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Review

Hereditary systemic autoinflammatory diseases

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ABSTRACT

Systemic autoinflammatory diseases encompass different rare clinical entities characterized by recurrent acute inflammatory episodes secondary to a dysregulated inflammatory process. Since their first clinical descriptions, the Mendelian hereditary nature of some of them became evident, with their genetic and molecular basis being recently elucidated. There are disease-causing mutations in genes encoding for different proteins involved in the innate immune response and inflammation. Herein, we will introduce the reader to an updated review of the main clinical, physiopathological and therapeutic features of the different hereditary systemic autoinflammatory diseases.

Enfermedades autoinflamatorias sistémicas hereditarias

Palabras clave:
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RESUMEN

Las enfermedades autoinflamatorias sistémicas engloban un conjunto de enfermedades poco frecuentes caracterizadas todas ellas por la presencia de episodios inflamatorios agudos y recurrentes, que son consecuencia de una disregulación del control del proceso inflamatorio. Desde sus respectivas descripciones clínicas, se había observado un claro patrón hereditario mendeliano para algunas de ellas. En fechas recientes se han identificado los defectos genéticos y moleculares subyacentes al identificarse mutaciones responsables de enfermedad en diferentes genes relacionados con la respuesta inmune innata y con la inflamación. A lo largo de la presente revisión se abordarán de una manera actualizada los principales aspectos clínicos, fisiopatológicos y terapéuticos de las diferentes enfermedades autoinflamatorias hereditarias.

The concept of systemic auto-inflammatory disease was put forth in 1999 by Dr. Kastner, of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), to encompass certain diseases with apparently similar clinical manifestations and physiopathological bases (recurrent febrile and inflammatory episodes). Ever since it appeared, a counterposition was set up between these diseases and autoimmune diseases, with which they may share certain clinical similarities, although they present evident physiopathological differences, in that autoimmune response markers (high titre auto-antibodies or self antigen–specific T cells) are not detected in auto-inflammatory diseases.[1] At present, the dysregulation of the inflammatory process has been posited as the common physiopathological basis for all auto-inflammatory diseases. As we will see throughout this revision, some of these auto-inflammatory diseases are hereditary, with a typical Mendelian pattern, the consequence of mutations affecting genes that code for proteins directly involved in inflammation and its regulation.[2]

Ever since it was defined, the number of hereditary auto-inflammatory diseases has slowly increased, due to the greater knowledge about them that has been acquired and thanks to advances in the field of genetics.[3] Although there are various different classifications, this revision will use the one based on the criterion of periodicity or persistence of the underlying inflammatory process with a clear distinction between 2 large groups: hereditary periodic fever syndromes and persistent hereditary auto-inflammatory diseases (see Table 1).

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Table 1
Classification of hereditary systemic auto-inflammatory diseases, genes responsible and type of inheritance

Hereditary periodic fever syndromes	Familial Mediterranean fever–FMF		*MEFV*-AR Gene
	TNF receptor associated periodic syndrome–TRAPS		*NFRSF1A*-AD Gene
	Hyper-IgD and periodic fever syndrome–HIDS		*MVK*-AR Gene
Persistent auto-inflammatory diseases	Criopyrinopathies or criopyrin-associated periodic syndromes (CAPS)	Familial cold-induced auto-inflammatory syndrome–FCAS	*NLRP3* (*CIAS1*)-AD Gene
		Muckle–Wells syndrome	
		CINCA-NOMID syndrome	
	Paediatric granulomatous arthritis	Blau syndrome	*NOD2*-AD Gene
		Early onset sarcoidosis	
	Pyogenic aseptic arthritis, pyoderma gangrenosum, and cystic acne syndrome–PAPA		CD2BP1-AD Gene

AD indicates autosomal dominant; AR, autosomal recessive.

