Review

Autoinflammatory diseases: the hereditary periodic fever syndromes

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Abstract. Human autoinflammatory diseases (HAIDs) are a heterogeneous group of genetically determined affections characterized by seemingly unprovoked inflammation, in the absence of autoimmune or infective causes. The hereditary periodic fever syndromes (HPFSs) are a HAID subset consisting of three main nosologic entities: familial Mediterranean fever (FMF), hyperimmunoglobulinemia D and periodic fever syndrome (HIDS), and tumor necrosis factor receptor superfamily 1A-associated periodic syndrome (TRAPS). FMF and HIDS are autosomal recessive diseases, while TRAPS is dominantly inherited. Although each HPFS presents genetic and phenotypic peculiarities, globally these affections share an intermittent expression, in form of acute attacks of fever variably associated with serosal, synovial and/or cutaneous inflammation, usually self-limiting. Amyloidosis is the most severe, life-threatening complication of FMF and TRAPS, whereas it has not been till now reported in HIDS. The HPFS molecular bases have been recently identified. In this paper, the most recent information on HPFSs is reviewed and summarized.

Key words: Human autoinflammatory diseases, hereditary periodic fever syndromes, familial Mediterranean fever, hyperimmunoglobulinemia D and periodic fever syndrome, tumor necrosis factor receptor superfamily 1A-associated periodic syndrome

Introduction

The term “human autoinflammatory diseases” (HAIDs) was recently proposed to describe a heterogeneous group of rare, genetically determined disorders characterized by seemingly unprovoked inflammation, in the absence of autoimmune or infective causes (1, 2) (Table 1). The hereditary periodic fever syndromes (HPFSs) constitute a HAID subset consisting of three main nosologic entities, such as familial Mediterranean fever (FMF), hyperimmunoglobulinemia D and periodic fever syndrome (HIDS), and tumor necrosis factor receptor superfamily 1A-associated periodic syndrome (TRAPS) (1, 3, 4). Familial cold urticaria and Muckle-Wells syndrome, classified as familial urticarial syndromes (1) (Table 1), and other less characterized affections, such as periodic fever aphtous stomatitis and adenitis, and chronic infantile neurological cutaneous and articular syndrome (also termed neonatal onset multisystem inflammatory disease), might be also included in HPFSs (3, 5).

Among HPFSs, FMF and HIDS are autosomal recessive diseases, while TRAPS is dominantly inherited (1, 3, 4, 6) (Table 2). Although each HPFS presents genetic and phenotypic peculiarities, globally they share an intermittent expression, in form of recurrent episodes of fever variably associated with serosal, synovial and/or cutaneous inflammation, usually self-limiting (1, 3). Moreover, the attacks are characterized by a marked systemic acute phase response (APR) and a prominent neutrophilia in the affected anatomical sites (5). Amyloidosis is the most severe,

Table 1. Proposed classification of the human autoinflammatory diseases (1)

Hereditary periodic fever syndromes
Familial Mediterranean fever
Hyperimmunoglobulinemia D and periodic fever syndrome
Tumor necrosis factor receptor superfamily 1A-associated periodic syndrome
Familial urticarial syndromes
Familial cold urticaria
Muckle-Wells syndrome
Complement disorders
Hereditary angioedema
Granulomatous disorders
Chronic granulomatous synovitis with uveitis and cranial neuropathy (Blau syndrome)
Metabolic disorders
Gout
Familial chondrocalcinosis (pseudogout)
Storage diseases
Gaucher's disease
Hermansky-Pudlak syndrome
Fibrosing disorders
Idiopathic pulmonary fibrosis
Vasculitic syndromes
Behçet's disease

life-threatening complication of both FMF and TRAPS, whereas it has not been till now reported in HIDS (3) (Table 2). Often such affections remain unrecognized and undiagnosed for years and the patient's history encompasses extensive diagnostic investigations, including laparoscopies or laparotomies. The HPFS molecular bases have been described only in the last decades. In this paper, the most recent information on HPFSs is reviewed and summarized.

