0021-7557/10/86-05/353
Jornal de Pediatria

Pediatric hereditary autoinflammatory syndromes

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Abstract

Objective: To describe the most prevalent pediatric hereditary autoinflammatory syndromes.

Sources: A review of the literature including relevant references from the PubMed and SciELO was carried out using the keywords autoinflammatory syndromes and child.

Summary of the findings: The hereditary autoinflammatory syndromes are caused by monogenic defects of innate immunity and are classified as primary immunodeficiencies. These syndromes are characterized by recurrent or persistent systemic inflammatory symptoms and must be distinguished from infectious diseases, autoimmune diseases, and other primary immunodeficiencies. This review describes the epidemiological, clinical and laboratory features, prognosis, and treatment of the main autoinflammatory syndromes, namely: familial Mediterranean fever; TNF receptor associated periodic syndrome; the cryopyrinopathies; mevalonate kinase deficiency; pediatric granulomatous arthritis; pyogenic arthritis, pyoderma gangrenosum and acne syndrome; Majeed syndrome; and deficiency of interleukin 1 receptor antagonist. The cryopyrinopathies discussed include neonatal-onset multisystem inflammatory disease (also known as chronic infantile neurologic, cutaneous and articular syndrome) Muckle-Wells syndrome, and familial cold autoinflammatory syndrome.

Conclusions: Pediatricians must recognize the clinical features of the most prevalent autoinflammatory syndromes. Early referral to a pediatric rheumatologist may allow early diagnosis and institution of treatment, with improvement in the quality of life of these patients.

J Pediatr (Rio J). 2010;86(5):353-366: Autoinflammatory syndromes, child, familial Mediterranean fever, cryopyrinopathies, TRAPS, NOMID.

Introduction

Over the past 12 years, the clinical and pathophysiological features of the pediatric autoinflammatory syndromes (AIS) have been the subject of intense research and broad recognition.[1,2] The milestone event that marked the beginning of this new era of discovery on the pathophysiology of autoinflammatory diseases was the 1997 description of the underlying genetic cause of familial Mediterranean fever (FFM), the most prevalent AIS.[3,4]

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No conflicts of interest declared concerning the publication of this article.

Suggested citation: Jesus AA, Oliveira JB, Hilário MO, Terreri MT, Fujihira E, Watase M, et al. Pediatric hereditary autoinflammatory syndromes. J Pediatr (Rio J). 2010;86(5):353-366.

Manuscript submitted Apr 06 2010, accepted for publication Apr 23 2010.

doi:10.2223/JPED.2015

The autoinflammatory syndromes are caused by monogenic defects of innate immunity and are classified as primary immunodeficiencies.[5] The clinical picture of these syndromes is characterized by recurrent or persistent inflammatory symptoms affecting various organs and body systems, and the AIS must be distinguished from infectious diseases, autoimmune conditions, and other primary immunodeficiencies.[6] Unlike in pediatric autoimmune conditions such as juvenile idiopathic arthritis (JIA), juvenile systemic lupus erythematosus, or juvenile dermatomyositis, self-reactive T cells or high circulating autoantibody titers are not found in the AIS spectrum. Hence, the conditions in this group were termed "autoinflammatory."[7,8]

In the vast majority of cases, the symptoms of autoinflammatory syndromes arise in childhood.[8] Recurrent fever is the most prevalent manifestation, and is accompanied by other signs and symptoms of inflammation, particularly affecting the skin, eyes, bones, joints, gastrointestinal tract, CNS, and serous membranes.[6-9] Fever may recur in precise or irregular intervals, or, in rare cases, may even be continuous.[10]

Due to the importance of fever in diagnosing AIS, they are also known as periodic fever syndromes.[6] The presence of fever is not, however, indispensable for establishing a diagnosis; in some syndromes, such as the pyogenic AIS, fever is actually rare or altogether absent.[7]

This review seeks to describe the main autoinflammatory syndromes and their epidemiologic features, clinical manifestations, associated laboratory changes, prognosis, and management.

Sources

A literature search was performed in the PubMed and SciELO databases using the keywords "autoinflammatory syndromes" and "child." Relevant references were used to construct a review of the literature.

Summary of findings

The present article addresses the following syndromes: FMF; TNF receptor associated periodic syndrome (TRAPS); the cryopyrinopathies; mevalonate kinase deficiency (MKD); pediatric granulomatous arthritis (PGA); pyogenic arthritis, pyoderma gangrenosum and acne (PAPA); Majeed syndrome; and deficiency of interleukin 1 receptor antagonist (DIRA).

The clinical spectrum of cryopyrinopathy includes neonatal-onset multisystem inflammatory disease (NOMID, also known as chronic infantile neurologic, cutaneous and articular syndrome or CINCA syndrome), Muckle-Wells syndrome (MWS), and familial cold autoinflammatory syndrome (FCAS).

Table 1 lists the main features useful in distinguishing the various monogenic autoinflammatory syndromes.

