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Autoinflammatory syndromes behind the scenes of recurrent fevers in children

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Summary

Many children experience recurrent fevers with no easily identifiable source and only a careful follow-up helps in the early identification of other presenting symptoms of other defined conditions which require medical intervention. Autoinflammatory syndromes are rare childhood-onset disorders of the innate immunity in which recurrent flares of fever and inflammation affecting skin, joints, the gastrointestinal tube, or serous membranes are the most striking signs, without any evidence of autoantibody production or underlying infections. Among the pediatric conditions belonging to this group we can consider hereditary recurrent fevers (familial Mediterranean fever, mevalonate kinase deficiency syndrome, tumor necrosis factor receptor-associated periodic syndrome, cryopyrin-associated periodic syndromes), pyogenic disorders (PAPA syndrome, CRMO syndrome, Majeed syndrome), immune-mediated granulomatous diseases (Blau syndrome, Crohn's disease), and idiopathic febrile syndromes (systemic-onset juvenile idiopathic arthritis, PFAPA syndrome, Behçet syndrome). Their genetic background has only been partially elucidated and advances in their molecular pathogenesis are shedding new light on the innate immune system, whilst more and more diseases are being reconsidered at a pathogenetic level and included in this new chapter of postgenomic medicine. The diagnosis of most autoinflammatory syndromes relies on clinical history, demonstration of an increased acute-phase response during inflammatory attacks, and, possibly, genetic confirmation, which is still elusive especially for idiopathic febrile syndromes. This astonishing progress in the awareness and knowledge of autoinflammatory syndromes has anticipated the actual possibilities of medical intervention and rationalized treatment with targeted biologic agents.

key words: **autoinflammatory syndrome • recurrent fever • child**

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BACKGROUND

A harrowing labyrinth is the landscape which primary care pediatricians have to face when they are called upon to choose a diagnostic path and possibly find a resolutive cure for children with recurrent fevers (RF). The complaint of RF is a very frequent referral to clinical investigation for a pediatrician, which means expenditure of time at the pediatrician's office and expense for examinations or medications. It is no wonder that the parents of these children look bewildered when they enter our first-aid ambulatory: their histories heavily threaten all family plans and tie up their children's destiny. The concern of RF is clearly frustrating for both physicians and parents in the sense that numerous examinations frequently fail to substantiate any cause of the problem.

The chasm of recurrent fevers in children

A fundamental distinction must include infectious and non-infectious causes of RF. It has been estimated that at least 6% of Italian children younger than 6 years of age present recurrent respiratory infections as the most frequent etiology of RF without any other recognized predisposing disease, although some of these children might display persistent signs of infection in the nasopharynx with tonsil and adenoid disease, perturbed intestinal flora, or concomitant allergic diathesis [1]. The first two years of life are characterized by substantial modifications of the pulmonary structure and are a period of life in which airway susceptibility to infections of different severity is higher [2]. Heterogeneous abnormalities of the innate immune system can be demonstrated in only a minority of children, while increased environmental exposure combined with nursery-school or day-care attendance, air pollution, parental smoking, and home dampness appear to be strong risk factors in all age groups [3]. The main problem is to discriminate whether RF derives from increased exposure to the ever-changing microbial flora or from host-related factors, in other words to determine if these children are normal with high infection frequency or affected by another underlying pathological condition [4]. Discerning a trademark and disclosing the cause of RF in children at first evaluation is unlikely, but family history, ethnic origin, early onset within the first year of life or neonatal period, concomitant manifestations, and course might suggest another group of diseases manifesting with RF which are called "autoinflammatory syndromes" (AIS).

Autoinflammatory syndromes concealed behind recurrent fevers

The possibility that systemic AIS might be concealed beneath the simple appearance of RF can no longer be overlooked. All inherited and acquired AIS are characterized by lifelong, spontaneously relapsing bouts of fever and systemic inflammation without any apparent involvement of antigen-specific T cells, auto-antibody production, or evidence of infection [5]. Each typical attack of AIS is self-limited, lasts from a few days to some weeks, is followed by complete spontaneous resolution of every tissue manifestation, and is separated by symptom-free intervals of different duration [6]. Despite the rather recent nosological characterization, AIS have probably afflicted mankind throughout many centuries, even when considered ethnically restricted to small groups of populations living around the Mediterranean basin and in northwestern Europe [7]. The family of AIS is in continuous expansion, but if we restrict them to the pediatric age only, AIS encompass hereditary recurrent fevers, pyogenic disorders, immune-mediated granulomatous diseases, and idiopathic febrile syndromes.