Familial Mediterranean fever

FMF, the most common and the longest known HPFS, is an autosomal recessive disease affecting predominantly the populations surrounding the Mediterranean basin, such as Jews (mostly Sephardic), Armenians, Turks and Arabs, but well-documented cases in non-Mediterranean ethnic groups have also been reported (7). FMF generally develops in childhood or adolescence (7). A late-onset usually corresponds to a clinically more benign disease (8). The affection occurs in form of recurrent acute episodes of fever, variably associated with serosal, synovial and cutaneous inflammation, usually lasting from 12 to 96 hours and spontaneously subsiding (3,7) (Table 2). Flares may be precipitated by menses, emotional stress, exercise, infections or surgery (7). Fever is generally above 38°C, with a rapid rise accompanied by chills. Constitutional symptoms are common (9). The sterile serositis is represented mostly by peritonitis and pleurisy, rarely by pericarditis or acute scrotum (3, 7, 9) (Table 2). Among cutaneous signs, the erysipelas-like erythema, usually unilateral and located on the extensor surface of the leg, ankle or foot dorsum, is regarded as pathognomonic (3, 7, 9). Severe, protracted myalgia is infrequent (3, 7). Non-erosive monoarthritis with effusion, affecting mostly leg large joints, is common and may be the sole manifestation of an attack in 75% of patients (3, 7). Chronic destructive arthritis (predominantly in hips or knees) or migratory polyarthritis are infrequent (3, 7). An unusual manifestation is spondylarthropathy, always HLA-B27 negative and with minimal radiographic spinal involvement (10). The most severe manifestation of FMF is the development of amyloidosis, due to the serum amyloid A (SAA) deposition in various organs, with kidney predilection (7). Notably, amyloidosis may occur independently of the disease severity, and in phenotype II constitutes the FMF presenting manifestation (7, 9, 11). The incidence of this phenotype ranges from 7% to 25% of the patients with amyloidosis (11).

FMF is due to recessive mutations in the *MEFV* (for ME diterranean FeVer) gene, located on the short arm of the chromosome 16 (16p13.3), consisting of 10 exons and 781 codons (12). The type and combination of the mutations define a severely or weakly expressed phenotype (phenotype I) (13-15), but, on the other hand, subjects carrying two mutations may not express the disease (phenotype III) (16). The mutation penetrance is probably incomplete in females, being the male : female ratio greater than 1 (7). At present, more than forty mutations have been detected, mostly of missense type, among which M694V (replacement of

Table 2. Salient features of hereditary periodic fever syndromes

Clinical features	FMF	HIDS	TRAPS
Ethnic background	Jewish, Armenian, Arab, Turkish	Dutch, French, other European	Northern European and any ethnicity
Inheritance	Autosomal recessive	Autosomal recessive	Autosomal dominant
Underlying gene	*MEFV* (chr 16p13)	*MVK* (chr 12q24)	*TNFRSF1A* (chr 12p13)
Gene product	Marenostrin/pyrin	Mevalonate kinase	TNF receptor 1A
Age at onset (yrs)	<20	<1	≤20
Attack duration	1-3 days	3-7 days	Often > 1 week and more
Skin involvement	Erysipeloid erythema	Maculo-papular rash	Centrifugal migratory macular rash, usually overlying area of myalgia is frequent
Musculoskeletal involvement	Monoarthritis is common	Symmetric polyarthritis or oligoarthritis, rarely myalgia	Severe, centrifugal migratory myalgia is common, occasionally monoarthritis
Abdominal involvement	Sterile peritonitis ~85%	Severe pain is common	Severe pain is common
Other features	Pericarditis, acute scrotum	Cervical lymphadenopathy	Conjunctivitis, peri-orbital edema
Amyloidosis	Common	To date not observed	Seen in ~ 25% of cases
Treatment	Colchicine	Etanercept?	Corticosteroids, etanercept

methionine with valine at codon 694) and V726A (substitution of valine with alanine at codon 726) are the prevalent ones (3). M694V mutation is practically fully penetrant and in homozygosity is associated with more severe disease and higher risk of amyloidosis, whereas the E148Q homozygosity accounts for a mild phenotype and low penetrance (7,17). The V694V mutation is related to FMF arthritis (18). However, patients with identical genotype may demonstrate different FMF manifestations and outcome, due to *MEFV*–independent modifying genetic and epigenetic factors (3,15). At this regard, the MHC class I chain-related gene A polymorphism may influence the disease severity (19), and the SAA 1 α/α genotype is a strong risk factor for amyloidosis susceptibility (20). The sex may act similarly, since the amyloidosis prevalence is four-time higher in males than in females, independently of allelic variations (4, 7). Moreover, environmental influences likely have a role, owing to the resident Armenians show a higher frequency of amyloidosis, whereas American-Armenians, even carrying the same mutations, rarely develop this complication (15). Recently, a severe autosomal dominant periodic inflammatory disorder with renal amyloidosis and colchicine resistance, associated with heterozygosity for a new H478Y *MEFV* variant, has been described in a Spanish kindred, suggesting an unusual FMF phenotype or another *MEFV*-associated periodic inflammatory affection (21).