Familial Mediterranean fever (FMF)

FMF is the most prevalent autoinflammatory syndrome, affecting more than 100,000 individuals worldwide.[11,12] The first case description of FMF was published in 1908 by Janeway & Mosenthal,[13] and the first case series was reported by Siegal in 1945.[14] FMF chiefly affects people of eastern Mediterranean descent (Sephardi Jewish, Armenian, Turkish, and Arab populations); the prevalence of FMF in this region ranges from 1 in 200 to 1 in 1,000. Both genders are affected equally, although some studies have suggested slight male predominance.[15-17]

The gene associated with FMF, the Mediterranean fever gene (MEFV), was isolated in 1997, and is located on the short arm of chromosome 16 (locus 16p13).[3,4] FMF [Online Mendelian Inheritance in Man (OMIM) accession no. 249100] follows an autosomal recessive pattern of inheritance; thus far, at least 188 pathogenic mutations have been described, most of which are found within exons 2 and 10 of MEFV.[18] MEFV codes for a 781-amino acid-long protein known as pyrin or marenostrin.[3,4] The five most common mutations in individuals affected by FMF are M694V, M680I, M694I, E148Q, and E726A.[3,15,19]

The pathophysiology of FMF has yet to be fully elucidated, but several studies have suggested that pyrin plays a role in modulating production of interleukin 1-beta (IL-1β), a major proinflammatory cytokine.[16,20,21] Pyrin, alongside cryopyrin, ASC, and caspase-1, is one of the constituents of a protein complex known as the inflammasome.[22] The inflammasome regulates the rate of production of active IL1-β from its inactive precursor, pro-IL-1β.[23,24] Pyrin mutations are believed to lead to increased inflammasome activation with excess IL-1β release, which would consequently produce the systemic inflammatory symptoms of FMF.[23]

The clinical manifestations of FMF arise before the age of 30 in the overwhelming majority of patients.[16] The disease is characterized by recurrent fever associated with abdominal or chest pain (due to serositis) and arthritis of the large joints.[7] Episodes last 1 to 4 days and occur with varying regularity, usually from one per week to one every 4 months; in rare cases, attacks occur no more than once a year.[11] Patients present with sudden onset of high fever (38.5-40 °C), which resolves spontaneously within 6 to 96 hours, accompanied by malaise and incapacitating pain. The intercritical periods are asymptomatic.[7,8,23]

Other than fever, abdominal pain is the most frequent manifestation of FMF (95%)[8]. Pain is due to generalized acute peritonitis, is moderate to severe in intensity and characterized by sudden onset.[25] It is most severe in the first 6 to 20 hours of each attack, and subsides within 24 to 48 hours.[25] Abdominal examination reveals guarding,

rebound tenderness, and abdominal distension, and may mimic surgical acute abdomen[8,16,25]. Around 30 to 40% of FMF patients are estimated to undergo unnecessary appendectomy or cholecystectomy.[16] Other gastrointestinal symptoms include constipation and, less commonly, diarrhea.[17,25]

Acute arthritis may occur in 54 to 75% of patients.[26] Attacks last approximately 1 week, and are often monoarticular, affecting the large joints of the lower limbs.[16] Joint involvement may occur spontaneously or be preceded by trauma or prolonged exertion.[16,26] Roughly 5% of patients may have chronic arthritis of the hip, knee,

Table 1 - Main features of the hereditary autoinflammatory syndromes

Condition	Gene	Inheritance	Protein	Duration of fever	Most specific clinical manifestations	Amyloidosis rate	Treatment
FMF	MEFV	AR	Pyrin	1-3 days	Peritonitis, pleuritis, erysipelas-like rash, large-joint arthritis	13%	Colchicine
TRAPS	TNFRSF1A	AD	TNF receptor p55	7-14 days	Abdominal pain, localized myalgias and erythema, periorbital edema	14% (64% when cysteine mutations are present)	Etanercept, anakinra
FCAS	CIAS1	AD	Cryopyrin	6-24 hours	Symptoms triggered by cold	2%	Anakinra, rilonacept
MWS	CIAS1	AD	Cryopyrin	1-2 days	Sensorineural hearing loss	25-33%	Anakinra, canakinumab
NOMID	CIAS1	AD	Cryopyrin	Continuous	Developmental delay, aseptic meningitis, papilledema, epiphyseal overgrowth, distinctive facial appearance	Higher risk	Anakinra, thalidomide
MKD	MVK	AR	Mevalonate kinase	3-7 days	Abdominal pain, diarrhea, vomiting, bilateral cervical lymphadenopathy, elevated IgD and urinary mevalonate levels	Three reported cases	Simvastatin, etanercept,
AGP	NOD2	AD	NOD2	Not common	Chronic granulomatous arthritis, uveitis, rash	No reports	NSAIDs, corticosteroids, methotrexate, ciclosporin, etanercept, infliximab and adalimumab
PAPA	PSTPIP1	AD	PSTPIP1	Not common	Pyoderma gangrenosum, pyogenic aseptic arthritis, acne	No reports	NSAIDs, corticosteroids
Majeed	LPIN2	AR	LIPIN2	Not common	Neutrophilic dermatitis, chronic recurrent multifocal osteomyelitis, dyserythropoietic anemia	No reports	NSAIDs, corticosteroids, interferon alpha or gamma, bisphosphonates, anti-TNF agents
DIRA	IL1RN	AR	ILRa	Not common	Neonatal onset, pustular dermatitis, chronic recurrent multifocal osteomyelitis	No reports	Anakinra

AD = autosomal dominant; AR = autosomal recessive; DIRA = deficiency of interleukin-1 receptor antagonist; FCAS = familial cold autoinflammatory syndrome; FMF = familial Mediterranean fever; MKD = mevalonate kinase deficiency; MWS = Muckle-Wells syndrome; NOMID = neonatal-onset multisystem inflammatory disease; NSAID = non-steroidal anti-inflammatory drug; PAPA = pyogenic arthritis, pyoderma gangrenosum and acne; PGA = pediatric granulomatous arthritis; TNF = tumor necrosis factor; TRAPS = TNF receptor associated periodic syndrome.

ankle, or (rarely) temporomandibular joint, mimicking the systemic form of juvenile idiopathic arthritis.[27] Another musculoskeletal symptom is myalgia, which occurs in 10% of patients, usually affects the calves and is triggered by physical activity.[7,16,28] FMF may also present as "protracted febrile myalgia," which is characterized by severe bilateral lower extremity pain, prolonged fever, and abdominal pain. Each episode may last up to 6 weeks.[29]

