Autoinflammatory Diseases in Children

Subjects: Genetics & Heredity

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Abnormalities of the innate immunity machinery make up a motley group of rare diseases named ‘autoinflammatory’, which are caused by mutations in genes involved in different immune pathways. Self-limited inflammatory bouts involving skin, serosal membranes, joints, gut and other districts of the human body burst and recur with variable periodicity in most autoinflammatory diseases (ADs), often leading to secondary amyloidosis as a long-term complication. Dysregulated inflammasome activity, overproduction of interleukin (IL)-1 or other IL-1-related cytokines and delayed shutdown of inflammation are pivotal keys in the majority of ADs. The recent progress of cellular biology has clarified many molecular mechanisms behind monogenic ADs, such as familial Mediterranean fever, tumor necrosis factor receptor-associated periodic syndrome (or ‘autosomal dominant familial periodic fever’), cryopyrin-associated periodic syndrome, mevalonate kinase deficiency, hereditary pyogenic diseases, idiopathic granulomatous diseases and defects of the ubiquitin-proteasome pathway. A long-lasting history of recurrent fevers should require the ruling out of chronic infections and malignancies before considering ADs in children.

Keywords: autoinflammation ; periodic fever ; child

1. Prelude to the Concept of Autoinflammation

Innate immunity exploits biochemical weapons in different tissues of the human body and has its main alarm system switch in the “inflammasome,” a multiprotein complex made of pattern recognition receptors and caspase-1, which processes pro-interleukin (IL)-1 into its mature form, IL-1β. All activated innate immune cells display their antibacterial activity through the inflammasome-mediated production of powerful inflammatory cytokines, such as IL-1β, to counteract microbial threats [1][2]. The discovery of monogenic defects in the innate immunity has clarified that both inflammasome activity and IL-1 release are altered in a cluster of rare diseases marked by recurrent inflammatory symptoms affecting skin, serosal membranes, joints, gut, central nervous system and other tissues, in which IL-1β represents the main driver of inflammation [3][4]. The word “autoinflammatory” in ‘autoinflammatory diseases’ (ADs) describes the “apparent” spontaneous burst of inflammation, as infectious triggers, autoreactive T lymphocytes and/or specific autoantibodies are absent [5]. ADs are caused by impaired production of pro-inflammatory cytokines, with IL-1β playing a seminal role, along with a delayed shut-down of the immune response, leading to recurrent episodes of fever, and in some cases, inflammation limited to specific organs [6]. These diseases can be categorized in hereditary monogenic and multifactorial polygenic disorders encompassing many protean conditions such as periodic fever/aphthous stomatitis/pharyngitis/cervical adenopathy (PFAPA) syndrome, which is still the most mysterious cause of idiopathic recurrent fevers in childhood [7]. All these disorders represent a diagnostic challenge because their symptoms are nonspecific and sometimes refer to infectious or malignant diseases. Although many classification criteria have been developed to help diagnose rare monogenic ADs, patients with recurrent fevers and inflammatory symptoms experience a general delay in identification of the disease, which can lead to further morbidities and dreadful complications, such as AA-amyloidosis [8][9]. The repertoire of ADs was expanded to include inflammatory diseases such as Behçet’s disease, gout and idiopathic recurrent pericarditis, all of which have autoinflammatory-mediated mechanisms and a presumed polygenic basis [10]. Identification of the causative genes has also allowed for the confirmation of the clinical diagnosis in familial Mediterranean fever (FMF); tumor necrosis factor receptor-associated periodic syndrome (TRAPS); cryopyrin-associated periodic syndrome (CAPS), which includes familial cold-induced autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and chronic infantile neurological cutaneous articular (CINCA) syndrome; mevalonate kinase deficiency (MKD); pyogenic diseases including pyogenic arthritis/pyoderma gangrenosum/acne (PAPA) syndrome, Majeed syndrome (MS) and deficiency of the IL-1 receptor antagonist (DIRA); Blau syndrome (BS); OTULIN-related autoinflammatory syndrome (ORAS) and proteasome-associated autoinflammatory syndromes (PRAAS). A summary of the monogenic ADs is listed in **Table 1**. Genes associated with these diseases have been sequentially identified since 1997 onwards, and with the exception of MKD, the majority of them encode for proteins involved in the inflammasome architecture or in programmed cell death [11]. In particular, inflammasomes, structured with a central sensor protein, an

adaptor protein and CASPASE-1, modulate IL-1β release and work as platforms to protect the human body from the outnumber of pathogenic organisms [12].