MEFV gene, predominantly expressed in myeloid cells and granulocytes (22), encodes a 86kDa weighted protein called marenostrin/pyrin belonging along with cryopyrin to the death-domain superfamily, likely involved in the innate immune response (5). Cryopyrin, the product of the *CIAS1* locus, is mutated in familial cold urticaria, Muckle-Wells syndrome and

chronic infantile neurological cutaneous and articular syndrome (5). Both pyrin and cryopyrin share an approximately 90-AA N-terminal sequence known as pyrin domain, by which they interact with a common adaptor protein called ASC (apoptosis-associated speck-like protein with a caspase recruitment domain), that participates in the regulation of apoptosis, inflammation and cytokine processing (5). Thus, the defective pyrin may lead to an impaired control of the inflammation (22,23), especially of the T helper (Th)1 type that characterizes the affection (24). The Th1 polarization may protect FMF patients and carriers from disorders Th2 response-related and help to better react to the various pathogens, constituting from the biblical times a possible, even if controversial (16), selective advantage for heterozygotes (24), as suggested by the very high carrier rate in certain ethnic groups (from 1:3 to 1:16) (3, 7, 16). During the attack-free periods, FMF patients show increased interferon (IFN)-γ serum levels (24) and enhanced mRNA production in circulating leukocytes of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6 and IL-8 (25), reflecting an ongoing inflammation. Also heterozygotes, compared to age matched controls, show an elevated IFN-γ production (24). Moreover, the observed increments of the serum soluble Fas protein levels in attack-free FMF patients may represent dysregulated apoptosis of polymorphonucleates (PMNs) together with a subclinical inflammatory activity (26). Still unexplained is the question of why FMF attacks show a strong preference for serosal and synovial membranes, since *MEFV* is not locally expressed (27). Likely, the tissue specificity may be related to a pyrin-mediated regulation of PMN adhesion molecules in serosal or sinovial vascular beds (27).

FMF is a clinical diagnosis. There is no specific biologic marker for FMF and, to date, the role of genetic test is evolving, but partial. Clinical diagnostic criteria have been performed (28). During the flares, laboratory findings include leukocytosis with neutrophilia and very high APR, particularly of C-reactive protein (CRP) (29), as well as increased plasma levels of IL-6 (30,31), TNF-α (31), both soluble TNF receptor superfamily (sTNFRSF)1A and 1B (30) and of sIL-2r (31). In two thirds of the FMF patients, a continuing APR is present between the attacks (29). Elevated immunoglobulin D (IgD) plasma values have been found in FMF patients with specific *MEFV* mutations (homozygotic status for M694V and V726A) (32). A transient haematuria and albuminuria may be present during the attacks, whereas a persistent proteinuria (more than 0.5 g/24 hours) is highly suggestive for amyloidosis. When a joint effusion occurs, synovial fluid usually contains a large number of granulocytes, that also characterize the sterile exudate of the FMF serositis (9).

The prognosis of the affection is changed with the introduction of the daily colchicine treatment, that not only controls the attacks in the majority of cases, but also prevents the amyloidosis development (7,15,33), even in the clinically not-responder patients (about 5-10%) (9). New therapeutic options are currently investigated, such as IFN-α, thalidomide, anti-TNF agents and plant extracts (34).

Hyperimmunoglobulinemia D and periodic fever syndrome

HIDS is a rare autosomal recessive disease with a worldwide distribution, in the past termed Dutch type periodic fever, being the majority of cases reported from the Netherlands and France (35). The disease onset is generally within the first year of life, in form of acute attacks usually lasting 3-7 days and recurring every 2-8 weeks mainly in childhood and adolescence (3) (Table 2), often precipitated by immunizations, infections, physical trauma or emotional stress (3, 35, 36). The flares consist of fever preceded by chills, variably associated with sterile serositis, arthralgia/arthritis, skin rash and a typical lymphadenopathy (36) (Table 2). A severe abdominal pain with vomiting and diarrhea is common. Unlike FMF, in HIDS the joint involvement expresses itself characteristically as symmetrical polyarthritis or, occasionally, as oligoarthritis (Table 2). Another clinical distinguishing feature is the tender bilateral cervical lymphadenopathy, nearly constant in HIDS, but uncommon in FMF (35). Moreover, the HIDS skin involvement usually appears as maculo-papular rash or as petechiae and purpura (3, 36). Oral and genital ulcers may be present (3, 35). Finally,

