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Review

Monogenic autoinflammatory diseases: General concepts and presentation in adult patients☆

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ABSTRACT

Monogenic autoinflammatory diseases (AIFD) are rare disorders characterized by an uncontrolled increase of the systemic inflammatory response, which is caused by mutations in genes involved in inflammatory pathways. Over the last few years, new genes and proteins responsible for new monogenic AIFD have been identified and a substantial improvement in their treatment has been achieved. Monogenic AIFD manifestations typically begin during childhood, but they can also occur in adults. Compared to paediatric patients, adults usually present with a less severe disease and fewer long-term complications. In addition, patients with adult-onset disease carry low-penetrance mutations more often than pathogenic variants. A late-onset of AIFD may be occasionally associated with the presence of somatic mutations. In this study, we review the most frequent monogenic AIFD, and others recently described, which may occur during adulthood.

Enfermedades autoinflamatorias monogénicas: conceptos generales y presentación en pacientes adultos

Palabras clave:
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Enfermedades autoinflamatorias indiferenciadas
Inicio en edad adulta

RESUMEN

Las enfermedades autoinflamatorias (EAIF) monogénicas son enfermedades minoritarias caracterizadas por un aumento descontrolado de la respuesta inflamatoria sistémica, que es causado por mutaciones en genes que participan en ciertas vías inflamatorias. En los últimos años, se han identificado genes y proteínas responsables de nuevas EAIF, y se ha producido una mejora sustancial en su tratamiento. Las EAIF monogénicas se inician típicamente en la edad pediátrica, pero también se presentan en adultos. A diferencia de los pacientes pediátricos, los adultos suelen manifestar síntomas menos graves y con menos complicaciones a largo plazo. Además, en los pacientes que comienzan en la edad adulta tienden a predominar las variantes genéticas de baja penetrancia sobre las patogénicas. Ocasionalmente, el inicio tardío se puede asociar a la presencia de mutaciones somáticas. En esta revisión se describen las EAIF monogénicas que pueden iniciarse en la edad adulta, entre las que se encuentran las más conocidas y frecuentes hasta la fecha, y otras de reciente descripción.

General concepts

Definition and historical perspective

Monogenic autoinflammatory diseases (AID), previously known as hereditary periodic fever syndromes, are rare diseases characterized by episodes of fever and an entourage of systemic and organ-specific manifestations, in the context of an exaggerated systemic inflammatory response, which is generated by mutations

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in genes that participate in certain inflammatory pathways. They involve an alteration of innate immunity, in which neither antigen-specific autoantibodies nor T lymphocytes participate.[1]

The term "autoinflammatory disease" was used for the first time in 1999[1] after the discovery of the genes that caused two periodic fever syndromes, such as familial Mediterranean fever (FMF)[2,3] and the periodic syndrome associated with the tumour necrosis factor receptor (TNF) or *TNF receptor associated periodic syndrome* (TRAPS).[1] Subsequently, mutations were identified in the gene encoding the intracellular receptor CIAS1 (or NLRP3), responsible for *cryopyrin associated autoinflammatory syndromes* (CAPS), which include *familial cold-associated periodic syndrome* (FCAS), Muckle-Wells syndrome and *chronic infantile neurologic, cutaneous and articular* (CINCA) syndrome, also known as *neonatal onset multisystem inflammatory disease* NOMID.[4,5]

Inflammasome and new pathogenic mechanisms

The pathogenic mechanism shared by the CAPS is the activation of the intracellular NLRP3 receptor in response to exogenous microbial agents and endogenous stress molecules, which finally produces the activation of caspase-1, which transforms the inactive form of IL-1 into active IL-1.[6] In 2002, the NLRP3 inflammasome was defined as a multiprotein machine or complex formed by the NLRP3 intracellular receptor and the rest of the molecules that participate in the inflammatory cascade until caspase induces an increased production of active proinflammatory cytokines, such as IL-1 and IL-18 (Fig. 1).[6] Inflammasome also participates in the pathogenesis of other monogenic AID, which are called inflammasome-associated diseases. Among these are FMF, *hyper-IgD syndrome* (HIDS),[7] *deficiency of the IL-1 receptor antagonist* (DIRA)[8] and *pyogenic arthritis, pyoderma gangrenosum and acne* (PAPA).[9]

