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A practical approach to the diagnosis of autoinflammatory diseases in childhood

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A B S T R A C T

Autoinflammatory diseases are characterized by the presence of chronic or recurrent systemic inflammation secondary to abnormal activation of innate immunity pathways. Many of these diseases have been found to have mutations in the genes within these pathways. Due to their rarity, non-specific symptoms and the very recent genetic and phenotypic identification and recognition, a delay in diagnosis is common. Nevertheless, some specific clinical features should help the clinician to make the diagnosis. The purpose of this article is to provide a brief clinical description of these conditions and to present clinical flow-charts useful for a correct diagnosis of children with suspected autoinflammatory syndromes.

Introduction

The autoinflammatory diseases are a group of rare diseases characterized by the presence of chronic or recurrent systemic inflammation, and defined by the over-activation of innate immunity mediators and cells (e.g. neutrophils, monocytes/macrophages). In contrast to the more common autoimmune diseases, cells of the adaptive immunity pathways (e.g. T and B lymphocytes) are only secondarily involved, as demonstrated by the persistent absence of autoantibodies and a lack of disease association with HLA class II genes [1,2].

In many cases of autoinflammatory diseases there is a family history of a similar illness. Mutations of genes that encode proteins essential in the recognition of foreign particles and the regulation of the inflammatory response have been found in the so-called monogenic or hereditary autoinflammatory

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diseases. New syndromes and genetic mutations continue to be added to the current list. In addition to the monogenic diseases, there is increasing evidence that the same mechanisms that initiate and maintain the inflammation in these rare disorders are also involved in a growing number of more common conditions, now identified as multifactorial autoinflammatory syndromes (see chapter by Ombrello et al. in this issue). In these conditions, there is overlap of dysfunction in both innate and adaptive immune systems (such as gout, systemic onset juvenile idiopathic arthritis, adult Still's disease, Crohn's disease, Behcet's disease, etc.) (Table 1) [1,2].

In this chapter we have proposed a rational and practical diagnostic approach to the most common monogenic and multifactorial autoinflammatory diseases with a paediatric onset, based on the most characteristic clinical presentation of these disorders.

Monogenic diseases

The child with periodic or recurrent fever

Fever is a very common symptom in children and, in most cases, is due to infections. Upper respiratory tract bacterial or viral infections (such as pharyngitis, tonsillitis and otitis media) and urinary tract infections are the most frequent causes of fever. In general, an infectious aetiology is the most common cause of recurrent fever in children under 6 years of age while autoimmune or inflammatory conditions (connective tissue diseases, inflammatory bowel diseases) are more common after the age of 6. Haematologocal malignancies may affect all age groups.

In these autoinflammatory diseases, the fever is recurrent, also described as periodic. Differential diagnoses of periodic fever in children are shown in Table 1.

The heritable autoinflammatory diseases occurring with periodic/recurrent fever are familial Mediterranean fever (FMF), tumor necrosis factor receptor associated periodic syndrome (TRAPS) and Mevalonate kinase deficiency (MKD) previously known as Hyper-IgD syndrome (HIDS) [3–7]. Many patients with very similar clinical features do not have the mutations described so far and so the hunt for new genes remains an active area of research. A clear example of this is PFAPA (Periodic Fever, Aphthous stomatitis, Pharyngitis Adenitis) syndrome, the most common periodic fever syndrome of childhood, that does not have a known genetic association [8,9].

How to recognize an autoinflammatory disease with periodic fever?

Fever. The child with a periodic fever syndrome has repeated, usually unprovoked, febrile episodes with temperature often above 39° in the absence of infection. The intervals between fever episodes can

Table 1
Main causes of periodic fever in childhood.

Infectious diseases	Recurrent upper respiratory tract infections
	Urinary tract infections
	Viral infections (EBV, Parvovirus B19, HSV1 and HSV2)
	Bacterial Infections (Borrelia, Brucella, salmonella, TBC)
	Parasitic diseases (Malaria, toxoplasmosis)
Congenital immune defects	Primary immunodeficiencies
	Cyclic neutropenia
Multifactorial Inflammatory diseases	Bechet's disease
	Systemic Lupus Erythematous (SLE)
	Crohn disease
Hereditary monogenic fevers	Familial Mediterranean fever
	Crypyrin associated periodic fevers (FCAS, MWS, CINCA/NOMID)
	TRAPS syndrome
	Mevalonate Kinase deficiency
Neoplastic diseases	Acute lymphoblastic leukemia
	Acute myeloid leukemia
	Lymphoma (Pel Epstein fever)
Idiopathic forms	PFAPA syndrome