Recurrent pleurisy as a cause of chest pain is reported in 39% of patients, whereas pericarditis is rare (1 to 2.4% of cases).[27,30] The most common and specific cutaneous manifestation of FMF is erysipelas-like erythema, which occurs in 7 to 40% of cases[16,19] and is characterized by erythematous, vesicular, and bullous lesions mostly affecting the lower extremities.[16] These lesions may persist for 24 to 48 hours, and the attending signs of inflammation are often misdiagnosed as cellulitis, prompting antibiotic therapy.[16,19]

The diagnosis of FMF is based on clinical criteria, family history, exclusion of other periodic fever syndromes, and a clinical response to colchicine. In 1997, Livneh et al. proposed a set of diagnostic criteria for FMF.[31] These criteria have been validated for pediatric use, with 98.8% sensitivity and 54.6% specificity for diagnosing FMF in children and adolescents. The same group of researchers has since proposed a new set of highly sensitive (86.5%) and specific (93.6%) diagnostic criteria.[32]

Laboratory testing may reveal leukocytosis and elevated acute phase reactants, such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum amyloid A (SAA); the latter is considered the best laboratory marker of subclinical inflammation.[8,16,33] Definitive diagnosis requires a finding of MEFV mutations.[6,7]

The main complication of FMF is secondary AA-type amyloidosis, which occurs in up to 13% of patients. The kidneys are most affected, usually by worsening proteinuria that progresses to nephrotic syndrome and, occasionally, chronic renal failure.[8,17,34] FMF patients should be systematically tested for proteinuria every 3 to 6 months.

Colchicine is still the most effective treatment; it can induce complete remission or reduction in frequency, duration, and severity of attacks in most FMF patients.[35] Colchicine is also useful in preventing, slowing the progression of or even reverting renal amyloidosis.[17,36] The recommended dose is 0.03 mg/kg/day, which can be carefully increased up to 3.0 mg/day in the 5 to 10% of patients that are unresponsive to this initial dosage.[16] Colchicine therapy is relatively safe, even during pregnancy. The most common adverse effects are diarrhea and abdominal pain; rarely, rash, hair loss, leukopenia, thrombocytopenia, neuropathy, myopathy, liver injury, and impaired spermatogenesis may occur.[35-37] In patients unresponsive to or unable to tolerate colchicine, treatment with interferon gamma[38] and combination therapy with thalidomide[39] have been reported. More recently, immunobiologics such as the IL-1 receptor antagonist anakinra and the anti-TNF agents etanercept and infliximab have also been used in refractory cases, with encouraging results.[15,40]

TNF receptor associated periodic syndrome (TRAPS)

TRAPS (OMIM accession no. 142680) is the second most prevalent of the autoinflammatory syndromes, and its underlying genetic defect was described in 1999.[41] It is caused by mutations in the TNFRSF1A gene and inherited in an autosomal dominant pattern.[41] This gene, which codes for the p55 TNF receptor (TNFR1), has 10 exons and is located on the short arm of chromosome 12.[41] Thus far, 93 TRAPS-related mutations have been described, mostly in exons 2, 3, 4, and 6, and also in intron 4.[18] Mutations involving the cysteine residues of the extracellular portion of the receptor are associated with increased severity and amyloidosis risk.[21,41]

The TNFR1 receptor is an important mediator of TNF-alpha signaling; this cytokine plays an essential role in the inflammatory response. The pathophysiology of TRAPS is believed to involve multiple factors.[42] Some affected individuals have decreased shedding of the mutant receptor from the cell surface. Receptor shedding is believed to be necessary for blocking TNF-alpha activity and preventing exacerbated inflammatory response.[42,43] Additional studies have suggested that the mutated receptor has defective intracellular trafficking; it is retained in the endoplasmic reticulum. This intracellular buildup of the receptor could lead to spontaneous activation, triggering an inflammatory response.[44,45] Another pathophysiological mechanism is a defect in neutrophil apoptosis that occurs in some patients with TRAPS and is believed to possibly perpetuate the inflammatory response.[45,46]

The clinical manifestations of TRAPS usually arise in childhood or adolescence (mean age, 10 years; range, 1 to 63 years).[6,7] Duration of fever is longer than in any other AIS: 14 days on average, ranging from 2 to 56 days. The intercritical period (months to years) and severity are highly variable.[47] Fever is most often accompanied by severe, sudden-onset abdominal pain (77%), which leads to negative laparotomy in 33% of patients.[6,21]

The second most common symptom is localized, migratory muscle pain, which occurs in 64% of patients.[48] This myalgia is characterized by pain and erythematous rash overlying the affected area, and is caused by a monocytic fasciitis which can be detected on biopsy and MRI.[48] Roughly half of all patients have erythematous macules or, more rarely, edematous, urticaria-like plaques over myalgic areas.[21,43] Less commonly, the rash is disseminated and

takes on a serpiginous or reticular appearance.[47] Ocular manifestations are frequent (49% of cases) and may include conjunctivitis and uveitis, with periorbital pain, erythema, and/or edema.[6,47] Figure 1 shows conjunctivitis and eyelid edema in a patient with TRAPS.