HEREDITARY RECURRENT FEVERS

Hereditary recurrent fevers are caused by mutations of gene complexes which encode recognition receptors or signal proteins involved in inflammatory pathways and which invariably lead to final proinflammatory cytokine imbalance. Though lacking a strict periodicity, all AIS display a spontaneously relapsing activation of cells of the innate immunity in the absence of specific ligands [8]. Two autosomal-recessively and one dominantly inherited disorders are included in this group, the first two being familial Mediterranean fever (FMF, OMIM 249100), which is the most common cause of hereditary RF worldwide, and mevalonate kinase deficiency syndrome (MKD), considerably less common than FMF, and the last being tumor necrosis factor receptor-associated periodic syndrome (TRAPS). The most relevant clinical signs and features of FMF, MKD, and TRAPS are listed in Table 1. Their relatively limited area of geographical distribution, the Mediterranean basin for FMF and north-central Europe for MKD and TRAPS, probably support the theory of a selective evolutionary advantage [9]. Nevertheless, population migrations throughout the centuries, such as the Greek colonization, the Jewish diaspora, the Arab expansion, and the international travel from the southern Caucasus, have all contributed to the spread of these conditions all over the Old and New Worlds. Under this heading we can also include "cryopyrinopathies", rare monogenetic diseases driven by uncontrolled interleukin-1 production that represent a spectrum of one single disease with varying degrees of severity [10].

Familial Mediterranean fever (FMF)

The gene causing FMF (designated *MEFV*, 16p13.3) was discovered independently by both international and French consortia in 1997 and the *MEFV* product, called pyrin (also called marenostrin), specifically expressed in the cytoplasm of myeloid cells, acts as a negative regulator of apoptosis-associated proteins and inflammatory circuits [11,12]. FMF's clinical picture has been appreciably expanded in the last years, but most of its manifestations (short and self-resolving attacks of RF with abdominal, thoracic, or joint pain varying from mild to incapacitating) can be reversed by colchicine administration, whilst systemic amyloidosis of different magnitude can slowly take place in untreated or in colchicine-resistant patients [13]. Attacks of FMF occur irregularly and apparently in a spontaneous manner, although they might be precipitated by physical and emotional stress. FMF's prevalence in some countries, such as Turkey, Israel, and Armenia, is so high that its pattern of inheritance might sometimes resemble that of a dominant trait and is now increasingly recognized worldwide and is no longer considered a rare condition [14]. Genotype analysis might support the diagnostic work-up, although FMF's identification remains essentially clinical and centers on the history of self-limiting idiopathic RF attacks and serositis/synovitis that can be prevented by colchicine. The Sheba Medical Center in Tel Hashomer is the oldest referral center for the diagnosis and management of FMF and the current diagnostic criteria were worked out by

Table 1. Differential diagnosis of hereditary recurrent fevers.

	Familial Mediterranean fever	Mevalonate kinase deficiency syndrome	Tumor necrosis factor receptor-associated periodic syndrome
Onset	Childhood or adolescence	Infancy (usually in the first year of life)	3–20 years
Inheritance	Recessive	Recessive	Dominant
Gene	*MEFV*	*MVK*	*TNFRSF1A*
Chromosomal locus	16p13.3	12q24	12p13.3
Usual ethnicity	Non-Sephardic Jewish, Armenian, Arab, Turkish	Dutch and other Northern European	Northern European, any ethnicity
Protein involved	Pyrin (marenostrin)	Mevalonate kinase	Tumor necrosis factor receptor 1 (p55) or CD120a
Fever duration	1–4 days	3–7 days	1 or more weeks
Abdominal distress	Very common (sterile peritonitis)	Very common (abdominal pain, vomiting, diarrhea)	Common (abdominal pain, diarrhea, constipation)
Chest involvement	Pleurisy, often unilateral	Infrequent	Pleuritis
Skin involvement	Erysipelas-like rash	Polymorphic rash	Painful migratory eruption, edematous plaques
Articular involvement	Arthritides or arthralgias	Arthralgias	Migratory arthralgias, non-erosive arthritides
Other signs	Pericardial effusion, scrotal pain	Cephalalgia, lymph node enlargement	Periorbital edema, conjunctivitis, localized myalgia, muscle tenderness, monocytic fascitis
IgD	Elevated in 15% of cases	Almost constantly elevated (>100 IU/ml)	Elevated in 10% of cases (<100 IU/ml)
IgA	Elevated in 25% of cases	Elevated in 85% of cases	–
Treatment	Colchicine	Anakinra, simvastatine	Corticosteroids, etanercept, anakinra
Amyloidosis	Common in colchicine-resistant and in untreated patients	Rare (5% of patients)	15-25% of patients

