Periodic fevers and autoinflammatory conditions

Jyoti Bakshi
Nick Wilkinson

Abstract

Autoinflammatory syndromes (AIS) are a spectrum of immune-mediated disorders that typically present in childhood with recurrent fevers, high inflammatory markers and systemic involvement. The quintessential periodic fever is familial Mediterranean fever, which is relatively common in Middle Eastern populations, but in general, these conditions are rare and diagnostically challenging. As a group of conditions they are typified by a delay in diagnosis of several years with repeated hospital visits, unnecessary investigations and treatment, impact on quality of life and an increased risk of the most severe complication of systemic AA amyloidosis.

The purpose of this review is to help clinicians suspect and diagnose AIS in children presenting with (recurrent) fevers or multisystem inflammation of unknown aetiology after common causes such as infection and autoimmune diseases have been excluded. We will identify when to consider AIS through a systematic approach of pattern recognition. We will discuss the presentation and differential diagnosis of recurrent fevers in neonates (the cryopyrinopathies), in childhood (hereditary periodic fevers) and pathognomonic rashes associated with AIS. Although, by no means exhaustive, we will also discuss other forms of AIS and provide an overview of the principles of treatment of AIS.

Keywords autoinflammatory syndromes; childhood; inflammasome; multisystem inflammation; recurrent fever

Introduction

AIS are rare monogenetic childhood-onset disorders caused by mutations of genes coding for proteins that play a pivotal role in immune regulation especially of the innate immune system. The spectrum of recognised disorders and their gene defect can be found in Table 1. Most, when untreated, are characterised by lifelong, spontaneously relapsing bouts of fever and systemic inflammation with symptom-free intervals. Recurrent episodes of fever are associated with systemic inflammation typically affecting skin, joints, GI system or serous membranes. A diagnosis of AIS is suspected when a child presents with recurrent fevers of unknown aetiology and requires the exclusion of an underlying infection, neoplastic or autoimmune cause.

Epidemiology

Whereas the prototypical AIS, familial Mediterranean fever (FMF), has a carrier frequency in Middle Eastern populations of 1:3 to 1:5, most AIS are rare. Less than 200 families have been reported with tumour necrosis factor (TNF) receptor associated periodic syndrome (TRAPS) worldwide, 100 cases of Familial cold autoinflammatory syndrome (FCAS) and Muckle—Wells Syndrome (MWS) have been reported mainly in Europe and North America. There are less than 10 families reported to have Majeed syndrome mostly arising from Jordan.

Pathogenesis

In contrast to autoimmune diseases, which are generally regarded as being mediated by the adaptive immune system, AIS are disorders of the innate immune system. Innate immunity not only serves to discriminate between "self" from "non-self" but serves as a system for sensing threat, by detecting specific danger signals, such as lipopolysaccharide or peptidoglycan, presented by pathogenic microbes or host derived molecules of cellular stress such as extracellular ATP. The small molecular motifs expressed by microbes are highly conserved through evolution and now known as PAMPs (Pathogen Associated Molecular Patterns). These are detected by intracellular pattern-recognition receptors (PRRs) such as Toll like receptors (TLRs) and nucleotide-binding oligomerization domain receptors, in short NOD-like receptors (NLRs), which are expressed by front line cells of the innate host defence including macrophages, monocytes, neutrophils and also lymphocytes of the adaptive immune system. This typically forms the first line of defence against infection. These receptors converge on a common set of signalling transcription factors that drive proinflammatory cytokine production. It is disruption of these pathways that result in AIS and increased levels of proinflammatory cytokines.

Examples of such disruption to the innate immune system includes mutations of the NOD2 gene associated with Crohn's disease and Blau syndrome, a sarcoid-like illness presenting in early childhood. Disruption of a molecular platform called the "inflammasome" which comprises NLRs, pyrin and CARDs (caspase activation and recruitment domain) results in gout and another form of AIS called cryopyrin-associated period syndrome (CAPS). This disruption results in excess interleukin-1β (IL-1β), a key proinflammatory cytokine.