Table 2
Main characteristics of hereditary periodic fever syndromes

	FMF	HIDS	TRAPS
Time parameters			
Debut	<20 years	<12 months	<10 years
Duration	1-3 days	4-6 days	>7 days
Periodicity	10-12 a year	9-10 a year	3-6 a year
Fever	Yes	Yes	Yes
Digestive manifestations	Very common	Common	Very common
	Sterile peritonitis	Abdominal pain, diarrhoea	Abdominal pain
Joint manifestations	Common	Common	Common
	Polyarthralgias/monoarthritis	Polyarthralgias/occasional arthritis	Polyarthralgias/monoarthritis
Myalgias	Occasional	Occasional	Very common/migratory
Skin manifestations	Erythema erisipela	Maculopapular exanthema	Migratory erythematous exanthema
Eye manifestations	Uncommon	Uncommon	Very common/periorbital oedema/ conjunctivitis
Adenopathies	Occasional	Very frequent (98%)	Occasional
Amyloidosis	Variable	Very uncommon	Variable (2%-25%)
Gene	*MEFV*	*MVK*	*TNFRSF1A*
Protein	Pyrin/marenostrin	Mevalonate kinase	TNF receptor 1
Pattern of inheritance	Autosomal recessive (in discussion)	Autosomal recessive	Autosomal dominant

FMF indicates Familial Mediterranean Fever; HIDS, hyper-IgD and periodic fever syndrome; TRAPS, TNF receptor 1.

Before getting into details, we feel it would be wise to comment on a series of premises that are valid for all these diseases. Given their low prevalence, they should be considered rare diseases (fewer than 5 cases/10,000 inhabitants, according to the EU criterion), and, as such, it is possible that their dissemination in the medical community is quite limited. On the other hand, despite the fact that they are hereditary diseases, the presence of a positive family history of illness tends to be low (≈10% of all cases), which makes a definite diagnosis difficult. Finally, there are no specific laboratory markers for each of these diseases, with the exception of genetic testing. For all these reasons, it is not easy to establish a definitive diagnosis in ordinary clinical practice, with more or less delay seen between the debut of the illness until its diagnosis, multiple complementary testing being carried out, and the appearance of complications during the natural course of the illness.

Hereditary periodic fever syndromes

This group encompasses a set of diseases characterized by the appearance of acute, self-limiting, inflammatory episodes of varying duration that recur periodically.[4] Time parameters can be identified in them (age at onset and duration and periodicity of the episodes) that are tremendously useful for their differential diagnosis. The main diseases in this group are Familial Mediterranean Fever (FMF), the periodic syndrome associated with the TNF receptor 1 (TRAPS) and hyper-IgD and periodic fever syndrome (HIDS) (Table 2).

Familial Mediterranean fever

FMF is the most common hereditary auto-inflammatory disease in the world. It basically affects populations adjacent to the Mediterranean, with a high incidence in certain populations on its Eastern basin (Turks, Armenians, Jews, and Arabs).[4-6] There are no data regarding its true incidence in our country. Nevertheless, the fact that it is better known in the medical community and the availability of genetic analyses for its definitive diagnosis has made it possible to identify several cases in our country over the course of the last decade.

The first descriptions of FMF date back to the 20th century, when it was already observed that it is an illness that courses with brief (48-72 h) acute inflammatory episodes that recur periodically every 3-5 weeks, albeit with a fair degree of variability from one patient to the next. The chief clinical manifestations are: 1) fever (96%); 2) sterile inflammatory serositis, the peritoneum and pleura being the most commonly affected serous membranes (92% and 57%, respectively); 3) musculoskeletal manifestations, such as polyarthralgias, polymyalgias, and, less commonly, arthritis; 4) skin manifestations, and 5) an intense acute phase reaction.[2,4-6] During the intercritical

intervals, patients may be totally symptom-free or they may present less intense symptoms.

As a consequence of these uncontrolled recurrent inflammatory episodes over the years, some patients develop clinical symptoms due to the deposition of the amyloid protein in different organs (secondary amyloidosis), with the kidney being the most often affected, generally presenting as chronic kidney failure.[5,7] Oddly enough, before the appearance of colchicine, early-onset kidney failure (in 3rd or 4th decade of life) was one of the main causes of mortality in FMF patients. At present, the treatment of choice is colchicine *per os*, which is efficacious in totally or partially controlling episodes in 85%-95% of the cases.[8-10]

It has long been thought that FMF was a disease handed down to the offspring, and classically, it was assigned an autosomal recessive pattern of inheritance. In 1997, 2 international groups discovered its genetic basis, by identifying the mutations that cause the illness in a new gene called *MEFV* (for MEditerranean FeVer), which codes for the pyrin/marenostrin protein.[11,12] Many of its functions are unknown, but different research papers have pointed toward a possible role as a negative inflammasome regulator, a multiprotein complex in charge of generating the active form of caspase 1 and of the pro-inflammatory cytokines IL-1beta, IL-18, and IL-33.[13]