this scientific group: two major criteria (RF accompanied by serositis or synovitis, AA amyloidosis without a predisposing disease, favorable response to colchicine treatment) or one major criterion and two minor ones (RF episodes, erysipelas-like erythema, FMF in a first-degree relative) are required for a definite diagnosis [15]. Supportive measures are required during acute attacks, but the mainstay of management is long-term prophylactic treatment with low-dose colchicine [16].

Mevalonate kinase deficiency syndrome (MKD)

The gene causing MKD (designated *MVK*, 12q24) was identified in 1999 and the disease is a clinical spectrum with symptoms varying between psychomotor retardation with heterogeneous inflammatory attacks in mevalonic aciduria (OMIM 610377) and milder signs in hyper-immunoglobulin D/periodic fever syndrome, (OMIM 260920), respectively caused by either absolute (<1%) or partial (>1%) residual activity of the enzyme mevalonate kinase, the first committed enzyme of cholesterol biosynthesis [17,18]. The prognosis of mevalonic aciduria is poor and its diagnosis can be established by detecting highly elevated urinary levels of mevalonic acid [19]. Hyper-immunoglobulin D/periodic fever, particularly diffuse in the Netherlands, usually starts in early childhood and is characterized by episodic fever lasting 3–7 days with lymphadenopathy, abdominal complaints, arthralgia, aphthous ulcers, and polymorphic rash [20]. The pathophysiological implications of *MVK* mutations are presumably related to the temporary deficiency of isoprenoid end-products, which induces the inflammatory cascade and the clinical expression of the disease in irregularly recurring attacks [21]. The diagnosis of MKD is supported by a neither specific nor causative high serum IgD concentration (at levels >100 IU/ml or 14.1 mg/dl) during and between attacks in children older than 3 years of age, while during attacks it is possible to demonstrate a transient marked acute-phase response and largely excreted mevalonic acid in the urine [22]. Therapeutic benefits for MKD can be achieved with naproxen, corticosteroids, simvastatine, etanercept, and anakinra, although long-term success seems disappointing and the best treatment is still debated [23].

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS)

TRAPS (OMIM 142680) was mostly recognized in northern Europe and is caused by more than 50 different mu-

Table 2. Differential diagnosis of cryopyrin-associated periodic syndromes.

	Familial cold autoinflammatory syndrome	Muckle-Wells syndrome	CINCA syndrome (Neonatal-onset multisystem inflammatory disease)
Onset	Infancy	Infancy or adolescence	Early neonatal period
Inheritance	Dominant	Dominant	Dominant
Gene	*CIAS1*	*CIAS1*	*CIAS1*
Chromosomal locus	1q44	1q44	1q44
Usual ethnicity	Any ethnicity	Northern European	European
Protein involved	Cryopyrin	Cryopyrin	Cryopyrin
Fever duration	<24 hours	1–2 days	Continuous (with flares)
Skin involvement	Cold-induced urticarial rash	Evanescent urticarial rash	Polymorphic urticaria-like rash
Articular involvement	Arthralgias or joint stiffness	Non erosive transient polyarthritides	Deforming knee osteo-arthropathy
Neurological involvement	–	–	Chronic meningitis, hydrocephalus, pseudopapilledema, uveitis
Neurosensorial deafness	–	Present	Present
Amyloidosis	2–4%	25%	20%
Treatment	Cold avoidance, anakinra	Anakinra, rilonacept, canakinumab	Anakinra, rilonacept, canakinumab