Table 1. Brief summary of the hereditary monogenic autoinflammatory diseases.

	Gene Locus	Protein	Inheritance	Main Manifestations and Complications	Available Treatments
FMF	*MEFV* 16p13.3	PYRIN or marenostrin	AR	serositis, limb pain or transient arthritis, erysipelas-like eruption on the legs, nonspecific skin manifestations (like urticaria, angioedema, erythema nodosum, vasculitis), risk of amyloidosis	Colchicine, canakinumab, anakinra
TRAPS	*TNFRSF1A* 12p13	TNFRSF1A, TNF receptor	AD	severe migrating muscle pain, arthralgia or arthritis, serositis, painful orbital edema, painful conjunctivitis, risk of amyloidosis	Canakinumab, anakinra, corticosteroids
FCAS	*NLRP3* 1q44	CRYOPYRIN	AD	cold-induced urticaria-like rashes, conjunctivitis, arthralgia	Anakinra, rilonacept, canakinumab
MWS				cold-induced urticaria-like rash, conjunctivitis, episcleritis, arthralgia, neurosensorial deafness, risk of amyloidosis	
CINCA				migrating non-itchy urticaria-like rash, uveitis, papilledema, deforming arthritis involving large joints, aseptic chronic meningopathy, retinal dystrophy, neurosensorial deafness, risk of amyloidosis	
MKD	*MVK* 12q24	MEVALONATE KINASE	AR	fatigue, painful generalized lymph node enlargement, vomiting, diarrhea, abdominal pain, arthralgia, skin rashes of varying severity, oral and/or genital aphthosis, splenomegaly during flares	Anti-inflammatory drugs, corticosteroids, anakinra 'on demand', canakinumab
PAPA	*PSTPIP1* 15q24–25	PSTPIP1 (proline-serine-threonine phosphatase interacting protein 1)	AD	sterile pyogenic arthritis, pyoderma gangrenosum, severe acne, skin abscesses, recurrent non-healing sterile ulcers	Corticosteroids, infliximab, anakinra, immunosuppressive agents
MS	*LPIN2* 18p11.31	LIPIN2 (phosphatidate phosphatase)	AR	recurrent multifocal osteomyelitis, neutrophilic dermatosis, dyserythropoietic anemia	Corticosteroids, bisphosphonates, TNF-α inhibitors, IL-1 antagonists (anakinra)
DIRA	*IL1RN* 2q14.1	IL1RN (interleukin-1 receptor antagonist)	AR	sterile multifocal osteomyelitis starting in the neonatal period, skin pustulosis, osteitis	Anakinra
BS	*NOD2 (CARD15)* 16q12.1–13	NOD2 (nucleotide binding oligomerization domain containing 2)	AD	non-erosive granulomatous polyarthritis ('boggy synovitis' with painless effusion and cyst-like swelling of joints), granulomatous panuveitis, skin granulomatous rash	Corticosteroids, TNF-α inhibitors (infliximab), IL-1 antagonists, JAK inhibitors (tofacitinib)

