

# Diagnosis and Management of Autoinflammatory Diseases in Childhood

Marco Gattorno · Silvia Federici ·  
Maria Antonietta Pelagatti · Roberta Caorsi ·  
Giacomo Brisca · Clara Malattia · Alberto Martini

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## Abstract

**Introduction** Autoinflammatory diseases are a group monogenic inflammatory conditions characterized by an early onset during childhood.

**Discussion** Under the term “periodic fevers” are gathered some monogenic diseases (familial Mediterranean fever, mevalonate kinase deficiency, and tumor necrosis factor receptor-associated syndrome) characterized by periodic or recurrent episodes of systemic inflammation causing fever often associated with rash, serositis (peritonitis, pleuritis), lymphadenopathy, arthritis, and other clinical manifestations. Systemic reactive (AA) amyloidosis may be a severe long-term complication. Cryopyrinopathies are a group of conditions associated to mutations of the gene *Cryopyrin* that are responsible for a spectrum of diseases (familial cold autoinflammatory syndrome, Muckle–Wells syndrome, and chronic infantile neurological cutaneous and articular syndrome) characterized by a chronic or recurrent systemic inflammation variably associated with a number of clinical features, such as urticarial-like rash, arthritis, sensorineural deafness, and central nervous system and bone involvement. Other disorders are dominated by the presence of sterile pyogen abscesses prevalently affecting the skin, joints, and bones (pyogenic disorders). These include

pyogenic sterile arthritis, pyoderma gangrenosum, and acne syndrome, and Majeed syndrome. Finally, some diseases, such as Blau’s syndrome, are characterized by the appearance of typical noncaseating granulomatous inflammation affecting the joints, skin, and uveal tract (granulomatous disorders). In the present review, we will focus on the clinical presentation of these disorders in childhood and report on the available therapeutic strategies.

**Keywords** Familial Mediterranean fever · mevalonate kinase deficiency · tumor necrosis factor (TNF) receptor-associated syndrome · cryopyrinopathies

## Introduction

Autoinflammatory diseases are a group of different conditions secondary to mutations of genes coding for proteins that play a pivotal role in the regulation of the inflammatory response. Most of these disorders have an early onset, ranging from the first hours to the first decade of life. However, because of the extreme rarity of most of these disorders, a delay of diagnosis is usually observed. The clinical spectrum of these disorders is extremely variable (Table I).

Hereditary *periodic fevers* are characterized by recurrent flares of systemic inflammation presenting as sudden fever episodes associated with a dramatic elevation of acute phase reactants and a number of clinical manifestations, such as rash, serositis (peritonitis, pleuritis), lymphadenopathy, and arthritis. Disease flares are usually separated by symptom-free intervals of variable duration, characterized by complete well-being, normal growth, and complete normalization of acute phase reactants. Three different conditions belong to this

M. Gattorno (✉)  
2nd Division of Pediatrics, “G. Gaslini” Scientific Institute,  
Largo G. Gaslini 5,  
16147, Genova, Italy  
e-mail: marcogattorno@ospedale-gaslini.ge.it

M. Gattorno · S. Federici · M. A. Pelagatti · R. Caorsi ·  
G. Brisca · C. Malattia · A. Martini  
2nd Division of Pediatrics, “G. Gaslini” Institute and Laboratory  
of Immunology of Rheumatic Diseases, Department of Pediatrics,  
University of Genoa,  
Genoa, Italy

