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Review

New mosaic tiles in childhood hereditary autoinflammatory disorders

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ABSTRACT

The protean clinical phenotypes of hereditary autoinflammatory disorders (HAID) are caused by abnormal activation of innate immunity and consist of seemingly unprovoked inflammatory flares localized to multiple organs, such as the skin, joints, serosal membranes, gut, and central nervous system. Different mutations in genes implied in activation of the interleukin-1 (IL-1)-structured inflammasome, cytoskeletal signaling and apoptosis contribute to the pathogenesis of different HAID, which mostly start in childhood with self-limited flares unrelated to infectious agents, autoantibody production or autoreactive cells. Though IL-1 remains pivotal in many inflammasome-mediated diseases, other cytokinopathies involving IL-18, nuclear factorκ-B, interferons, and tumor necrosis factor have provided new horizons in the definition of HAID of children: the list of HAID has expanded as a consequence of a better understanding of their pathogenetic molecular mechanisms and also application of new genetic technologies. However, diagnosis of most HAID is clinical and focused on several evidence-based criteria sets: their discrimination remains challenging for unexperienced pediatricians as there are no universally accepted algorithms, and a still relevant number of patients may linger without any clarifying genetic analysis, whose interpretation combined with processing of treatment options should be discussed on a multidisciplinary basis.

1. Introduction to abnormal innate immunity patterns of disease

The innate immunity relies on physiological barriers of the human body and on specific assets of immune responses operated by phagocytic cells, which have been preserved throughout millennia of evolution. Immune cells recognize invasive microbes or signs of danger in different organs and sound "alarms" that recruit other responder cells via specific receptors, initiating an immediate defensive reaction. An awesome alarm is triggered by cytosolic sensors of infections that assemble into multimolecular complexes called inflammasomes, key-components of such defensive machinery, which command the production of inflammatory cytokines to destroy foreign pathogens or deject danger signals, with interleukin 1 (IL-1) being the ancestor among different safeguard molecules [1].

The concept of autoinflammation was proposed in 1999 to identify a group of diseases with subverted innate immunity activation, occurring without any pathogens as well as without circulating autoantibodies and self-reactive cells: these hereditary autoinflammatory disorders (HAID) can be basically defined as inborn errors of innate immunity [2] and primarily include inflammasomopathies, in which the most striking feature is an exaggerated IL-1-mediated response leading to the recurrence of transient self-limited sterile inflammation, followed by symptom-free periods of variable duration [3]. The field of HAID is every day expanding more and more with the improvement of sequencing technologies, and many novel progresses have obfuscated the boundaries between autoimmunity, immunodeficiency and autoinflammation [4]. Indeed, many novel disorders with an autoinflammatory underlayer have been described, such as nuclear factor (NF)-κB-mediated disorders, type 1 interferonopathies and defects in ubiquitination [5]. What is of relevant significance is that recurrent inflammation in HAID might lead to potentially irreversible chronic damage over time in terms of joint restriction, kidney failure, serosal scarring, osteoporosis, hearing loss, blindness, pubertal delay, infertility, growth failure or cognitive impairment in the pre-diagnostic or in the pre-therapeutic phase of a specific disorder [6,7]. This review is conceived as a concise summary of HAID encountered in children, for which manifold mechanisms have been found as the basic ground of abnormal innate immunity expression.

2. Familial mediterranean fever (FMF)

FMF is the most common monogenic autosomal recessive disease among HAID, mostly observed in Turkish, Armenian, Arabic, Sephardic Jewish communities and in people living around the Mediterranean sea, caused by mutations within the *MEFV* gene, which were first recognized in 1997 by two different research groups, encoding variants of the protein pyrin [8]. Pyrin works physiologically as an intracellular regulator of IL-1 production, though conflicting results have been reported

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in relationship with the exact effect of FMF-associated pyrin mutants: although it does not seem to bind directly to bacterial products, a recent study has shown that it is phosphorylated in a RhoA GTPase-dependent manner, leading to inactivation of the pyrin inflammasome formation in the absence of any infections. The pyrin inflammasome works as an innate immunity sensor to detect bacterial-induced modifications of RhoA, but mutated pyrins result in RhoA inactivation and pathogen-independent hyperproduction of IL-1β [9]. FMF is inherited in a recessive manner, and most patients hold biallelic gain-of-function *MEFV* mutations, though 1/3 of patients with a clinically overt FMF might have only one mutated allele, suggesting a dominant segregation of some mutations. Additionally, even mutation-free patients have been reported, revealing the existence of alternative pathogenetic mechanisms for FMF, such as epigenetic dysregulation [10]. Over 300 pyrin variants with different clinical penetrance have been reported in the website http://fmf.igh.cnrs.fr/ISSAID/infevers, and the most severe involve the exon 10, encoding the B30.2/SPRY domain, which is necessary for a regular pyrin function [11]. The highly preserved pyrin inflammasome has a crucial role in host innate immunity, and FMF-associated mutations might have conferred benefits against various infectious diseases, such as tuberculosis, brucellosis and plague, as a result of selective advantage.