Ever since 1997, the mutational analysis of the *MEFV* gene has been consolidated as the definitive diagnostic test for FMF, making it possible to distinguish it from other auto-inflammatory diseases and to provide appropriate genetic counselling. However, one of the consequences of these studies is the reconsideration of its inheritance pattern, currently subject to debate due to the fact that up to 40% of patients with a clinical diagnosis of FMF in Western countries are carriers of a single mutated allele, a result that would be consistent with a dominant inheritance pattern.[14]

TNF-receptor associated periodic syndrome (TRAPS)

The first description of this illness dates back to 1982, when a large Irish family came to light with several of its members affected by a hereditary periodic fever syndrome. The illness presented certain similarities with FMF, but there were evident differences, such as a clear dominant hereditary pattern and protracted inflammatory episodes, lasting for up to several weeks. In light of all this and in contrast with FMF, the first name it received was familial Hibernian fever (FHF).[15] Subsequently, new cases were reported, both familial and sporadic, and received different names such as benign periodic fever, dominant FMF, and dominant periodic fever with amyloidosis.[16,17]

From a clinical point of view, the disease debuts during childhood (under the age of 10 years) and presents prolonged acute episodes (1-4 weeks) that recur periodically every 3-4 months. The main clinical manifestations are: 1) fever; 2) migratory myalgias, due to inflammatory fascitis; 3) migratory, centrifuge cutaneous exanthema, located in skin areas on the surface of the muscle groups affected by the fascitis; 4) aseptic inflammatory serositis, with the peritoneum being the serous membrane most often affected (92%); 5) eye manifestations, such as periorbital oedema and conjunctivitis, and 6) an intense acute phase reaction.[18] As in FMF, secondary amyloidosis is the main complication associated with it, appearing with greater prevalence than in FMF (up to 25% of the cases).[18] Curiously, the main risk factor for said complication appears to be the type of mutation responsible for the illness.

From the first description of the syndrome, an autosomal dominant pattern of heritance was clearly evident. In 1999, its genetic foundation was discovered with the identification of the disease-causing mutations in the *TNFRSF1A* gene, which codes for TNF receptor 1 (also known as p55 and CD120a). In an attempt to unify the different names that had been given to the illness and associate it with its physiopathological basis, the acronym TRAPS *(TNF-Receptor Associated Periodic Syndrome)* was proposed in 1999.[1] Since then, more than 50 mutations have been reported to cause the disease, available in the INFEVERS mutational database (e-mail: http://fmf.igh.cnrs.fr/ISSAID/infevers).[19]

Until 1999, the main treatment for the TRAPS syndrome was steroids, generally given at high doses and for protracted periods.[18] The side effects of this treatment, associated with the young age of many of the patients, made it necessary to search for alternative treatments. The identification of one of the TNF receptors as the molecular basis for the illness made it possible to use TNF blockers (etanercept) with highly satisfactory clinical outcomes.[18,20] However, a dissociation was seen with these drugs between the clinical response (generally very good) and the biochemical response (highly variable, with important oscillations of the inflammatory parameters).[21,22] For all these reasons, in an effort to achieve good clinical and biochemical responses and, consequently, to decrease the risk of amyloidosis, the IL-1 blocker anakinra has recently been used successfully.[23,24]

Hyper-IgD and periodic fever syndrome (HIDS)

Also known as Dutch Fever, this syndrome was described in 1984 by Dr. van der Meer.[25] There are currently more than 200 cases identified in the international registry of the illness (http://www.hids.net). Although most of the people initially affected were of Central European descent, especially Dutch and French, several cases have now been identified among non-Central European populations.