Assessment of possible AIS in a child with recurrent fever

The salient features in the history of a child presenting with AIS would include recurrent self-limiting unexplained fevers often accompanied by a rash and possibly abdominal or limb pain. Family history, ethnicity, early onset of fever within first year of life and concomitant manifestations are also important clues to AIS. A thorough systemic examination including skin, joints and eyes during febrile periods is essential. High inflammatory markers (ESR/CRP) and a neutrophilia are typical during febrile episodes and normalise during disease free intervals. Blood and urine cultures are important to exclude an infectious cause. A urinalysis should be requested to screen for proteinuria which raises the possibility of secondary AA amyloidosis. Confirmation of AIS should be sought with genetic testing. However, it is important to remember that over 50% of AIS patients presenting with typical features have negative genetic results. Genetic tests are sent to a specialist centre for analysis. In the UK this is the National Amyloidosis centre at University College Hospital

Jyoti Bakshi *BSc MBBS MRCP is Rheumatology Registrar in the Rheumatology Department at the Nuffield Orthopedic Centre, Oxford, UK. Conflicts of interest: none.*

Nick Wilkinson *MBChB MRCP MRCPCH DM is a Consultant Paediatrician and Paediatric Rheumatologist in the Rheumatology Department at Nuffield Orthopedic Centre, Oxford, UK. Conflicts of interest: none.*

The autoinflammatory syndromes

	Disease	Gene/Chromosome	Protein
Periodic fevers	FMF	MEFV/16p13.3	Pyrin
	MKD	MVK/12q24	Mevalonate kinase
	TRAPS	TNFRSF1A/12p13	p55 TNF receptor
Cryopyrinopathies	FCAS, MWS, CINCA	NLRP3	Cryopyrin
Granulomatous	Blau's syndrome	CARD15/NOD2/16q12	CARD15
Pyogenic disorders	PAPA syndrome	PSTPIP1/15q24-q25.1	PSTPIP1
	Majeed's syndrome	LPIN2/18p	LPIN2
	CROMO	PSTP1P2/18p	PSTPIP2
Inflammatory bowel disease (IBD)	IBD 25	IL 10RB/21q22.11	Interleukin 10 receptor beta
	IBD 28	IL 10RA/11q23.3	Interleukin 10 receptor alpha

Note: FMF – familial Mediterranean fever; TRAPS – TNF receptor-associated periodic syndrome; MKD – mevalonate kinase deficiency; FCAS – familial cold autoinflammatory syndrome; MWS – Muckle-Wells syndrome; CINCA – chronic infantile neurologic cutaneous articular syndrome; PAPA – pyogenic arthritis pyoderma grangrenosa acne syndrome; CRMO – chronic recurrent multifocal osteomyelitis; IBD – inflammatory bowel disease.

Table 1

(www.ucl.ac.uk/amyloidosis) in London. Information about the latest genetic abnormalities is available on the In-Fever website at http://fmf.igh.cnrs.fr/ISSAID/infevers/.

Neonatal and infantile fevers

A fever in a neonate or infant will result in a comprehensive search for infection and prompt and appropriate treatment with antibiotics. This fever may be associated with recognisable patterns of rash, as with Streptococcal or viral infections. In circumstances where the rash is persistent or unusual, the fever unresponsive to antibiotics or recurrent and there are atypical features, such as bone oedema, alternative diagnoses should be considered. These should include alloimmune conditions such as neonatal lupus and autoimmune conditions in an infant such as Kawasaki Disease. Systemic onset juvenile idiopathic arthritis and Behçet's disease can also present in the first year of life and are now thought to be on the spectrum of AIS.

Established AIS in the first year of life includes CINCA (chronic infantile neurological cutaneous and articular syndrome) a severe form of cryopyrin-associated periodic syndromes (CAPS), that are also known in the US as NOMID (neonatal-onset multisystem inflammatory disease). Other forms of AIS in infancy include Majeed syndrome, Blau syndrome and chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE).

Majeed syndrome is defined by the association of recurrent multifocal osteomyelitis, congenital dyserythropoietic anaemia, neutrophil dermatosis and recurrent fevers.

Cryopyrin-associated periodic syndromes (CAPS) and the inflammasome

CAPS are a group of AIS that share the same gene mutation but present at different ages with variations of roughly the same phenotype. They are all autosomal-dominant diseases with NLRP3 gene (nucleotide binding oligomerization domain, leucine rich-

Differential diagnoses of CAPS

	CINCA	FCAS	MWS
Onset	Neonatal	Infancy to adulthood	Adolescence to adulthood
Fever duration	Continuous (with flares)	<24 hours	1–2 days
Skin	Polymorphic urticaria-like rash	Cold induced urticarial rash	Evanescent urticarial rash
Articular	Deforming knee osteo-arthropathy	Arthralgias	Non erosive transient polyarthritis
Ocular	Anterior uveitis, optic disc changes and blindness	Conjunctivitis	Conjunctivitis and episcleritis
Amyloidosis	20%	2–4%	25%
Distinctive features	Aseptic meningitis and naturopathy	Cold induced urticarial rash	Sensorineural hearing loss
Other findings	Mental retardation	Myalgias, headache and drowsiness	Myalgia, drowsiness
Treatment	Anakinra, rilonacept, canakinumab	Cold avoidance, Anakinra	Anakinra, rilonacept, canakinumab

Table 2