	Gene Locus	Protein	Inheritance	Main Manifestations and Complications	Available Treatments
DITRA	*IL36RN* 2q14.1	IL36RN (interleukin-36 receptor antagonist)	AR	severe pustular psoriasis (generalized or limited to the distal part of limbs)	TNF-α inhibitors (adalimumab), IL-12/23 antagonists, IL-17 antagonists
CAMPS	*CARD14* 17q25.3	CARD14 (caspase recruitment domain-containing protein 14)	AD	psoriasis in a wide range of phenotypes	Methotrexate, corticosteroids, cyclosporine, phototherapy, acitretin, vitamin D analogs, TNF-α inhibitors, IL-12/23 antagonists, IL-17 antagonists
ORAS	*OTULIN* 5p15.2	OTULIN (deubiquitinase)	AR	fever starting in the neonatal period, neutrophilic dermatosis associated with panniculitis, growth retardation	TNF-α inhibitors
HA20	*TNFAIP3* 6q23.3	TNFAIP3 (tumor necrosis factor alpha-induced protein 3, A20)	AD	recurrent mucosal ulcerations of the oral cavity, gastrointestinal tube and urogenital tract, skin rashes, polyarthritis, uveitis, vasculitides, recurrent fevers, association with different autoimmune disorders (systemic lupus erythematosus, psoriatic arthritis, juvenile idiopathic arthritis, autoimmune hepatitis and Hashimoto thyroiditis)	TNF-α inhibitors, colchicine
FCAS2	*NLRP12* 19q13.42	NLRP12 (nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain containing 12)	AD	cold-induced rashes, joint pain, abdominal pain, sensorineural deafness, headache	Anakinra, TNF-α inhibitors, IL-6 antagonists (tocilizumab)
PRAAS	*PSMB8*	PSMB8 (proteasome 20s subunit beta 8)	AR	chronic atypical neutrophilic dermatosis, lipodystrophy, erythema nodosum-like panniculitis, abnormal growth of lips, muscular weakness and atrophy, severe joint contractures, basal ganglia calcifications, ear and nose chondritis, aseptic meningitis, conjunctivitis, hepatosplenomegaly, lymph node enlargement, arthralgia	Corticosteroids, immunosuppressive agents, anakinra, IL-6 antagonists (tocilizumab), TNF-α inhibitors, dapsone, JAK inhibitors (baricitinib)
SAVI	*STING1* (TMEM173) 5q31.2	STING1 (stimulator of interferon genes protein 1)	AD	vasculopathy causing severe skin lesions on face, ears, nose and digits, resulting in ulcerations, necrosis or amputations, chronic interstitial lung disease	JAK inhibitors (ruxolitinib)

	Gene Locus	Protein	Inheritance	Main Manifestations and Complications	Available Treatments
AGS	***TREX1, RNASEH2B, RNASEH2C, RNASEH2A, SAMHD1, ADAR, IFIH1*** **3p21.31, 13q14.3, 11q13.1, 19p13.13, 20q11.23, 1q21.3, 2q24.2**	**Enzymes involved in the duplication, repair and recombination of nucleic acids**	**AR (AD for *IFIH1*)**	**leukoencephalopathy (mimicking transplacental infections), calcifications in cerebral and basal ganglia, dystonia, microcephaly, cognitive impairment, abnormal eye movements, glaucoma, livedo reticularis, digital chilblain lesions on hands and feet, hepatosplenomegaly, jaundice, silent positivity of autoantibodies**	**No cure is available, corticosteroids and intravenous immunoglobulin may control systemic and organ inflammation**

FMF: familial Mediterranean fever; TRAPS: tumor necrosis factor receptor-associated periodic syndrome (autosomal dominant familial periodic fever); FCAS: familial cold-induced autoinflammatory syndrome; MWS: Muckle-Wells syndrome; CINCA s.: chronic infantile neurologic cutaneous articular syndrome; MKD: mevalonate kinase deficiency (hyper-IgD syndrome); PAPA s.: pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome; MS: Majeed syndrome; DIRA: deficiency of IL-1 receptor antagonist; BS: Blau syndrome; DITRA: deficiency of the interleukin-36 receptor antagonist; CAMPS: CARD14-mediated psoriasis; HA20: haploinsufficiency of A20; ORAS: OTULIN-related autoinflammatory syndrome; FCAS2: familial cold autoinflammatory syndrome 2 (*NLRP12*-associated autoinflammatory disorder); PRAAS: proteasome-associated autoinflammatory syndrome; SAVI: *STING*-associated vasculopathy with onset in infancy; AGS: Aicardi-Goutières syndrome. AR: autosomic recessive; AD: autosomic dominant; TNF: tumor necrosis factor; IL-1: interleukin-1; JAK: Janus kinase.