Clinically, the illness debuts at very early ages (under the age of 12 months) and presents acute inflammatory episodes of intermediate duration (5-6 days), recurring periodically every 5-6 weeks. Curiously, immunizations included on the vaccination schedule have been identified as triggering acute episodes. The main clinical manifestations are: 1) fever; 2) bilateral, laterocervical, inflammatory lymphadenopathies; 3) mouth ulcers; 4) cutaneous exanthema; 5) aseptic inflammatory serositis; 6) acute phase reaction; 7) polyclonal increase of IgD and IgA, and 8) increased urinary excretion of mevalonic acid during the acute episodes, not during intercritical intervals.[26,27] Unlike what has been said about FMF and TRAPS syndrome, secondary amyloidosis is not a common complication of this syndrome, with only 3 cases having been reported thus far.[28,29]

The HIDS syndrome presents an autosomal recessive pattern of inheritance, and in 1999, its genetic base was discovered when disease-causing mutations were identified in the MVK gene, which codes for the mevalonate kinase enzyme.[30,31] Oddly, this same gene had been identified as being responsible for mevalonic aciduria, a serious metabolic pathology.[32] It is currently believed that both diseases represent the extremes of a continuous spectrum of seriousness. Thus, the mevalonic aciduria would constitute the most severe form, as a result of the total and permanent loss of activity of the mevalonate kinase enzyme, whereas HIDS would be the most mild form, caused by the partial, but not total loss of the enzyme's activity.[33] This hypothesis is founded on the high prevalence of the p.V377I mutation in HIDS, which has been proven to generate a protein with residual enzymatic activity (3%-5%).[30,31,34]

From a treatment perspective, any number of anti-inflammatory approaches have been used in these patients (NSAIDs, colchicine, thalidomide, IV immunoglobulins, steroids, statins, TNF blockers,…) with highly disparate responses from one patient to another.[35-38] The recent identification of the physiopathological link between the HIDS syndrome and the inflammasome and IL-1 have made it possible to apply the IL-1 blocker anakinra in the treatment of this syndrome, with clearly promising results.[39,40]

Persistent hereditary auto-inflammatory diseases

A set of auto-inflammatory diseases are encompassed in this section, all of which follow a chronic, non-episodic course that

can present exacerbations. This heading includes the criopyrin-associated periodic syndromes (CAPS), paediatric granulomatous arthritis, and pyogenic aseptic arthritis, pyoderma gangrenosum and acne syndrome (PAPA).

Criopyrin-associated periodic syndromes (CAPS) or criopyrinopathies

Also known as familial urticariform syndromes, this section includes 3 diseases [familial cold-induced auto-inflammatory syndrome (FCAS), Muckle–Wells syndrome, and CINCA-NOMID syndrome], initially described as unrelated entities. All three follow an autosomal dominant pattern of inheritance, share a single molecular mechanism, and represent different degrees of severity along a continuum.

The first clinical reports of the FCAS syndrome go back to the 1940s and represent the mildest form within CAPS.[41,42] It debuts early, oftentimes at birth, and is characterized by the appearance of urticariform exanthema following generalized exposure to cold, which may be accompanied by low-grade fever, abdominal discomfort, conjunctivitis and arthromyalgias. The Muckle-Wells syndrome was described in 1962 and represents an intermediate degree of severity.[43] It debuts during childhood and is characterized by the appearance of urticariform exanthema accompanied by recurrent fever, abdominal pain, arthromyalgias and arthritis. During later stages (3rd decade of life) the complications defining the syndrome may appear: secondary amyloidosis (25% of cases) and progressive sensorineural hearing loss (35%). The CINCA-NOMID syndrome was described at the beginning of the 1980s as an independent rheumatic entity and different from systemic onset JAI.[44,45] It debuts during the neonatal period and is characterized by the presence of urticariform exanthema, an important degree of joint involvement (recurrent arthritis or arthropathies), significant neurological involvement (chronic aseptic meningitis, papilloedema, convulsions, sensorineural hearing loss), recurrent fever and dysmorphic traits.

In 2001, the molecular basis of the FCAS and Muckle-Wells syndromes was discovered when disease-causing mutations were identified in a new gene, then named *CIAS1* and currently known as *NLRP3*.[46] In 2002, two independent groups identified mutations in the *CIAS1* gene in patients with CINCA-NOMID syndrome, thus establishing the concept of gradient of severity.[47,48] The *NLRP3* gene codes for the criopyrin protein or Nalp3, a member of the cytoplasmic Nod-like receptor (NLR) family, involved in the innate immune response. This protein is part of the inflammasome, a multiprotein cytosolic complex that, once assembled, aims to generate the active form of caspase-1, which, in turn, generates the active form of the inflammatory cytokines IL-1 beta, IL-18, and IL-33.[13] At present, it is thought that the mutations responsible for CAPS syndromes generate a hyperfunctioning criopyrin, which translates into an excessive, uncontrolled production of the said inflammatory cytokines.[48]