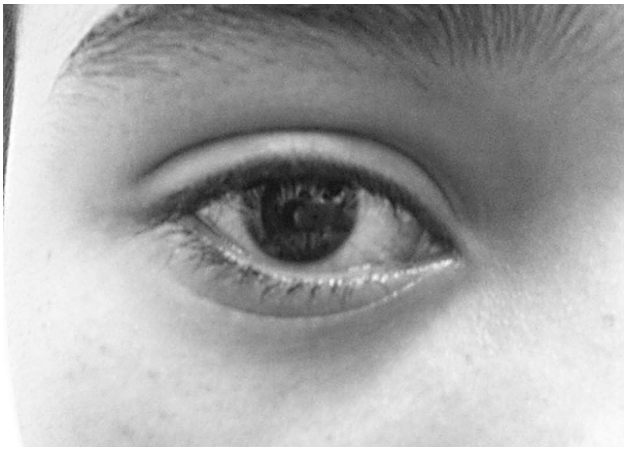

Figure 1 - Conjunctivitis and eyelid edema in a patient with TNF receptor associated periodic syndrome (TRAPS)

Other common symptoms include arthralgia or arthritis (51%), pleurisy (32%), and headache (68%).[47] Various central nervous system (CNS) manifestations have also been reported, such as meningitis, optic neuritis, and behavioral changes.[49] Sporadic reports of scrotal pain, pericarditis, pharyngitis, and cervical lymphadenopathy have been published.[8] In addition, three cases of TRAPS with no fever were recently published.[50,51]

Laboratory testing during attacks may reveal increased levels of inflammatory markers, such as ESR, CRP, and SAA, as well as moderate leukocytosis and thrombocytosis.[8] Depending on disease severity, inflammatory markers may remain elevated even in the afebrile intercritical period.[43] Normocytic/normochromic anemia is also often present.[8,43] Definitive diagnosis is established by DNA sequencing of the TNFRSF1A gene.[47,52] Mutations are found in 32 to 50% of patients with a family history of TRAPS, and in less than 10% of sporadic cases.[53]

The main complication of TRAPS is secondary amyloidosis progressing to renal failure.[54] Patients with cysteine residue mutations have a 64% chance of developing amyloidosis, compared with 14% of affected patients as a whole.[43] This greater risk may be associated with increased disease severity in this subgroup of TRAPS patients.

The TNF inhibitor etanercept (Enbrel®; recombinant soluble TNF receptor fusion protein, p75-TNFR-Fc), is the treatment of choice for TRAPS.[43] Etanercept significantly reduces the number and severity of episodes, although its efficacy may decrease with prolonged use.[55] Successful use of IL-1 receptor antagonist (anakinra) in etanercept-refractory cases has been reported.[56-58] The use of infliximab, another anti-TNF biologic, should not be encouraged, as induction of proinflammatory activity has been reported in some patients with TRAPS.[59] The management of TRAPS may also include corticosteroid therapy during flares, but chronic corticosteroid therapy does not prevent or blunt the severity of later attacks.[6,7] Unlike in FMF, colchicine is of limited efficacy in TRAPS; less than 22% of patients are responsive.[2,43] Non-steroidal anti-inflammatory drugs (NSAIDs) usually offer no relief beyond suppression of fever.[6,7]

Cryopyrin-associated periodic syndrome (CAPS) or cryopyrinopathies

The cryopyrin-associated periodic syndrome spectrum, which encompass FCAS, MWS, and NOMID (CINCA syndrome), is caused by mutations in the cold induced autoinflammatory syndrome 1 (CIAS1) gene, first identified in 2001.[60] CIAS1 codes for the protein cryopyrin, also known as NALP3 or PYPAF1.[61] The cryopyrinopathies are transmitted in an autosomal dominant pattern, and, thus far, 118 CAPS-associated mutations have been described.[18] The CIAS1 gene is located on chromosome 1q44 and has 9 exons.[60] Roughly 85% of CIAS1 mutations occur in exon 3.[62,63] Cryopyrin is one of the constituents of the inflammasome, which plays a key role in the regulation of intracellular defense in response to bacterial toxins and compounds released during cell injury or stress.[22,64,65] This protein is essential for activation of caspase-1, the enzyme that cleaves pro-IL1-β into its active form, IL1-beta, which in turn is a major proinflammatory cytokine.[66] In healthy individuals, activation of the inflammasome is inhibited by an interaction between distinct portions of the cryopyrin molecule itself.[42] CIAS1 mutations lead to a disruption of this inactive conformation of cryopyrin, leading to activation of the inflammasome, increasing IL1-beta secretion and triggering systemic inflammatory symptoms.[66-68]

Clinical manifestations vary among the three cryopyrinopathies, but several common features are often found, such as fever, pseudourticarial rash, joint involvement, and profoundly elevated inflammatory markers.[7,61] The most consistent finding across the CAPS spectrum is a migratory, maculopapular, urticaria-like, and usually nonpruritic rash.[61,69] Skin biopsy reveals polymorphonuclear perivascular infiltration of the dermis, which contrasts with the biopsy findings of classical urticaria.[61,70] The unique features of each of the cryopyrinopathies are described below.

Familial cold autoinflammatory syndrome (FCAS)

FCAS (OMIM accession no. 120100), also known as familial cold urticaria, is at the benign end of the CAPS spectrum, and has the most favorable prognosis of all the cryopyrinopathies.[6,61,71] FCAS is characterized by episodes of low-grade fever (93%), polyarthralgia (96%), and nonpruritic pseudourticarial rash (100%) appearing 1-2 hours after cold exposure (range: 30 min to 6 h) and persisting for approximately 12 hours.[7,71,72] Other commonly reported symptoms include conjunctivitis (84%), profuse sweating (78%), dizziness (67%), headache (58%), nausea (51%), and extreme thirst (53%).[72] Symptoms are most intense in young adults, but may begin as early as childhood.[73] Less commonly, the syndrome may present as recurrent fever, mild arthralgia, inflammatory cardiomyopathy, nephropathy, and thyroiditis, with no skin involvement.[8,74] Secondary amyloidosis is the main cause of death, occurring in up to 2% of cases.[28,75] Treatment includes prevention of cold exposure and, in more severe cases, anakinra.[7,57] A recent study of rilonacept, a long-acting soluble receptor that binds IL-1, found good efficacy and safety in 44 patients with FCAS.[76] NSAIDs and corticosteroids are variably effective, and antihistamines are not effective at all.[70,77]