2. Insights on the Polygenic and Multifactorial Autoinflammatory Disorders in Children

Autoinflammatory diseases of unknown etiology with a presumed either polygenic or multifactorial origin have been recognized in adult people, including Behçet's disease, idiopathic recurrent pericarditis, crystal-induced arthropathies and adult-onset Still's disease, but also in children, including systemic juvenile idiopathic arthritis (sJIA), Kawasaki disease (KD) and PFAPA syndrome. These conditions are largely characterized by dysregulation of the innate immune network and upregulation of inflammasome-associated genes [13]. The whole IL-1 cytokine family is abundantly involved in polygenic/multifactorial ADs, and different randomized placebo-controlled clinical trials have confirmed the efficacy of IL-1 inhibitors in their management [14]. Symptoms of such complex heterogeneous diseases, including recurrent fevers, synovitis and serositis, may overlap with monogenic ADs; in addition, some well-known life-threatening complications as macrophage activation syndrome or reactive amyloidosis might occur [15][16][17]. In particular, sJIA, part of the group of childhood arthritides, has peculiar characteristics derived from uncontrolled activation of phagocytes and hypersecretion of both IL-1 and IL-6, differently from other forms of juvenile idiopathic arthritis. Indeed, sJIA is marked by extra-articular signs that include spiking fevers, rash, hepatosplenomegaly, generalized lymphadenopathy and serositis [18]. **Table 2** defines sJIA according to the PRINTO classification criteria [19].

Table 2. Classification criteria of systemic juvenile idiopathic arthritis (according to PRINTO organization): fever has to be associated with 2 major criteria or with 1 major criterion and 2 minor criteria, after exclusion of infectious, neoplastic, autoimmune and hereditary autoinflammatory diseases.

Cardinal Sign	*Major Criteria*	*Minor Criteria*
Fever of unknown origin that is documented to be daily (until 39 °C once a day with intermittent course) for at least 3 consecutive days and reoccurring over an observation period of at least two weeks	(a) evanescent nonfixed erythematous rash (b) arthritis	(1) generalized lymph node enlargement and/or hepatomegaly and/or splenomegaly (2) serositis (3) arthralgia lasting 2 weeks or longer (in the absence of arthritis) (4) leukocytosis (≥15,000/mm^3) with neutrophilia

Another febrile disorder with a supposed autoinflammatory basis is KD, an acute self-limiting vasculitis of unknown etiology, usually affecting children younger than 5 years, particularly those of Asian descent. This condition has a typical monophasic course characterized by unremitting high fever combined with a constellation of nonspecific skin, orofacial or cervical signs: the risk of coronary artery damage in 1/4 of untreated patients makes KD the most common cause of acquired heart disease for children living in the developed world [20][21]. Despite more than 5 decades of enquiries, the underlying mechanisms provoking coronary artery suffering in KD remain unknown: some scientific gaps include genetic predisposition to KD, dysregulated activation of autoinflammatory pathways and tendency to recur in a minority of cases. A series of studies indicate that the *primum movens* may be an abnormal immune response to different infectious agents, causing both endothelial cell malfunction and turbulent inflammatory cascade in a genetically-predisposed child [22]. Treatment with intravenous immunoglobulin during the first 10 days of disease decreases the risk of developing coronary artery aneurysms by five-fold, but non-responders are those with the higher risk of developing heart complications [23][24]. The multi-systemic inflammatory syndrome seen in children with ‘coronavirus disease 2019′ has been described to partially overlap with KD, but the upregulation of autoinflammation-related genes and hypersecretion of IL-1α, IL-6 and TNF are typical of KD [25]. Early identification of KD patients refractory to immunoglobulin might allow a more intensive treatment to prevent coronary artery abnormalities: for instance, Koné-Paut et al. recently found that intravenous immunoglobulin-resistant KD patients could be successfully treated with IL-1 blockade (i.e., anakinra) to obtain temperature normalization and overall improvement of vasculitis-related manifestations [26].