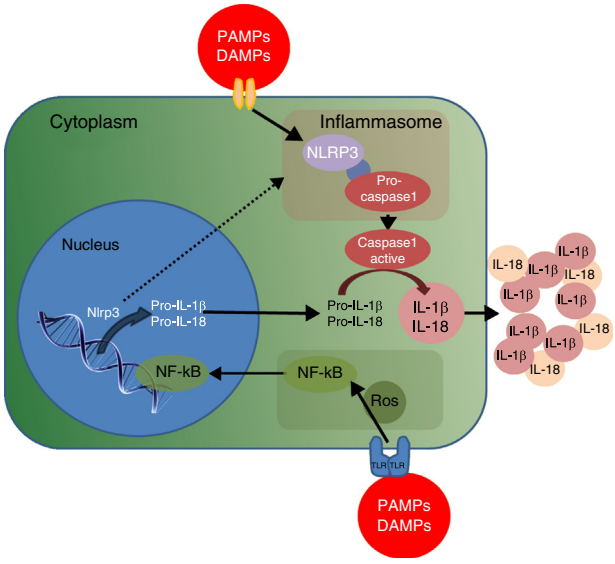

Fig. 1. Physiological functioning of inflammasome and the NF-κB pathway. In situations of tissue damage and/or loss of homeostatic equilibrium (dangerous), the release of certain molecules that act as danger signals or molecular patterns associated with damage or danger, known as DAMP *(danger* or *damage associated molecular patterns)*, is triggered. On the one hand, they function by activating inflammasome, and on the other, they activate the NF-κB transcription factor pathway, by TLR *(toll-like receptor)*, through the production of reactive oxygen species (ROS). Inflammasome is formed after NLR *(nod-like receptors)* oligomerization of the innate immune system, and its function culminates with the activation of caspase-1, which processes the inactive precursors of the proinflammatory cytokines produced in response to the NF-κB pathway, such as interleukin-1 beta (IL-1β) and IL-18, inducing its activation and release from the cell. These cytokines will participate in the inflammatory response after binding to their receptors.

Twenty years after the identification of the *MEFV* (1997) as the first gene involved in an AID,[2,3] new monogenic AID have been characterized, and their responsible genes have been discovered simultaneously or sequentially. Likewise, new pathogenic mechanisms different from the inflammasome pathway have been described, such as those involved in the NF-κB transcription factor pathway (Fig. 1), in the interferon pathway, or in the proliferation and differentiation of macrophages and lymphocytes. In addition, epigenetic changes have been detected in the methylation of genes related to inflammasome in patients suffering from CAPS and FMF, which are modulated or reversed with anti-IL-1 treatment. In this way epigenetics could also contribute to the existence of different clinical phenotypes or different responses to treatment in patients with the same AID.[10]

These relevant clinical, genetic, epigenetic and molecular advances have been made possible thanks to the international collaboration in the identification of unrelated individuals and families suffering from similar clinical phenotypes, and to the development of genomic technology, such as the application of *next-generation sequencing* techniques and the human genome and exome sequencing. Knowledge of inflammasome and other inflammatory pathways has also been important in the rational use of treatments aimed at blocking target molecules in AID.

Classification and diagnostic criteria

Monogenic AID usually present with unspecific symptoms, and are biologically characterized by an increase in acute phase reactants (APR), such as C-reactive protein (CRP), serum amyloid-associated protein (SAA) and erythrocyte sedimentation rate, in addition to leukocytosis, thrombocytosis and anaemia of chronic disorders. Although genetic analysis can help in the confirmation of cases with a well-defined phenotype and in the diagnostic approach of atypical cases, clinical and biological criteria that allow the diagnosis or classification of these entities are still required. For FMF, the diagnostic criteria of Tel Hashomer stand out (Israel, 1997),[11] subsequently modified for paediatric patients.[11] Diagnostic criteria have also been developed for CAPS[12] and provisional classification criteria for FMF, TRAPS, HIDS and CAPS, and for *periodic fever with aphthous stomatitis, pharyngitis and cervical adenitis* (PFAPA), which is considered polygenic.[13] These classification criteria have recently been used in some clinical studies.[14,15]

Classification of genetic variants

In a recent consensus guide,[16] the different genetic variants were classified according to their degree of causal implication, as follows: (1) *pathogenic or structural variants*: disease-causing mutations, and usually associated with more severe clinical expression; (2) *variants of uncertain significance*: (2a) *variants of low or incomplete penetrance*: mutations normally associated with moderate forms of presentation, although they can also be found with certain frequency (>1%) in the general population and in asymptomatic members of the same family; and (2b) *new description variants*: mutations for which functional data or intrafamilial segregation are not available; and (3) *single nucleotide polymorphisms* (SNPs): variants considered not causing disease, since they are detected in a high percentage of the general population.[16] In this sense, the *American College of Medical Genetics and Genomics* has published some recommendations for a better interpretation of the new genetic variants identified.[17]

It should be noted that the contribution of certain low penetrance mutations or polymorphisms in the pathogenesis of some monogenic AID, both in homozygotes and as part of heterozygous compounds together with pathogenic mutations, is not entirely