tations in a gene designated *TNFRSF1A* (12p13.2) encoding the ectodomain of the 55-kDa tumor necrosis factor receptor superfamily 1A (TNFRSF1A, also named TNFR1, TNFR p55, or CD120a) [24]. It is widely recognized that tumor necrosis factor is a key mediator of inflammation with pleiotropic actions, including pyrexia, leukocyte activation, induction of cytokine secretion, and expression of adhesion molecules [25]. Whilst the cleavage of certain TNFR1 variants is impaired, producing a "shedding defect", other TRAPS-causing mutations produce effects through conformational changes in TNFR1, giving rise to enhanced or prolonged signaling and the upregulation of multiple pro-inflammatory genes [26]. The disease is characterized by repeated febrile attacks, variably combined with organ-localized inflammation, lasting even for some weeks [27]. During quiescent periods the plasma concentration of soluble TNFR1 may be abnormally low (<1 ng/ml) in TRAPS patients with decreased receptor shedding, but genetic testing remains crucial to the diagnosis in most cases. Despite high initial hopes for response to tumor necrosis factor antagonists such as etanercept, treatment of TRAPS still appears challenging; acute attacks usually might respond to high-dose corticosteroids, etanercept, and anakinra [28].

Cryopyrin-associated periodic syndromes (CAPS)

Cryopyrinopathies can be now defined as cryopyrin-associated periodic syndromes (CAPS) and three similar conditions are distinguished which lie along a phenotypical continuum with increasing levels of severity, but all dominated by a characteristic urticarial rash associated with a number of other clinical manifestations: familial cold autoinflammatory syndrome (FCAS, OMIM 120100), Muckle-Wells syndrome (MWS, OMIM 191900), and CINCA syndrome (OMIM 607115, also known as neonatal-onset multisystem inflammatory disease or NOMID). This last is characterized by chronic sterile meningitis, sensorineural hearing loss, peculiar knee osteopathy deriving from a deranged endochondral bone formation, and non-itching urticaria-like rash, all starting in the neonatal period [29]. A susceptibility gene for CAPS (previously designated *CIAS1*, for cold-induced autoinflammatory syndrome, and now named *NLRP3*, 1q44) was first reported in 2001 and shown to cause FCAS, MWS, and CINCA syndrome. The gene encodes cryopyrin, a leukocyte-specific member of the inflammation and apoptosis regulating system, although *NLRP3* mutations leading to tertiary structure disruption of cryopyrin and potentiating the "inflammasome" assembly are found only in 50% of patients with clinically diagnosed cryopyrinopathies [30]. All CAPS are followed by caspase-1 activation with subsequent interleukin-1 oversecretion, so that direct continuous interleukin-1 inhibition with anakinra, rilonacept, and canakinumab dramatically ameliorates every clinical manifestation, with the exception of bony overgrowth in CINCA syndrome [31,32]. Features of FCAS, MWS, and CINCA syndrome are listed in Table 2. A similar condition which requires differentiation from CAPS is Schnitzler syndrome, first reported in 1972 and characterized by chronic urticarial rash and RF which recur with a frequency ranging from once a day to twice a year, which is associated with monoclonal immunoglobulin M gammopathy and joint and bone pain. This disease has been reported only in adult patients and can be framed in the context of an acquired AIS [33].

Pyogenic Disorders

Children with recurrent purulent manifestations involving joints, eye, skin, and bones can now be studied by genetic analysis to establish a definitive diagnosis of rare

Table 3. Differential diagnosis of pyogenic disorders.

	PAPA syndrome	CRMO syndrome	Majeed syndrome
Onset	Infancy	Childhood and adolescence	First infancy
Inheritance	Dominant	Recessive	Recessive
Gene	*PSTPIP1*	–	*LPIN2*
Chromosomal locus	15q24-q25.1	18q21.3-22	18p11.31
Protein involved	Proline/serine/threonine phosphatase-interacting protein 1, PSTPIP1 (CD2 antigen-binding protein 1, CD2BP1)	–	Lipin 2 (LPIN2)
Skin involvement	Pyoderma gangrenosum, cystic acne, ulcerative dermatitis	Pustulous palmo-plantaris dermatosis, psoriasis, pyoderma gangrenosum, acne	Neutrophilic dermatosis
Articular and skeletal involvement	Sterile pyogenic arthritides	Recurrent multifocal osteomyelitis (especially in the long bones)	Recurrent multifocal osteomyelitis
Blood involvement	–	–	Congenital dyserythropoietic microcitic hypochromic anemia
Treatment	Corticosteroids, tacrolimus, infliximab, anakinra, rilonacept	Anti-inflammatory drugs (indomethacin), corticosteroids, bisphosphonates (pamidronate), interferons, infliximab	Corticosteroids, interferon-α