in HIDS, amyloidosis has not been till now reported and pleural involvement or myalgias are rare (36). During the acute episodes, leukocytosis with neutrophilia and an intense APR occur, with a significant elevation of serum CRP, SAA, IL-6, TNF-α, IFN-γ, IL-1 receptor antagonist and both sTNFRSF1A and 1B levels (37, 38). Between attacks, stimulated peripheral blood mononuclear cells of HIDS patients in vitro produce increased TNF-α and IL-1β amounts (39). A persistent polyclonal hyperimmunoglobulinemia D (>100 U/ml) is the hallmark of the disorder (3, 35), despite normal or low levels have been reported in some patients (36). More than 80% of patients have also high IgA serum levels (3). An elevated urinary excretion of neopterin, a marker of activated cellular immune response, reflects the disease activity (40).

HIDS is caused by recessive mutations in mevalonate kinase (MK, ATP: mevalonate 5-phosphotransferase) gene (*MVK*) at long arm of chromosome 12 (12q24), encoding an enzyme predominantly localized in peroxisomes and involved in cholesterol and isoprenoid biosynthesis (38, 41). The large majority of patients are compound heterozygotes for two mutations, mostly of missense type, but deletion, absence of an allele expression, as well as novel polymorphisms have also been found (41). The most prevalent is V377I, originating from a common ancestor, likely of Dutch origin (42). In HIDS, the mutations determine a decreased MK activity, however not so profound as in mevalonic aciduria, an affection characterized by a near-complete MK defect and a more severe clinical presentation, with episodic fever, dysmorphisms and mental retardation (43). In both diseases, the MK defect causes increased plasma levels of mevalonic acid, which is excreted in enhanced amounts in the urine (41, 44). However, the relationship between isoprenoid end-product deficiency and HIDS features is not completely understood. Likely, the impaired prenylation of proteins involved in the ligand-induced cellular activation may have a role in the pro-inflammatory cytokine hyper-production that characterizes HIDS (45).

At present, there is no completely effective treatment for HIDS. If the excess of mevalonic acid was the cause of symptoms, the treatment with statins could be beneficial. Instead, the experience with statins has been disappointing, with severe inflammatory attacks apparently provoked by the drug (3). There are some anedoctal reports of benefits with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, intravenous immunoglobulins, colchicine, cyclosporine, but not widely confirmed (3). In a recent trial, thalidomide has failed to reduce the disease activity (46). Etanercept reduces the frequency of the flares and attenuates, but not suppresses, the HIDS clinical manifestations (47).

Tumor necrosis factor receptor superfamily 1A-associated periodic syndrome

TRAPS, formerly known as familial Hibernian fever, is a rare autosomal dominantly inherited HPFS, usually affecting Caucasians, mostly of northern European ancestry, although recent reports highlight that it is more common worldwide than previously appreciated (48). TRAPS was first described as a distinct nosologic entity in 1999 (49). The affection has relapsing and remitting nature, and the disease onset tends to be later and the duration of the attacks longer than in other HPFSs (Table 2), with marked variability even within the same family (6). The episodes usually last a week or more (48, 50, 51) (Table 2) and, sometimes, patients may experience a nearly continuous inflammation (1). The flares may be triggered by emotional stress, exercise or physical trauma (6,50). Pregnancy can improve TRAPS symptomatology, whereas menses may exacerbate it (6) and post-partum hormonal state may induce attacks (50). The observed male : female ratio is of 3 : 2, without gender-specific differences in phenotypic expression (6). Patients with TRAPS present high-grade fever with chills, variably associated with sterile serositis, conjunctivitis, skin rash, arthralgia, and severe myalgias, which are nearly always present (6,48) (Table 2). Fever is practically constant in childhood, but may be absent during some attacks in adults (6). Severe abdominal pain with nausea and vomiting is common and pleurisy is frequent. Testicular and scrotal pain may be present (6). An increased incidence of inguinal hernia among men in some families has been reported (6). Distinguishing clinical features from other HPFSs are mono- or bilateral painful conjunctivitis and/or pe-

riorbital edema, as well as severe pain and tightness of trunk or limb muscle groups, that begin proximally and move distally (6, 51) (Table 2). Patients often describe the discomfort as severely disabling (6). The skin involvement is common and mostly occurs on the limbs as a painless, non-pruritic centrifugally migratory macular eruption, often overlying the area of myalgia (6,51). Arthralgia of large joints is common, but a frank arthritis is infrequent (3). When it occurs, arthritis is monoarticular, non-erosive and affects primarily large joints (6).