Muckle-Wells syndrome (MWS)

In 1962, Muckle & Wells described a familial syndrome of urticaria, deafness, and amyloidosis affecting nine individuals.[78] The symptoms of MWS (OMIM accession no. 191100) arise in childhood, as an urticaria-like rash with low-grade fever and arthralgia.[8] Recurring episodes of arthritis and conjunctivitis may also occur.[79] The most characteristic manifestation of MWS is sensorineural hearing loss, which is due to chronic inflammation of the organ of Corti with cochlear nerve atrophy.[79] Less common findings include oral and genital ulcers, cystinuria, ichthyosis, recurrent abdominal pain, and microscopic hematuria.[8,79] Secondary amyloidosis is common, and may occur in 1/3 to 1/4 of patients.[6,75] A finding of CIAS1 mutation confirms the diagnosis.[18] Other laboratory findings include thrombocytopenia, anemia, and increased levels of acute-phase reactants.[61,80] As in the other cryopyrinopathies, IL-1 receptor inhibition with anakinra can reverse the clinical manifestations of MWS, including hearing loss.[57,80] A recent study of 33 MWS patients found good clinical and laboratory response to canakinumab, a human anti-IL-1beta monoclonal antibody.

Neonatal onset multisystem inflammatory disease/ chronic infantile neurologic, cutaneous, and articular syndrome (NOMID or CINCA syndrome)

NOMID, or CINCA syndrome (OMIM accession no. 607115), is the most severe phenotype of the cryopyrinopathy spectrum, and was first described by Prieur & Griscelli in 1981.[82] The disease is characterized by a triad of rash, chronic aseptic meningitis, and arthropathy.[69,82] Clinical manifestations arise in the first weeks of life; the cutaneous lesions often appear within hours of birth.[69] Inflammatory symptoms (such as fever) are practically continuous, with occasional flares, and affected children have severe growth retardation.[7,69,71]

Skin lesions are found in nearly 100% of cases.[69] CNS involvement is the second most common feature, typically presenting as chronic aseptic meningitis with leukocyte infiltration of the cerebrospinal fluid, which leads to a broad range of symptoms including chronic irritability, headaches, seizures, transient hemiplegia, and lower limb spasticity.[69,70] If left untreated, approximately 80% of patients will develop sensorineural hearing loss and ocular disease, such as conjunctivitis, anterior and posterior uveitis, papilledema, and optic nerve atrophy with loss of vision.[70,83] Other findings include developmental delay and mental retardation.[8,83] Patients with NOMID/CINCA syndrome have a typical facial appearance, characterized by frontal bossing, macrocrania, and saddle nose.[69,70] Figures 2A and 2B show the characteristic facies of NOMID in three affected patients.

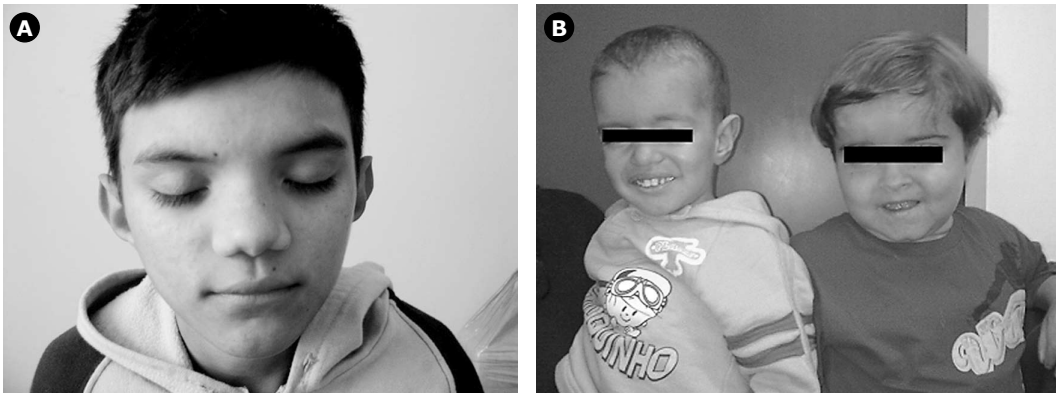

Figure 2 - A) Characteristic facies (saddle nose) and urticaria-like rash of neonatal onset multisystem inflammatory disease; B) Characteristic facies (frontal bossing) in two patients with neonatal onset multisystem inflammatory disease

The musculoskeletal changes of NOMID/CINCA syndrome can range from asymptomatic arthritis to deforming arthropathy.[8,83] Most patients show inflammatory changes of the long-bone epiphyses and metaphyses, with abnormal epiphyseal calcification and cartilage overgrowth, leading to shortened limbs and joint deformities. Premature ossification of the patella, with symmetrical patellar overgrowth, is a characteristic finding.[69,71,84] The typical arthropathy of NOMID is found in 50% of patients.[69]

Nonspecific laboratory changes are as in other autoinflammatory syndromes, and may include anemia, thrombocytosis, moderately increased white blood cell counts, and increased inflammatory markers, such as ESR and CRP levels.[8,69] The diagnosis of NOMID/CINCA syndrome relies on adequate clinical suspicion and confirmatory genetic testing.[18] However, only 50% of patients with a characteristic presentation of NOMID/CINCA syndrome have CIAS1 mutations, which suggests that other yet-unknown genes may also be involved in its pathophysiology.[69]

Without early identification and treatment, the prognosis for patients with NOMID/CINCA syndrome is guarded. In addition to deforming articular involvement and neurologic sequelae, the disease carries a high risk of secondary amyloidosis in the few patients who live to adulthood.[7,85]

