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Periodic fever syndromes

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Cryopyrin-associated periodic syndromes (CAPS)
Familial Mediterranean fever (FMF)
Tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS)
Mevalonate kinase deficiency (MKD)
Deficiency of IL-1 receptor antagonist (DIRA)
Deficiency of IL-36 receptor antagonist (DITRA)
Blau syndrome
Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome (CANDLE)
Deficiency of adenosine deaminase 2 (DADA2)
Aphthous stomatitis
Pharyngitis and cervical adenitis (PFAPA)

A B S T R A C T

Periodic fever syndromes are autoinflammatory diseases. The majority present in infancy or childhood and are characterised by recurrent episodes of fever and systemic inflammation that occur in the absence of autoantibody production or identifiable infection. The best recognised disorders include CAPS, FMF, TRAPS and MKD. Understanding the molecular pathogenesis of these disorders provides unique insights into the regulation of innate immunity. Diagnosis relies on clinical acumen and is supported by genetic testing. With the exception of FMF, which is prevalent in populations originating from the Mediterranean, these syndromes are rare and easily overlooked in the investigation of recurrent fevers. Disease severity varies from mild to life threatening, and one of the most feared complications is AA amyloidosis. Effective therapies are available for many of the syndromes, including colchicine, IL-1 blockade and anti-TNF therapies, and there is an increasing interest in blocking interferon pathways.

Introduction

Periodic fever syndromes are a group of disorders of innate immunity that cause multisystem inflammation, presenting as unexplained fluctuations or recurrent episodes of fever usually accompanied with inflammation in the joints, eyes, skin or serosal surfaces. The term autoinflammatory was coined in 1999 and defined as ‘clinical disorders marked by abnormally increased inflammation, mediated predominantly by the cells and molecules of the innate immune system, with a significant host predisposition’ [1].

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Over the last 20 years, at least 30 separate genes have been implicated in hereditary diseases (Infevers, http://fmf.igh.cnrs.fr/ISSAID/infevers) and in an increasing number of polygenic and/or acquired syndromes. It is now clear that autoinflammation can result from various pathogenic mechanisms including inflammasomopathies with dysregulated production of interleukin 1 (IL-1) as seen in familial Mediterranean fever (FMF) and cryopyrin-associated periodic fever syndromes (CAPS); intracellular stress that result in the production of reactive oxygen species, aberrant autophagy and activation of kinases as seen in tumour necrosis factor (TNF)-associated periodic syndrome (TRAPS) and mevalonate kinase deficiency (MKD); defective regulatory mechanisms affecting cytokine signalling or loss of function of inhibitors as seen in the deficiency of IL-1 receptor antagonist (DIRA) and deficiency of IL-36 receptor antagonist (DITRA); enhanced NF-κβ signalling as seen in Blau syndrome; increased interferon (IFN) signalling in SAVI and CANDLE or deficiency of enzymes such as adenosine deaminase 2 [2]. In addition to the inherited forms, the most prevalent disease seen in paediatric practice is PFAPA (Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Cervical Adenitis).

Recognising autoinflammatory diseases

Similar to all rare diseases, the diagnosis of autoinflammatory diseases relies on a high index of suspicion. As a group, systemic autoinflammatory diseases deserve considerable disease awareness because almost uniquely they combine severe disease, often with early onset, and a risk of irreversible long-term complications with, for the most often seen syndromes, excellent responses to highly specific and well tolerated, albeit often expensive, treatments. Unfortunately, there are still considerable diagnostic delays, and many patients will have seen five or more hospital specialities before a diagnosis is made [3].

Investigation of the patient with a suspected autoinflammatory disease is often challenging as the differential diagnosis is wide and somewhat age dependent [4]. Like most areas of medicine, the mainstay of diagnosis is a good clinical case history and physical examination. Many conditions can mimic autoinflammatory diseases. Immunodeficiencies including cyclic neutropaenia, occult or recurrent infections and malignancy and atypical connective tissue diseases are important differential diagnoses. It is vital to ascertain that symptomatic attacks are accompanied by a marked inflammatory response as this is a hallmark of systemic autoinflammatory disease. It is especially important to cover family history and ethnicity in detail. A patient's diary is often valuable in assessing the frequency and duration of attacks and symptoms and any evidence of precipitating factors.

The clinical picture will give a clue as to which hereditary periodic fever syndrome might cause the symptoms, but in the clinical presentation of different diseases, symptoms can overlap considerably. Furthermore, at least 40% of patients with a probable autoinflammatory disease do not fit with any of the known diseases. The understanding of these 'undifferentiated' disorders needs to be improved. However, the increasing knowledge of the pathogenesis of autoinflammatory diseases in combination with the development of functional assays and the potential for therapeutic trials of cytokine inhibitors can permit better treatment.

Inflammasomopathies

Cryopyrin-associated periodic syndromes (CAPS)

Pathogenesis

CAPS is due to gain-of-function mutations in NLRP3, which is a key component of the IL-1 inflammasome. Mutations result in the constitutive over-activation of the inflammasome and thus in the caspase 1-mediated cleavage of pro-IL-1 into active IL-1 β [5]. Although IL-1 production is regulated at multiple levels from gene expression onwards, CAPS provides clear evidence that cleavage by caspase 1 is the key step in the production of IL-1β and that the over production of IL-1β itself drives increased gene expression of components of the entire IL-1 pathway, thereby enhancing its own production [6]. The NLRP3 inflammasome can be activated by a range of factors, including potassium efflux, mitochondrial reactive oxygen species, changes in extracellular calcium levels and lysosomal release of cathepsin B and crystals such as uric acid, thus implicating this pathway in various acquired diseases such as gout, type 2 diabetes, atherosclerosis and fibrotic lung diseases.

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