AIS characterized by the development of multiple sterile abscesses and RF. These include PAPA syndrome (OMIM 604416), CRMO syndrome (OMIM 259680), and Majeed syndrome (OMIM 609628). Table 3 lists their most relevant signs. In particular, PAPA syndrome is mainly characterized by a destructing pyoarthritis with pauciarticular onset and high leukocyte activity in the inflammatory exudate, pyoderma gangrenosus, sometimes induced by trauma or worsening with puberty, and cystic acne with disfiguring consequences. Different degrees of clinical expression are determined by mutations in the gene encoding the cytoskeleton-organizing protein PSTPIP1 leading to abnormal pyrin ligation and persistent caspase-1 activation. Their final result is random migration with decreased apoptosis of leukocytes [34]. There is increasing evidence that PAPA syndrome can be efficaciously controlled by interleukin-1 blockade [35].

CRMO syndrome, characterized by multiple foci of chronic osteomyelitis, classically antibiotic resistant, which appear radiologically as a mixture of osteolysis/sclerosis, is variably associated with RF. It can be included under the heading of pyogenic disorders of undetermined origin, although evidence for a genetic basis, involving chromosome 18q, has been only hypothesized [36]. As the pathogenesis of CRMO is unknown, a targeted therapy is not available, although a wide variety of agents, including non-steroidal anti-inflammatory drugs, corticosteroids, and bisphosphonates (such as pamidronate), have been attempted to temper bone inflammatory involvement. Recent experiences indicate that interferons and tumor necrosis factor blockage (with infliximab) might be effective therapeutic options, particularly in patients refractory to the cited therapies [37].

Majeed syndrome, first described in 1989, has only been reported in Jordan and is caused by mutations in *LPIN2* on chromosome 18p. This rare disease is defined by the association of recurrent multifocal osteomyelitis, congenital dyserythropoietic anemia, neutrophilic dermatosis, and RF, although the role of lipin 2 in bone and skin-localized inflammatory phenomena remains unknown. Unlike isolated CRMO, bone manifestations show an earlier age of onset, and have less frequent remissions, resulting probably life-long. The congenital anemia might range from mild to transfusion dependent. Non-steroidal anti-inflammatory drugs are moderately helpful, and short courses of oral corticosteroids might control disease relapses [38].

Immune-mediated Granulomatous Diseases

There are granulomatous diseases with an immunologic pathogenesis which can be considered as belonging to the group of systemic AIS: Blau syndrome and Crohn's disease. Table 4 lists their noteworthy features.

First described in 1985, Blau syndrome (BS, OMIM 186580) is characterized by early-onset recurrent granulomatous inflammation of skin, eyes, and joints [39]. This disease shows phenotypic overlap with early-onset sarcoidosis (OMIM 609464) [40]. In 2002 the BS genetic locus was mapped to the chromosomal region 16q12.1-13, which also contains one of several susceptibility *loci* for inflammatory bowel disease: the caspase recruitment domain-containing protein 15 (*CARD15*) gene, previously named nucleotide-binding oligomerization domain 2 (*NOD2*). This locus has been identified as the gene responsible for both BS and as a major pathogenic clue to Crohn's disease (CD, OMIM 266600),

Table 4. Differential diagnosis of immune-mediated granulomatous diseases.

	Blau syndrome	Crohn's disease
Onset	Infancy (before 4 years)	All ages
Inheritance	Dominant	Complex non-Mendelian genetic trait
Gene	*NOD2/CARD15*	*NOD2/CARD15, MDR1, PXR/NRII2, DLG5, OCT1-2, etc.*
Chromosomal locus	16q12.1-13	16q12, 7q21, 3q13, 10q22, 5q31, etc.
Protein involved	NOD2/CARD15	NOD2/CARD15, P-glycoprotein 170, nuclear hormone receptor, MAGUK, organic cation transporters 1&2, etc.
Abdominal distress	Absent	Chronic relapsing intestinal inflammation with epithelioid granulomata
Skin involvement	Erythematous papular rash, painful panniculitis	Pyoderma gangrenosum, erythema multiforme/nodosum, necrotizing vasculitis
Articular involvement	Non-erosive granulomatous synovitis with painless cysts, "boutonniere" deformities of fingers, camptodactyly	Migratory polyarthritis, sacroileitis, ankylosing spondylitis
Ocular involvement	Granulomatous uveitis, risk of post-iritic blindness	Conjunctivitis, episcleritis, iritis, keratitis, xerophthalmia
Treatment	Corticosteroids, methotrexate, infliximab	Sulfasalazine, corticosteroids, azathioprine, infliximab, oral antibiotics, dietary arrangement

