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Editorial

Autoinflammatory diseases

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The term 'periodic disease' was first used in the medical literature in 1948 for the condition later named as 'familial Mediterranean fever' (FMF). Since then many different genetically determined diseases characterized by recurrent fever were collectively termed as 'hereditary periodic fevers' (HPFs). The spectrum of such diseases expanded as the underlying molecular mechanisms and genetic defects were revealed. Kastner first coined the term "autoinflammatory syndromes" in 1999 for such group of disorders that did not fit into the classical immune-mediated diseases. These, mainly monogenic, conditions share distinct clinicopathologic features and are characterized by recurrent episodes of inflammation, without high-titer autoantibodies or antigen-specific T cells. They are quite rare diseases with no gender predilection. The onset is usually before ten years of age.

This category of diseases is caused by autoinflammation resulting from dysregulation of the innate immunity system which constitutes the body's first line of immune defense. It is not antigen-specific and memory cells are not produced. The inflammatory cells mainly neutrophils and macrophages, cytokines and complement system make up the innate immune system. Interleukin (IL)-1, IL6 and tumour necrosis factor (TNF) are the important cytokines of this system which are responsible for many clinical presentations of these diseases. In contrast to the autoimmune diseases, which are triggered by (auto)antigens with the involvement of major histocompatibility complex (MHC) class II-associated adaptive responsive genes, in autoinflammatory diseases the cytokine and bacterial sensing genetic pathways are disturbed in response to an unknown cause. There are few or no autoantibodies or antigens detectable in the body and clinical features are recurrent and periodic as compared to the continuous progression in autoimmune diseases. The consequent recurrent episodes of inflammation are clinically manifested as fever, rash or joint swelling.

In 2006, McGonagle and McDermott proposed that the majority of inflammatory disorders are situated along an immunologic disease continuum (IDC), with genetic disorders of innate and adaptive immunity located at either end of the spectrum. HPFs are the prototypical genetically determined innate immune-mediated diseases. Autoinflammatory diseases can be both inherited/monogenic (autosomal recessive or autosomal dominant) or multifactorial/polygenic. Genetic defects in many conditions have been defined (**Table 1**). Based on the underlying mechanisms, autoinflammatory diseases can be categorized as, 1) IL-1β activation disorders (inflammasomopathies), activation of inflammasome, a complex of proteins, triggered by microbial products, cholesterol, uric acid or

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Table 1 Genetic defects, clinical features and treatment of inherited/monogenic autoinflammatory diseases [3].

Monogenic disease	*Gene*	*Clinical features*	*Treatment*
Hereditary periodic fevers			
Familial Mediterranean Fever (FMF)	Mediterranean fever (MEFV)	Fever, sterile peritonitis, monoarthritis, pleuritis, serositis, skin erythema	Colchicine in the main but some reports of IL-1 and TNF inhibitors
TNF receptor-associated periodic syndrome (TRAPS)	TNF receptor superfamily member 1A (TNFRSF1A)	Prolonged fever, peritonitis, myalgias, arthralgias, erysipelas-like rash, periorbital edema, amyloidosis	IL-1, IL-6 and TNF inhibitors, corticosteroids
Cryopyrin-associated periodic syndromes (CAPS); Familial cold auto-inflammatory syndrome(FCAS), Muckle-Wells syndrome (MWS) and chronic infantile neurological cutaneous and articular syndrome/neonatal-onset multisystem inflammatory disease (CINCA/NOMID)	Cold-induced autoinflammatory syndrome 1/ Nod-like receptor family, pyrin domain-containing protein 3 (CIAS1/NLRP3)	Urticaria, deafness and amyloidosis, arthralgias	IL-1 inhibitors
Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS)	Mevalonate kinase (MVK)	Fever associated with lymphadenopathy, abdominal pain and skin rash	IL-1 and TNF inhibitors
NLRP12-associated periodic syndrome (NAPS12)	NLRP12	High fever, arthralgia, myalgia, urticaria, sensorineural hearing loss.	IL-1 inhibitors
Pyogenic disorders			
Deficiency of the IL-1 receptor antagonist (DIRA)	Interleukin receptor antagonist (IL1RN)	Perinatal onset of skin pustulosis, joint swelling, bone malformations (osteolytic lesions, periostitis and heterotopic bone formation)	IL-1 inhibitors
Deficiency in thirty-six receptor antagonist (DITRA)	IL-36 receptor antagonist (IL-36RA)	Severe pustular psoriasis	IL-1 inhibitors
Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome (PAPA)	CD2-binding protein 1 (CD2BP1)	Arthritis, and pyoderma gangrenosum	Oral antibiotics, IL-1 and TNF inhibitors
Majeed's syndrome	Lipin 2 (LPIN2)	Chronic recurrent multifocal osteomyelitis, bone contractures, congenital dyserythropoietic anemia	NSAIDs
Proteasome disabilities			
joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced childhood-onset lipodystrophy (JMP), Nakajo-Nishimura syndrome (NNS), chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE), Japanese autoinflammatory	proteasome subunit, beta type 8 (PSMB8)	Neutrophilic dermatosis, lipodystrophy, elevated temperature, joint contractures, muscle atrophy, microcytic anemia	Prednisone, IL-6 inhibitor

syndrome with lipodystrophy (JASL)			
Granulomatous disorders			
Chronic recurrent multifocal osteomyelitis (CRMO)	Unknown	Multifocal osteomyelitis	NSAIDs and steroids.
Blau syndrome	Nucleotide-binding oligomerization domain containing 2 (NOD2)	Familial granulomatous arthritis, skin granulomas and sarcoidosis	NSAIDs, methotrexate, TNF inhibitors

proinflammatory cytokines and chemokines convert inactive prointerleukin 1β to the active proinflammatory cytokine IL-1β; 2) nuclear factor (NF)-kappa B (NF-κB) activation syndromes; 3) protein misfolding disorders; 4) complement regulatory diseases; 5) disturbances of cytokine signaling; and 6) macrophage activation syndromes. Substantive evidence suggests that a combination of environmental, immunogenic and genetic factors is instrumental in causing polygenic autoinflammatory and autoimmune diseases. As the evidence grows there is proposition to reclassify diseases like Behcet's disease, Crohn's disease, ankylosing spondylitis, psoriasis, psoriatic arthritis, gout, systemic-onset juvenile idiopathic arthritis, adult-onset Still's disease as autoinflammatory conditions.

Clinically, autoinflammatory disorders are a multisystem heterogeneous group (**Table 1**). Cutaneous features may include urticarial eruption, cellulitis-like rash, pustular psoriasis, pyoderma gangrenosum or granulomatous lesions. These inherited diseases are rare and usually start in childhood. The diagnosis, therefore, demands a high degree of clinical suspicion, experience and, when available, conformation by a genetic analysis. The diagnosis of autoinflammatory disease should be suspected once the more common clinical causes associated with fever and inflammation e.g. chronic infections, systemic autoimmune diseases and paraneoplastic inflammatory conditions, have been excluded. Periodic fever Aphthous stomatitis and Pharyngitis (PFAPA) and Schnitzler's syndrome, though clinically mimic HPFs are not considered as HPFs since they lack a clear genetic basis.

Regarding the management, the acute inflammation and complications like amyloidosis necessitates their treatment. Nonsteroidal anti-inflammatory drugs and analgesics and corticosteroids may give symptomatic relief. Anti-IL1 biologics including anakinra, rilonacept and canakinumab are treatment of choice in CAPS, TRAPS and HIDS. Anti-TNF drugs are helpful in conditions like ankylosing spondylitis, Crohn's disease and psoriasis.

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