TRAPS is due to mutations in the *TNFRSF1A* gene on chromosome 12 (12p13), consisting of 10 exons and encoding for TNFRSF1A (1,6). To date, at least 24 mutations, mostly of missense type, have been identified (52), generally located within the first or the second cysteine-rich N-terminal extracellular domain (CRD1 and 2) of the receptor. Although not all carrier patients present symptoms (3), CRD substitutions demonstrate a higher penetrance and increase the probability of developing amyloidosis (6). However, patients with sporadic TRAPS may be negative for *TNFRSF1A* mutations, probably carrying so far unidentified susceptibility genes (53, 54).

The impaired cleavage of the TNFRSF1A ectodomain upon cellular activation and the consequent reduction in plasma levels of the soluble receptor, that is the disease hallmark, have been proposed as a pathogenic mechanism underlying the hyper-inflammatory response in TRAPS (6, 49). In patients, the sTNFRSF1A plasma values are usually significantly lower than in controls not only during attacks, but also between them (6), and may vary according to the degree of inflammatory activity (54). Moreover, during the flares, laboratory findings include leukocytosis with neutrophilia and a very high APR, often persisting between symptomatic episodes (6). The 25% of TRAPS patients develop amyloidosis. The attack duration and severity, as well as the type of mutations, are risk factors of this complication (49, 51, 54), which, however, does not occur in all the affected components of the same family, suggesting that not yet-characterized modifier genes other than *TNFRSF1A* may be involved in modulating the disease expression (51).

Generally TRAPS patients respond poorly to the NSAIDs and colchicine treatment, showing a significant improvement with corticosteroids (usually more than 20 mg of prednisone), which are usually ineffective in FMF (1, 6, 48, 51, 55). The response to corticosteroids is initially dramatic, but decreases with time, requiring higher doses (3). Azathioprine, methotrexate, cyclosporine, tacrolimus, cyclophosphamide and thalidomide do not give clear clinical benefit (55). Etanercept does not abolish completely the inflammatory attacks, but improves the disease activity, decreasing the severity, duration and frequency of flares, and allows corticosteroid reduction (55). Moreover, it has been reported that etanercept can reverse renal amyloidosis and prevent its recurrence (6).

Conclusions

HPFSs are an amazing group of autoinflammatory diseases, frequently under-diagnosed. Although each of them recognizes a specific genetic background and phenotypic peculiarities, HPFSs globally express themselves in form of intermittent, apparently unprovoked episodes of fever and inflammation. It is intriguing that genetically and biochemically so different affections share a quite similar clinical expression.

FMF is induced by recessive mutations of *MEFV* gene, coding for the pyrin protein, likely involved in the innate immune response. It has been speculated that pyrin acts as a transcription factor regulating the PMN inflammatory response. HIDS is due to recessive mutations of *MVK* gene, causing a MK defect and a consequently reduced biosynthesis of isoprenoids, likely involved in the regulation of the pro-inflammatory cytokine production. Resolving the complete physiopathology of HIDS is a major challenge to give new insight into the role of isoprenoids in inflammation, as well as to provide novel therapeutic options. TRAPS depends on dominant mutations of *TNFRSF1A* gene and is the first example of a new pathogenic mechanism for a human disease, based on impaired cytokine receptor clearance.

However, in a substantial number of patients with periodic fever, a specific syndrome and presently known mutations cannot be identified. It is likely that some of these patients will have defects in genes encoding other pro-inflammatory molecules.

Further studies on the autoinflammatory diseases promise to extend our understanding on the fascinating molecular basis of the inflammation pathway.

Addendum

At the time of the revision of the gallery proofs, Simon A, et al (Clin Pharmacol Ther 2004; 75: 476-83) have reported the results of a double-blind study on simvastatin (80 mg/daily) treatment in six HIDS patients, exiting in a drop of urinary mevalonic acid concentration in all of them and in a decrease of the febrile attack length in 5 of 6 patients, without side effects.

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