the well-known multifactorial disorder resulting from transmural and discontinuous bowel inflammation with tendency to granuloma formation [41]. BS-associated *CARD15/NOD2* mutations affect the central nucleotide-binding NACHT domain (implicated in apoptosis control), resulting in increased NF-κB activation, while CD-associated mutations mostly affect the C-terminal protein domain, consisting of leucine-rich repeats and finally resulting in dysregulated NFκB signaling [42].

Idiopathic Febrile Syndromes

The disease spectrum of systemic-onset juvenile idiopathic arthritis (So-JIA), one of the six major types of chronic inflammatory arthritides in children, characterized by spiking fever accompanied or preceded by arthritis and at least one of the symptoms of erythematous rash, diffuse lymph node enlargement, serositis, and hepato-splenomegaly, has been recently included in the group of AIS [43]. So-JIA can be considered a complex genetic trait disease, which accounts for an increased morbidity and mortality compared with other forms of juvenile idiopathic arthritis. The etiology is unknown and the clinical picture is mainly determined by persistent activation of phagocytic cells and multi-cytokine overexpression [44]. Poor outcomes have been associated with persistent thrombocytosis, increased sedimentation rate, anemia, and prolonged corticosteroid use [45]. These patients often show resistance to the first-line treatment, which includes non-steroidal anti-inflammatory drugs, corticosteroids, or methotrexate, and recent advances in the study of So-JIA pathogenesis, evidencing a key-role of interleukin-1, -6, and -18, have justified a more rational, biological therapeutic approach [46].

Another febrile disease of unknown origin, widely underdiagnosed in the general practice, is periodic fever, aphthosis, pharyngitis, adenitis syndrome (or PFAPA syndrome). First reported in 1987, this disease needs to be considered in children younger than 5 years who show a regular febrile periodicity with high fevers lasting 3 to 6 days and recurring every 4 to 6 weeks, without signs of upper airway infection. These patients present at least one sign among latero-cervical adenopathy, pharynx inflammation, and aphthous stomatitis, but are completely asymptomatic between febrile attacks and grow brilliantly, even if the parents describe them as "continually ill". These children require strict differentiation from patients with other AIS, but also from those with cyclic neutropenia and recurrent respiratory infections. Although the mechanisms behind PFAPA syndrome are still unknown and there is no evidence-based treatment protocol, one single-dose administration of a corticosteroid at the onset of each attack or tonsillectomy should be taken into account, respectively, by the pediatrician and otorhinolaryngologist to modify its clinical picture and recurrence [47]. Cyclic neutropenia (OMIM 162800), a heterogeneous disorder of hematopoiesis characterized by absolute neutrophil counts below 0.5×10^9/l and caused by *ELA2* (19p13.3) mutations and transmitted with autosomal dominant inheritance, is very similar to PFAPA syndrome due to the three-week frequency of RF with almost regular 21-day intervals between febrile episodes associated with mucosal ulcers and skin lesions during neutrophil nadirs [48].

Another condition with a typical tendency for recurrence is juvenile Behçet syndrome (OMIM 109650), which might start with RF, but is mostly recognized when oral or genital ulcers, uveitis, and skin manifestations occur at unpredictable intervals under the influence of environmental and genetic factors. Diagnosis of Behçet syndrome remains basically clinical, especially in non-European populations, although considerable progress has been made in understanding its immunologic and genetic basis involving certain MHC genes, such as those encoding for HLA-B51, tumor

Table 5. Miscellaneous group of idiopathic febrile syndromes.

