartilage overgrowth around the knee. Patients have evidence of chronic inflammation, but also have intermittent acute flares. Most cases are sporadic, but autosomal dominant inheritance has been reported. Amyloidosis has been reported in older patients.[19]

MOLECULAR BASIS

Familial Mediterranean Fever (FMF)

The gene affected in FMF, *MEFV*, encodes the protein pyrin.[20, 21] The protein is made up of several well known domains and was the first protein described to possess a PYRIN domain, that has now been identified in a several proteins. Pyrin is mainly expressed as a cytoplasmic protein in neutrophils and monocytes.[22] The exact role of pyrin in the clinical manifestations of FMF has not been fully elucidated, but the PYRIN domain has been associated with caspase-1 regulation and therefore with IL-1β processing.[23, 24] Mutations in *MEFV* have also been found to be associated with other inflammatory diseases such as Behcet's disease, and may also have a modifying effect on the severity of rheumatoid arthritis.[25]

TNF-receptor associated periodic syndrome (TRAPS)

TRAPS results from mutations in the *TNFRSF1A* gene.[26, 27] It encodes TNFRSF1A, the 55 kDa receptor for tumour necrosis factor (TNF). In some cases, mutations cause an impaired receptor shedding, leading to increased or prolonged signalling through the TNF receptor and to a reduced generation of soluble TNF-receptor (sTNFRSF1A), the natural antagonist of TNF-α.[27] However, not all patients show defective receptor shedding, suggesting that there are additional mechanisms behind the fever attacks in TRAPS. Mutations with a low penetrance may lead to more general inflammatory disorders.[10, 28]

Hyper IgD syndrome (HIDS)

Mutations in the gene which codes for mevalonate kinase (MVK) were found to be the cause of HIDS.[29, 30] Previously mutations in the same gene were associated with a more severe phenotype of MVK deficiency, known as mevalonic aciduria. Mevalonate kinase is an enzyme in the cholesterol biosynthesis pathway. It is unclear how the metabolic defect leads to the clinical manifestations of hyper IgD, but evidence suggests that the shortage of specific isoprenylated proteins can induce IL-1β-mediated inflammation.

Cryopyrin Associated Periodic Syndromes (CAPS)

Cryopyrin is coded for by the gene *CIAS1*, and has also been referred to as NALP3 and PYPAF1 and recently NLRP4.[31-33] Cryopyrin, an intracellular protein expressed in monocytes and neutrophils, shares some structural features (PYRIN domain) with Pyrin and has also been implicated in the regulation of cytokine production, particularly interleukin-1β, by activating caspase-1 and NF-κB. Mutations are believed to be gain of function resulting in increased cytokine mediated inflammation.[34, 35]

PART II – DIAGNOSIS AND TREATMENT

Diagnosis

The periodic fever syndromes all characterized by recurrent inflammation. The first diagnostic step, therefore, is to examine the patient during an attack and to document an acute phase response including leukocytosis, erythrocyte sedimentation rate, C reactive protein, or Serum Amyloid A protein. A careful evaluation should be performed for occult infection. Another characteristic of most of the periodic fever syndromes is recovery between attacks. When the patient no longer fully recovers, chronic recurrent infections, autoimmune diseases, and malignancies must be ruled out.

In some cases, the clinical findings, such as age of onset, length of attacks, precipitating factors, associated symptoms, and family history is adequate to distinguish a known periodic fever syndrome. In patients with clinical findings consistent with HIDS, serum IgD and urine mevalonate may provide additional support for this diagnosis. However, in many patients there is no straightforward diagnosis, so the combination of epidemiology, signs, symptoms, and disease course, can lead to a tentative diagnosis, which may then be supported by genetic testing. Appropriate genetic testing for these genes is available at several commercial labs internationally, but in some cases comprehensive testing of certain genes can only be performed in specialized research labs. Unfortunately, there are some patients with classic presentation who do not have identifiable mutations.

There are a few non-hereditary conditions that also present with recurrent fever and inflammation such as Behcet's disease and Periodic fever with aphthous stomatitis, pharyngitis, and adenitis (PFAPA). Behcet's is characterized by recurrent mucosal ulcers (oral and genital), uveitis and other inflammatory eye disease, and erythema nodosum as well as other rashes. It is prevalent in the same ethnic populations as FMF. Onset is usually in childhood or young adulthood and while there is some association with HLA types, there is no clear genetic association and pathophysiology is not understood.[36] PFAPA is the most common cause of periodic fever in children. It is a non-hereditary autoinflammatory disease characterized by recurrent episodes of fever with one or more inflammatory symptoms including pharyngitis, cervical adenitis or adenopathy, and aphthous stomatitis. Additional symptoms are similar to those seen in many of the hereditary disorders including headache, malaise, abdominal pain, arthralgia and myalgia. Onset is usually between 2-5 years of age and attacks last between 3-6 days. Episodes are often extremely predictable occurring every 3-8 weeks and are separated by completely asymptomatic periods with normal growth and development. Unlike the hereditary disorders, this condition is self-limited and most children with PFAPA have a complete remission after 2-6 years of symptoms. Pathophysiology is unknown. There is no known long term morbidity associated with PFAPA and PFAPA symptoms are usually sensitive to systemic corticosteroid therapy.[37]

TREATMENT

Familial Mediterranean Fever (FMF)

The usual treatment of FMF is colchicine, which prevents inflammatory attacks in ~60% of the patients and

significantly reduces the number of attacks in another 20-30%.[38, 39] Colchicine treatment reduced the incidence of amyloidosis from over 60% to less than 5%.[40] Its mode of action in FMF is poorly understood. Nonsteroidal antiinflammatory drugs (NSAIDS) are often used for pain.

TNF-receptor associated periodic syndrome (TRAPS)

TRAPS can be treated with NSAIDs and glucocorticoids to alleviate the symptoms, but these drugs do not affect the frequency of attacks, or the development of amyloidosis. Clinical trials with etanercept, have been more successful. Frequency, duration and/or severity of attacks were reduced in the majority of patients.[11, 41] The use of etanercept has also been shown to reverse amyloidosis in TRAPS.[42]

Hyper IgD syndrome (HIDS)

HIDS is resistant to therapy. Colchicine, thalidomide and immunosuppressive agents seem largely ineffective.[15, 43, 44] Treatment with simvastatin may induce a modest improvement[45] and there have been case reports on successful treatment with etanercept.[46] Recently studies have begun with the recombinant interleukin-1 receptor antagonist.

Cryopyrin Associated Periodic Syndromes (CAPS)

Treatment, until recently, has been limited to avoidance of cold exposure and nonsteroidal anti-inflammatory medications for FCAS patients, and high dose steroids for more severe FCAS, MWS and NOMID patients. Recently, numerous case reports have demonstrated the effectiveness of the IL-1 receptor antagonist in all three diseases.[47-49] Additional therapies targeting IL-1 are also being studied.

CONCLUSION

In the last decade there have been significant advances in elucidating the periodic fever disorders. The identification of the genes responsible for these disorders has allowed for better characterization of the clinical features, improved diagnosis, and novel treatment. Further study of this field will likely yield additional diseases, genes, and inflammatory pathways that may be involved in common inflammatory diseases.

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