Given the different severity of each entity, the treatments used in each has differed historically, ranging from antihistamines and protective measures against the cold in FCAS syndrome to high-dose steroids in the case of CINCA-NOMID syndrome. Ever since the role of IL-1 beta was discovered in the physiopathology of these syndromes, the treatment of choice for them is IL-1 blockage, the most widely used drug being anakinra, which is the human recombinant form of IL-1 receptor antagonist.[49-52] Nevertheless, there are other IL-1 blocking compounds, with different mechanisms, in more or less advanced stages of clinical trials.[53,54]

Paediatric granulomatous arthritis

This group includes 2 diseases, early onset sarcoidosis (EOS) and Blau syndrome (BS), described as independent clinical entities during the 1970s and 1980s.[55-58] Despite the significant clinical and pathological similarities between the two, there was intense medical debate for more than 20 years as to whether they were actually one or two diseases, due to the fact that patients with EOS were individuals without a positive family history of the illness (sporadic cases), whereas those with BS did present a family history of the illness, with an autosomal dominant pattern of inheritance.[59] In 2005, it was established that the genetic foundation of both entities was one and the same, thereby resolving the debate and proposing the name paediatric granulomatous arthritis to cover both.[60,61]

From a clinical perspective, the illness debuts early (<4 years of age) with the following initial manifestations: 1) discreetly granular cutaneous erythematous exanthema and 2) symmetric chronic polyarthritis, which affects large and small joints and that is accompanied by intense tenosinovitis due to granulomatous infiltration of synovia. During the natural course of the disease, different manifestations may appear such as: 1) aggressive, generally multifocal uveitis, the leading cause of morbidity in these patients; 2) recurrent fever (50%); 3) granulomatous infiltration in different organs (kidney, liver, heart), and 4) adenopathies. There is no pulmonary involvement in the initial form, enabling differential diagnosis with adult-form sarcoidosis. From an anatomical-pathological point of view, multiple non-caseating granulomas are observed in different organs and tissues.[60-62]

In 2001, BS-causing mutations were identified in the *CARD15* gene (nowadays known as *NOD2*), which codes for the Nod2 protein, a member of the NLR family of receptors of the innate immune system.[63,64] In 2005, mutations in the same *CARD15* gene were identified in patients with EOS, some of them the same as had previously been described in BS.[65,66] The only difference between the two diseases is that in BS the mutations were identified in all the members of a family with the disease, whereas in EOS, the mutations identified were *de novo* mutations that appeared for the first time in the patient and are responsible for the absence of a positive family history of the disease (sporadic cases). Since 2001, more than 10 mutations have been identified as causing the illness, with the most prevalent mutations being located on codon 334 of the protein (p.R334Q and p.R334W).[60-62]

The leading treatment for this illness has been prolonged treatment with high-dose steroids; less potent anti-inflammatory therapies have proven to be for the most part ineffective. In the light of the side effects in paediatric patients, TNF blockers (infliximab) have recently been used with satisfactory clinical results.[61]

Sterile pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA)

Described for the first time in 1997, PAPA syndrome is one of the most uncommon hereditary auto-inflammatory syndromes.[67] It follows an autosomal dominant hereditary pattern, predominantly affecting joints and skin, presenting at different times in the patient's life. The illness debuts at early ages (<5 years); joint manifestations are the first to appear. The most common form is recurrent monoarthritis, generally of the large joints, which is destructive and presents purulent, sterile synovial fluid. As age increases, skin manifestations emerge, the most important of which are: 1) pyoderma gangrenosum, generally following small trauma or injections, which are difficult to treat, and 2) cystic acne, that tends to appear starting with puberty. Likewise, other less common clinical manifestations have been reported, such as hidradenitis suppurativa.[67,68]

The genetic basis for this disease was described in 2002, when the mutations responsible for the illness were identified in the *CD2BP1* gene, encoding for the pstpip1 protein and participating in inflammation regulation by physically interacting with the pyrin/marenostrin protein and acting on the inflammasome.[69,70]

Various different treatment approaches have been used in this disease; classically, the most widely used ones are with high-dose steroids. Since the introduction of cytokine blockers (TNF and IL-1),

different case reports have shown outstanding clinical responses to these drugs, hinting at the possibility of them being the treatment of choice for this disease.[71-73]

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