Anakinra, an IL-1 receptor antagonist, is currently the drug of choice for treatment of NOMID and has been widely used in this indication, providing significant improvement in all clinical manifestations of the disease and, consequently, patient quality of life.[57,69] Anakinra is currently unavailable in Brazil, and other anti-IL1 agents have yet to reach the Brazilian market. Corticosteroids and NSAIDs can provide symptomatic relief, but have no effect on articular or neurologic involvement.[8,69] Thalidomide has also been used in rare cases, with satisfactory results.[86]

Mevalonate kinase deficiency (MKD) or hyper-IgD and periodic fever syndrome (HIDS)

HIDS (OMIM accession no. 260920) follows an autosomal recessive pattern of inheritance, and is most often diagnosed in Northeastern Europe.[87] The disease is caused by mutations in the MVK (mevalonate kinase) gene, which was discovered in 1999.[87] Thus far, 108 HIDS-associated mutations have been discovered throughout the gene.[18] MVK, which has 11 exons and is located on the long arm of chromosome 12 (locus 12q24), codes for mevalonate kinase (MK), a 396-amino acid-long enzyme.[87] Most patients have a combination of two mutations, one of which is very often V377I.[87] HIDS-associated mutations lead to a major reduction in MK activity (1 to 10% of normal levels), whereas mutations that completely eliminate MK function lead to a condition known as mevalonic aciduria (MA).[88,89] MA is a rare disease characterized by periodic fever with severe CNS involvement, mental retardation, ataxia, myopathy, poor growth, and early death.[42,89]

MK plays an essential role in the isoprenoid and cholesterol synthesis pathways.[89] It catalyzes the conversion of mevalonic acid to mevalonate 5-phosphate during the synthesis of molecules such as cholesterol, vitamin D, biliary salts, corticosteroids, and non-steroidal isoprenoid compounds.[42,89] During cholesterol biosynthesis, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase (the enzyme inhibited by statins) converts HMG-CoA to mevalonate, which is then phosphorylated to mevalonate phosphate.[90] Mutations in the MVK gene block this pathway, preventing the conversion of mevalonate to mevalonate phosphate.[91] The absence of a negative feedback loop, which is naturally provided by the presence of the end products of synthesis, leads to increased HMG-CoA reductase activity, consequently increasing serum, tissue, and urine levels of mevalonic acid. [92] *In vitro* studies have shown that reduced synthesis of isoprenoids is associated with increased production of IL1-beta.[93] Another recent *in vitro* study showed that MK inhibition leads to increased secretion of IL1-beta due to activation of caspase-1, the enzyme that catalyzes formation of active IL1-beta from its precursor.[94] High levels of immunoglobulin D (IgD)[31] are characteristic of HIDS, but are apparently not associated with the severity of pathophysiology of the condition. [95]

In MKD, febrile attacks occur more frequently in the first year of life, lasting 3 to 7 days and recurring every 4 to 6 weeks.[8] However, the time elapsed between episodes can vary from patient to patient and even in a single individual.[96] Febrile episodes recur for years, most frequently in childhood and adolescence, but months to years can go by between flares.[96,97]. Episodes may be triggered by immunization, trauma, surgery, or stress, and, in 76% of patients, are characterized by high fever preceded by chills.[7,8] Lymphadenopathy is extremely common (94%); it is usually cervical, bilateral, and painful.[33,96] Abdominal pain is also a frequent symptom (72%), and may be accompanied by vomiting (56%) and/or diarrhea (82%).[96,98] Patients will also frequently report headache (52%), and splenomegaly and hepatomegaly are common (the latter less so).[96] Roughly 80% of patients report polyarthralgia, and 68% have non-erosive arthritis of the large joints, particularly of the knees and ankles.[8,96] Arthritis is usually polyarticular and symmetric.[8,96] Over 82% of patients have diffuse cutaneous lesions, which may consist of erythematous maculopapular rash, urticaria-like rash, erythematous nodules, petechiae, or purpura.[88,99] Rarely, patients may present with serositis or muscle pain, and a minority of patients has oral or vaginal ulcers.[8] Progression to amyloidosis is exceedingly rare, and has only been described in four patients thus far.[100-102] The first case of macrophage activation syndrome in a patient with MKD was also reported recently.[103]

Febrile episodes may be accompanied by sudden increase in acute phase reactant levels, including neutrophilic leukocytosis and elevated ESR, CRP, and SAA.[6] Measurement

of urinary mevalonate levels during attacks may be useful, particularly in patients with normal IgD levels.[90]

IgD levels are persistently high (≥100 U/mL) in most patients, and over 80% of patients have concomitant increase in immunoglobulin A levels (≥260 mg/dL).[90,104] Nonetheless, IgD levels may be within normal limits in some HIDS patients, especially children under the age of 3.[8,95] Furthermore, the finding of high IgD levels is not specific for HIDS, as it occurs in other inflammatory diseases, such as FMF and TRAPS.[95] In these conditions, however, IgD levels never exceed 100 U/mL, unlike in HIDS.[6,95] The utility of high IgD levels in the diagnosis of MKD was established in a study of 50 patients with the MKD phenotype.[95] The sensitivity and specificity of serum IgD measurement for the diagnosis of MKD were found to be 79 and 27% respectively, and the positive and negative predictive values were 50 and 58% respectively. In addition, five patients with MVK mutations were found to have normal immunoglobulin levels.[95]

The diagnosis of MKD is confirmed by a finding of MVK mutations.[18] However, the presence of a clinical phenotype consistent with the disease in conjunction with high serum IgD and urinary mevalonate levels may suggest the diagnosis.[6,95] To support diagnostic efforts, a clinical criterion has been developed for MKD screening in patients with recurrent fever.[105] The authors proposed that genetic screening for MKD in patients with recurrent fever be performed only in those patients younger than 5 years at disease onset or those with joint pain and periodic fever attacks lasting fewer than 14 days. Use of these criteria would avoid unnecessary molecular testing.[105]