Patients experience self-limiting febrile attacks characterized by 1-to-3-days' duration and inflammation of the serosal membranes, synovial fluid or skin: the serosal and synovial linings are important targets of the FMF inflammatory cascade, and severe abdominal or chest pain are typical symptoms, occurring in more than 90 and 40% of patients, respectively [12]. Many non-canonical FMF manifestations have been also reported, though suggestive for diagnosis if present is a recurrent erysipelas-like eruption on the calf [13]. Reactive AA amyloidosis, due to the deposition of serum amyloid-A, one of the acute reactants produced during disease flares in HAID, is the long-term deadly complication of FMF, which can be even found as the only clinical manifestation in otherwise asymptomatic individuals [14]. The products of amyloidogenesis can be deposited in a number of organs, including kidneys, adrenal glands, liver, spleen, thyroid gland, and heart: symptomatic amyloidosis clinically affecting one or more organs and confirmed by examination of tissue sections by Congo red dye is mostly observed in untreated or in noncompliant patients. However, the occurrence of AA amyloidosis is strongly correlated with the M694 V mutation and also with peculiar variations in *SAA* haplotype, the gene encoding serum amyloid-A [15]. Studies comparing patients with the same ancestry living in Turkey or in Germany have also allowed the determination of the impact of environment on FMF severity, accounting to as much as 12% of the phenotypic variation [16]. Diagnosis of FMF is clinical and requires information about ethnic background, family history, and response to colchicine, a tricyclic alkaloid extracted from lily plants which prevents microtubule polymerization in the cytoskeleton and activates RhoA, suppressing pyrin inflammasome activation: daily colchicine is the standard therapy for the prevention of both FMF attacks and also for the prevention of amyloid A-associated amyloidosis [17]. Treatment should be aimed to decrease subclinical chronic inflammation and its complications: taken on a life-long basis, colchicine reduces FMF attack frequency or attack severity and shortens the overall duration of attacks in most patients. Moreover, a favorable response to colchicine supports the diagnosis of FMF, especially in cases showing an atypical or incomplete phenotype [18]. The inhibitory effect on IL-1 release operated by colchicine and its prophylactic role on the recurrence of FMF attacks were discovered serendipitously, however alternative medications have strongly shown to be highly effective in colchicine nonresponders through different studies [19]. Children with colchicine-resistant FMF have been treated with tumor necrosis factor (TNF) inhibitors with unsatisfactory results [20], leading many investigators to speculate the superiority of blocking IL-1 over TNF. Both recombinant IL-1 receptor antagonist anakinra and the fully human anti-IL-1β monoclonal antibody canakinumab have been administered in refractory FMF patients, both reducing frequency of attacks and normalizing levels of serum amyloid-A [21,22].

3. Tumor necrosis factor receptor-associated periodic syndrome (TRAPS)

TRAPS is the most common autosomal dominant autoinflammatory disorder, caused by missense mutations in the *TNFRSF1A* gene, encoding the 55-kD receptor for TNF-α [23]. The discovery of TRAPS allowed the introduction of the "autoinflammation" concept, but our actual knowledge of this disease, its pathogenetic mechanisms and its genotype-phenotype correlations appears still fragmented due to both its rarity and continuous stream of newly discovered genetic variants [24]. Mutant TNF receptors display an altered conformation and stability or impaired intracellular trafficking to the cell surface with abnormal ligand binding and protean proinflammatory consequences, such as increased production of TNF, IL-1 and IL-6, altered NF-αB pathway, increased activation of mitogen-activated protein kinases, downregulated autophagy, and upregulated production of reactive oxygen species [25]. The molecular link between TRAPS and IL-1 is not clear: the pathogenesis may vary with each *TNFRSF1A* mutation, though aggregates of misfolded TNF receptors retained in the endoplasmic reticulum might trigger the reactive oxygen species-dependent hypersecretion of inflammatory cytokines, including IL-1 [26].

TRAPS clinical picture is characterized by quite long febrile episodes, differently from other HAID, combined with skin, muscular, joint, abdominal, and ocular manifestations, which occur spontaneously or after trivial triggers [27]. Molecular analysis is required for diagnosis of this disorder, and prognosis is mainly determined by the risk of renal amyloidosis, which can be observed in 25% of patients carrying peculiar mutations [28]. As well as 158 *TNFRSF1A* variants have been recognized and associated with TRAPS phenotype: some mutations are related to cysteine-rich domains of the ectodomain of mature TNFR and display higher penetrance; other low penetrance variants, such as P46L and R92Q, have a less severe impact on the TNFR structure of the protein and have been associated with a lower risk of amyloidosis and milder clinical picture [29]. A positive family history for pericarditis and a poor response to colchicine are clues of a potential presence of *TNFRSF1A* mutations in patients displaying idiopathic recurrent pericarditis [30].

Corticosteroids, given at the onset of a TRAPS attack, decrease its length and severity, without affecting attack frequency, while the anti-TNF biologic etanercept can mitigate disease activity and allow for corticosteroid dosage sparing at least in a minority of patients [31]. The humanized monoclonal antibody against IL-6 receptor tocilizumab has given transient improvements in a few patients [32], but there have been impressive benefits from the administration of anakinra and canakinumab in terms of stable remission and short-term prevention of disease relapses [33].

4. Cryopyrin-associated periodic syndrome (CAPS)

Mutations of the NOD-like receptor *NLRP3* gene are responsible for NLRP3 inflammasome overactivity and generation of CAPS phenotype: this is a complex family of HAID with unexplained episodes of fever and severe localized inflammation, distinguished in three variants of increasing severity: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome and CINCA (chronic infantile neurologic cutaneous and articular) syndrome, otherwise termed "neonatal-onset multi-system inflammatory disorder" [34]. They are all caused by missense mutations in the NACHT domain of the *NLRP3* gene, that encodes the protein cryopyrin, a key-component of the inflammasome complex, and they all lead to dysregulated processing and secretion of IL-1β [35]. Mutations in *NLRP3* are distributed worldwide, though more represented in the Caucasian populations, and result in a gain-of-function effect, probably through the loss of a regulatory step