The most frequent cause of recurrent fevers in children younger than 5 years remains PFAPA syndrome, defined by febrile attacks having “clockwork” periodicity with stereotyped signs affecting the oral cavity and neck alternated by periods of whole well-being: this autoinflammatory disease displays a negative impact on child’s and parents’ quality of life, though its outcome is generally favorable due to remission after an unpredictable period of months or years [27]. There are limited studies focusing on the cyclic nature of PFAPA symptom recurrence, though clock-related genes and their interaction with different immunologic activities have been proven [28]. PFAPA clinical picture overlaps with several other causes of recurring fevers in the pediatric population, such as recurrent tonsillitis, Behçet’s disease and mostly cyclic neutropenia, an ultra-rare hereditary condition diagnosed via demonstration of periodic oscillations of the neutrophil count every 21 days [29]. Adults with de novo PFAPA syndrome or with reappearance of PFAPA symptoms after a first disease resolution have been increasingly reported, but they have a less strict phenotype [30][31]. IL-1-mediated PFAPA pathogenesis suggests that the syndrome could be framed as a rhythmic self-limited dysregulation of innate immunity, disrupting the commensal oral ecosystem and specifically the microbial community in the tonsils [32]. The genetic susceptibility of PFAPA syndrome is yet to prove, although many overlapping symptoms with monogenic hereditary ADs, its dominant recurrency in about 10% of PFAPA patients, hyperexpression of inflammasome-associated genes during febrile flares, and therapeutic efficacy of IL-1 blockers suggest a potential genetic origin [33]. Recently, Sangiorgi et al. studied a small population of familial and sporadic cases of PFAPA-like patients identifying variants in the *ALPK1* gene [34]; a specific missense mutation (T237M) in this same gene has been also related to a new autosomal dominant autoinflammatory condition called ROSAH syndrome, characterized by retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis and migraine [35]. More studies are obviously needed to confirm the role of such rare *ALPK1* variants in larger cohorts of PFAPA patients. **Table 3** shows the definition of PFAPA syndrome in childhood according to Marshall’s criteria [36], criteria set off for adult patients [37], and according to Eurofever/PRINTO classification criteria [38].

Table 3. Definition of the periodic fever/aphthous stomatitis/pharyngitis/cervical adenopathy (PFAPA) syndrome in children, in adults and according to the Eurofever/PRINTO classification criteria.

PFAPA syndrome in children	**Periodically recurring high fevers (with "clockwork" periodism at intervals of 4–6 weeks)** **+** **Onset before 5 years** **+** **Child's complete wellness between attacks (with normal growth and no sequelae)**	**At least 1 among:** (a) aphthous stomatitis (b) pharyngitis (c) cervical lymphadenitis **Absence of respiratory infection-related symptoms**	**To rule out:** - Cyclic neutropenia - Recurrent upper respiratory infections - Monogenic hereditary sautoinflammatory disorders
PFAPA syndrome in adults (at least 16-year-old)	**Recurrent fevers** **+** **Increased inflammatory parameters during febrile attacks** **+** **Symptom-free intervals**	**At least 1 between:** - pharyngitis - cervical lymphadenitis	**To rule out:** - Infections - Autoimmune disorders - Monogenic hereditary autoinflammatory disorders
Eurofever/PRINTO classification criteria for PFAPA syndrome	**At least 7 out of the following 8 signs (either positive [from *a* to *d*] or negative [from *e* to *h*]):**	(a) pharyngotonsillitis (b) febrile flares lasting 3–6 days (c) cervical lymphadenitis (d) periodic recurrence of flares	(e) absence of diarrhea (f) absence of chest pain (g) absence of skin rash (h) absence of arthritis

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