Most of the usual treatments, such as NSAIDs, corticosteroids, IVIG, colchicine, and thalidomide, are ineffective in HIDS.[28] The involvement of MK in the cholesterol synthesis pathway has encouraged the introduction of statins in the management of MKD; the efficacy of simvastatin, an HMG-CoA reductase inhibitor, has been demonstrated in 5/6 of MKD patients.[106] Use of etanercept and anakinra in refractory cases has also been reported.[107-113]

Pediatric granulomatous arthritis (PGA)

The term PGA (OMIM accession no. 186580) is applied to two distinct conditions with a similar clinical phenotype: Blau syndrome, a familial disorder, and early onset sarcoidosis, a sporadic condition.[114] PGA follows an autosomal dominant pattern of inheritance and is caused by mutations in the NOD2 gene, also known as CARD15, located on chromosome 16.[18] This gene codes for the NOD2 protein, a member of the NOD-LRR family of pattern recognition receptors that bears a strong structural similarity to cryopyrin.[42,115]

NOD2 mutations are found in 50 to 90% of patients with the classic triad of arthritis, dermatitis, and uveitis.[116] Thus far, 15 PGA-related mutations have been described, most mapped to the NOD domain.[18] Interestingly, mutations in the leucine-rich repeats (LRR) domain of NOD2 are associated with Crohn's disease.[18,117] NOD2 is considered a sort of cytoplasmic sensor for detection of pathogen components, playing a role similar to that of toll-like receptors; NOD2 stimulation may lead to activation of the NF-κB and mitogen-activated protein kinase (MAPK) pathways, triggering production of cytokines involved in innate immune response, such as IL-1β and the defensins.[42]

PGA is characterized by chronic granulomatous inflammation of the eyes, joints and skin; onset usually precedes the fourth year of life.[118] Arthritis is universal; it is polyarticular in 96% of patients and oligoarticular in the remaining 4%.[116] Around 40% of patients have hypertrophic tenosynovitis, and articular involvement is symmetric in most cases.[116] Ocular involvement is found in 84% of patients, and follows a chronic, persistent course in the vast majority of cases.[116] Approximately 25% of affected individuals have anterior or intermediate uveitis, and 50% have panuveitis; uveitis is bilateral in most patients.[116,117] Fifty percent of patients develop cataracts, whereas 30% develop glaucoma and 40% go on to have severe visual impairment.[116] The typical rash of PGA is described as brown in color and ichthyosis-like, and is found in 88% of patients.[116,117] Less common findings include fever, camptodactyly, and cranial neuropathy.[114] Figure 3 shows a patient with PGA and ichthyosiform rash.

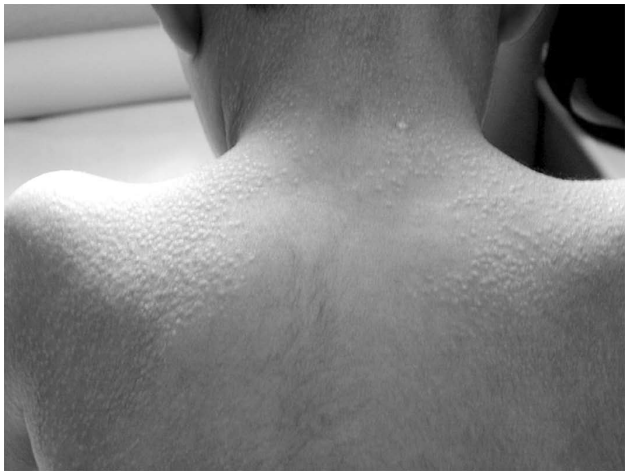

Figure 3 - Ichthyosiform rash in a patient with early onset sarcoidosis

Laboratory testing may reveal persistent leukocytosis, thrombocytosis, and increased ESR and CRP levels.[116] Non-caseous granulomas may be found in the synovial tissue, skin, and liver.[116,117] Definitive diagnosis can only be established by a finding of NOD2 mutation.[18]

Treatment is NSAID-based in patients with mild disease, whereas more severe manifestations require systemic corticosteroid therapy.[7,119] Other agents used in the treatment of PGA include methotrexate and ciclosporin, and the use of biologicals (etanercept, infliximab, and anakinra) has been reported, particularly in patients with refractory ocular involvement.[7,117,119]

Pyogenic aseptic arthritis, pyoderma gangrenosum, and acne syndrome (PAPA syndrome)

PAPA syndrome (OMIM accession no. 604416) is an autosomal dominant disease characterized by sterile, deforming arthritis, skin ulcers (pyoderma gangrenosum), and severe cystic acne.[42,120] Unlike other autoinflammatory syndromes, PAPA does not have fever as its most prominent symptom.[42]

PAPA syndrome is caused by mutations in the gene that codes proline-serine-threonine phosphatase interacting protein 1 (PSTPIP1), and only five associated mutations have been reported thus far.[18] PSTPIP1 is a 416-amino acid-long protein expressed mostly in neutrophils.[42] Mutations in PSTPIP1 are believed to lead to hyperphosphorylation of the protein, which could increase the potency of its binding to pyrin, with subsequent activation of IL-1β production, as seen in FMF.[121]

Majeed syndrome

Majeed syndrome (OMIM accession no. 146462), like PAPA syndrome, is considered a Pyogenic AIS, but is inherited in an autosomal recessive pattern.[122] It is caused by mutations in the LPIN2 gene, which codes for an eponymous protein.[123] Thus far, only nine associated mutations have been described.[18]

Patients with Majeed syndrome present with early (mostly neonatal) onset of chronic recurrent multifocal osteomyelitis, neutrophilic dermatitis, and congenital dyserythropoietic anemia.[124] Cutaneous involvement is characterized by pustular dermatitis, although psoriasis-like lesions have been described.[7,124] The osteomyelitis of Majeed syndrome may affect the clavicles, sternum, long bones, and, less commonly, the jaw or vertebrae.[122,125] Bone biopsy reveals nonspecific granulocytic infiltration.[123,125]