	Systemic-onset juvenile idiopathic arthritis	PFAPA syndrome	Behçet syndrome
Onset	Any age	Childhood (especially children aged less than 5 years)	Any age
Genetic association	–	–	Association with HLA-B51
Fever recurrence	Fever of at least 2 weeks' duration that is documented to be daily and accompanied by one or more of the following signs: a) non-fixed evanescent erythematous rash, b) generalized lymph node enlargement, c) hepatomegaly and/or splenomegaly, d) serositis	Typical periodicity with four/six-week frequency	Unpredictable
Musculo-skeletal involvement	Arthritis in one or more joints (compulsory sign)	–	Arthralgias, arthritides
Skin involvement	Evanescent erythematous rash appearing mostly during fever spikes	–	Nodous erythema, acne, folliculitis, positive pathergy test
Oral involvement	–	Pharyngitis, aphthous stomatitis	Recurrent oral ulcers
Systemic signs	Generalized lymph node enlargement, hepatomegaly, splenomegaly	Cervical lymph node enlargement	Thrombophlebitis
Neurological involvement	Risk of macrophage activation syndrome	–	Central nervous system vasculitis
Ocular involvement	–	–	Uveitis, retinal vasculitis, optic neuritis
Genital involvement	–	–	Recurrent genital ulcers, epididymitis
Laboratory involvement	Increased acute phase reactants, leukocytosis, anemia	Increased acute phase reactants, leukocytosis	Non-specific abnormalities
Treatment	Anti-inflammatory drugs, corticosteroids, methotrexate, anakinra, canakinumab	Single-dose of corticosteroid (at the onset of fever), tonsillectomy	Interferon-α, cyclosporin, infliximab

necrosis factor-alpha, interleukin-10 and -8, and endothelial nitric oxide synthase [49]. All these idiopathic febrile syndromes are depicted in the miscellaneous group of Table 5.

How to Discern a Possible Autoinflammatory Syndrome in a Child with Recurrent Fever

A child with RF presents an intriguing clinical challenge, but the etiology of RF often remains undefined despite exhaustive evaluation. All these children need to be attentively investigated with regard to past medical history and evaluated with a thorough objective examination, especially when accompanied by painful symptoms localized to skin, joints, the gastrointestinal tube, or serous membranes. A timely diagnosis of AIS concealed under the simple appearance of RF is a difficult process, although the first step is to review carefully all details of fever episodes, since examination between attacks is largely unrevealing, and to tailor the potentially enormous laboratory evaluation to a few tests focusing on specific, likely diagnoses. An apparently healthy child with RF needs only a complete blood cell count with inflammatory parameters and urine or blood cultures; additional serological tests might result useful in considering potential exposure, history, and examination. Children who have elevated inflammatory markers should have these studies repeated in an afebrile period because these generally remain elevated in diseases that require specific interventions (as occult bacterial infection, Crohn's disease, or So-JIA), whereas they decrease in conditions that either do not require intervention (such as milder cases of PFAPA syndrome) or require preventive measures (such as colchicine for FMF).

Our knowledge of AIS is expanding as more details become available in the medical literature, although the large number of reports does not reflect a patient's endless variability observed at the bedside. It is clear that not all children with RF can be considered in the context of AIS, even if their overall prevalence is higher than appreciated until now, since they are probably more mis- or under-diagnosed than truly rare [50]. The clinical significance of low-penetrance mutations/polymorphisms in inherited AIS genes remains unclear, but clinical vigilance in combination with a diagnostic strategy including close interaction between clinicians and geneticists remain fundamental steps to the definite identification of patients with AIS.

CONCLUSIONS

Life expectancy among most patients with AIS is near normal, with amyloidosis being the most dreadful complication, but it is expected to be excellent for those AIS for which there are now effective therapies available. The expansion of the clinical phenotypes of AIS and their recognition in patients of non-classical ethnic background suggest that more liberal genetic testing might be useful to formulate a definite diagnosis at least in some, although this process is still, unfortunately, complex. In addition, a genetic cause cannot be found in over 50% of probands with specific AIS, and still unknown genes, allelic and *loci* heterogeneity, or modulator effects by different *loci* are suspected to explain the absence of mutations in those children with very suggestive clinical pictures. The value of screening patients for fevers occurring in a periodic fashion is still under debate when there is a strong suspicion of an underlying genetic disorder, although standardized diagnostic protocols are yet not available. The host of unanswered questions that remain are about enhancing the quality of molecular tests, studying genome-wide associations and gene-environment interactions, and elucidating the intimate mechanisms which give rise to the inflammation cascade in order to find a resolutive cure based on the results of the biological information achieved. The multitude of studies currently in progress in both hereditary and acquired AIS are expected to shed further light and hopes during the next few years on aspects of the innate immune system and its mysteries.

"The pure and simple truth is seldom pure and never simple" – Oscar Wilde

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