Antibiotics are of no use in the treatment of Majeed syndrome.[7,125] Some patients may benefit from therapy with NSAIDs, corticosteroids, interferon gamma, bisphosphonates, and anti-TNF agents.[7]

Deficiency of interleukin-1–receptor antagonist (DIRA)

A new autosomal recessive AIS, caused by mutations in the IL1RN gene, which codes for interleukin-1 receptor antagonist (IL1Ra), was reported recently.[126] The syndrome, which was described in 10 patients, was given the name "deficiency of interleukin-1 receptor antagonist" (DIRA) and is characterized by early onset of symptoms, most frequently in the neonatal period.[126,127]

Patients with DIRA present with pustulosis, multifocal aseptic osteomyelitis, and markedly elevated ESR and CRP levels.[126,127] Skin involvement may range from sparse pustules to generalized pustular dermatitis or ichthyosiform lesions.[126] Skin biopsy may reveal neutrophilic infiltration of the epidermis and dermis, pustules in the stratum corneum, acanthosis, and hyperkeratosis.[126] All patients described in the report had osteomyelitis, characterized by pain with movement and periarticular swelling; the most frequent radiological findings were widening of the costal arches, periosteal elevation along long bones, and multifocal osteolytic lesions.[126,127]

As in the other Pyogenic autoinflammatory syndromes (PAPA and Majeed syndrome), fever is not a striking feature of DIRA, and was not present in any of the patients described.[126,127] Two of the 10 patients had interstitial lung disease, and three died before therapy could be attempted (at 2 months, 21 months, and 9 years of age respectively).[126,127]

The treatment of choice is recombinant IL-1RA (anakinra), which produces a dramatic response in skin and bone symptoms and in the quality of life of patients with DIRA.[126]

Final considerations

The past decade has witnessed major advances in our understanding of the pathophysiology and clinical features of autoinflammatory syndromes.[1] The periodic fever induced by these disorders must be distinguished from the fever caused by self-limited infections in healthy children, that caused by recurring infections in immunocompromised patients, and the fever of autoimmune disease.[9,10]

The recurring fever of AIS is not accompanied by respiratory symptoms and is unresponsive to antibiotics, which are often prescribed.[10] Furthermore, most children with autoinflammatory syndromes have good growth, unlike most of those with primary of secondary immunodeficiencies.[10] In addition, no specific antibodies associated with autoimmune disease are detectable, as self-reactive T cells and circulating autoantibodies are not involved in the pathophysiology of AIS.[6,10] The signs and symptoms presented in Tables 2 and 3 may be useful diagnostic red flags for suggesting or excluding the diagnosis of AIS.

Pediatricians must recognize the main clinical manifestations of the most prevalent autoinflammatory syndromes, as rheumatology referral can be the key to early diagnosis and treatment. Follow-up of patients with these syndromes must include assessment and prevention of the risk of amyloidosis (the foremost complication of the

Table 2 - Signs and symptoms suggestive of autoinflammatory syndrome

- Recurrent fever presenting at regular or irregular intervals, or of more than 6 months' duration
- Abrupt onset and resolution of attacks
- Absence of respiratory symptoms
- A similar course in all episodes or flares
- Asymptomatic intercritical period (in most syndromes)
- Normal health-related quality of life and growth (in most syndromes)
- Musculoskeletal symptoms, rash, abdominal pain, chest pain, cervical lymphadenopathy, hearing loss or developmental delay, and aseptic osteomyelitis
- Anemia, leukocytosis, thrombocytosis, and increased acute phase protein levels
- Negative autoantibody titers

Table 3 - Signs and symptoms not suggestive of autoinflammatory syndrome

- Fever-associated respiratory symptoms
- Clinical response to antibiotic treatment
- Unsatisfactory health-related quality of life and failure to thrive/short stature (with certain exceptions)
- Significant hepatosplenomegaly and widespread lymphadenopathy
- Bicytopenia, pancytopenia, and normal acute phase protein levels
- Presence of autoantibodies specifically associated with autoimmune conditions

majority of AIS) and genetic counseling. Specific therapies, such as IL-1 antagonists (IL-1 being the main cytokine involved in the pathogenesis of inflammatory symptoms in most AIS patients), have yet to become available in Brazil. Increased recognition of autoinflammatory syndromes in the country may provide a useful push for making these drugs available to Brazilian patients, which would significantly improve morbidity and mortality, particularly in early-onset syndromes and those associated with major impact on quality of life.

More recently, we have established a Brazilian working group, with international involvement, for clinical and genetic diagnosis of the most important AIS in the pediatric population. Brazil is a highly multiracial country and autoinflammatory syndromes may be underdiagnosed; proper recognition of these conditions is essential for individualized treatment.[43,71,128,129]

Conclusions

The autoinflammatory syndromes are caused by monogenic defects of innate immunity and are characterized by recurrent or persistent systemic inflammatory symptoms. The main conditions that should be recognized by pediatricians and, preferably, referred for pediatric rheumatology care are FMF, TRAPS, the cryopyrinopathies (NOMID or CINCA, MWS, FCAS), MKD, PAPA syndrome, Majeed syndrome, and DIRA.

Acknowledgements

This study was supported by grants from the São Paulo State Research Foundation (*Fundação de Amparo à Pesquisa do Estado de São Paulo*, FAPESP; grant no. 0568/09; recipient, CAAS) and the National Council for Scientific and Technological Development (*Conselho Nacional de Desenvolvimento Científico e Tecnológico*, CNPq; grant no. 300248/2008-3; recipient, CAAS).

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