**Table I** The Autoinflammatory Diseases

	Diseases	Gene chromosome	Protein	Transmission	Clinical features
Periodic/recurrent fevers	Familial Mediterranean fever	<i>MEVF</i> 16p13.3	Pyrin	AR	Short duration of fever episodes: 24–48 h. Abdominal and chest pain. Erysipelas-like erythema. High incidence of renal amyloidosis in untreated patients. Good response to colchicine. Possible response to IL-1 blockade.
	Mevalonate kinase deficiency	<i>MVK</i> 12q24	Mevalonate kinase	AR	Early onset (usually <12 months). Mean duration of fever episodes: 4–5 days. Poor conditions during fever episodes. Abdominal pain, vomiting and diarrhea; splenomegaly. Good response to steroids. High rate of self-resolution during adulthood. Amyloidosis is rare.
	TNF receptor-associated periodic syndrome	<i>TNFRSF1A</i> 12p13	p55 TNF receptor	AD	Prolonged fever episodes: 1–3 weeks. Periorbital edema, monocytic fasciitis. Incidence of renal amyloidosis. Response to TNF- and IL-1 blockade
Cryopyrinopathies	FCAS, MWS, CINCA	<i>CIAS1</i> 1q44	Cryopyrin	AD	FCAS: rash, fever and arthralgia after cold exposure. MWS: recurrent or subchronic urticaria-like lesions, sensorineural hearing loss, amyloidosis. CINCA: as above + mental retardation, chronic aseptic meningitis, and bone deformities. Good response to IL-1 blockade.
	Blau's syndrome	<i>CARD15/NOD2</i> 16q12	CARD15	AD	Early onset (<5 years). Polyarticular granulomatous arthritis, uveitis, and skin rash. Good response to anti-TNF monoclonal antibodies.
Granulomatous disorders	PAPA syndrome	<i>PSTPIP1</i> 15q24–q25.1	PSTPIP1	AD	Pyogenic sterile arthritis, pyogenic gangrenosum, and cystic acne. Good response to IL-1 blockade.
	Majeed's syndrome	<i>LPIN2</i> 18p	LPIN2	AR	Multifocal osteomyelitis, congenital dyserythropoietic anemia, and inflammatory dermatosis.
	CRMO (murine)	<i>PSTPIP2</i> 18p	PSTPIP2	AR	

## Identification of the gene defect

*FCAS*: familial cold autoinflammatory syndrome, *MWS*: Muckle–Wells syndrome, *CINCA*: chronic infantile neurological cutaneous and articular syndrome, *PAPA*: pyogenic sterile arthritis, pyoderma gangrenosum, and acne syndrome, *CRMO*: chronic recurrent multifocal osteomyelitis, *AR*: autosomal recessive, *AD*: autosomal dominant

group: familial Mediterranean fever (FMF, MIM 249100), mevalonate kinase deficiency (MKD, MIM 260920), and tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS, MIM 142680).

In the so-called *cryopyrinopathies*, the systemic inflammation is usually dominated by a characteristic urticarial rash that may be associated with a number of other clinical manifestations. Familial cold autoinflammatory syndrome

(FCAS, MIM 120100), Muckle–Wells syndrome (MWS, MIM 191900), and chronic infantile neurological cutaneous and articular syndrome (CINCA, MIM 607115) represent the clinical spectrum associated to different mutations of a gene named *cold-induced autoinflammatory syndrome 1* (*CIAS-1* or *NALP3*) coding for a protein called cryopyrin.

Other disorders are characterized by the appearance of typical granulomatous formations (*granulomatous disorders*).

Blau's syndrome (MIM 186580) or familial juvenile systemic granulomatosis includes noncaseating granulomatous inflammation affecting the joint, skin, and uveal tract (the triad of arthritis, dermatitis, and uveitis, respectively) and is associated with mutations of the NACHT domain of the gene *CARD15* (or *NOD2*). Of note, mutations in this same gene have been associated with Crohn's disease, another granulomatous disease.

Finally, other disorders are dominated by the presence of sterile pyogenic abscesses prevalently affecting the skin, joints, and bones (*pyogenic disorders*). This include pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome (MIM 604416) associated to mutations of the CD2-binding protein 1 (*CD2BP1*) gene, and Majeed syndrome (MIM 609628) characterized by chronic recurrent multifocal osteomyelitis, congenital dyserythropoietic anemia, and neutrophilic dermatosis and caused by mutations of *LPIN2* gene.

### Familial Mediterranean Fever

First described as an autonomous clinical entity in 1945, FMF is an autosomal recessive disease related to the mutation of the Mediterranean fever (*MEFV*) gene that was cloned in 1997 [1, 2]. *MEFV* encodes pyrin (or marenostriin) that has been suggested to play a role in the regulation of the so-called *inflammasome*, a cytoplasmatic multiprotein complex that plays a crucial role in the production and secretion of proinflammatory cytokines, such as interleukin (IL)-1 $\beta$ , and is involved in the pathogenesis of various autoinflammatory diseases (see below).

FMF has a typical ethnic distribution; it is more common in non-Ashkenazi Jews, Arabs, Turks, Armenian, and North African populations. In these populations, the average carrier frequency is extremely high, ranging from 1:3 to 1:6. However, the disease is also present in other populations living around the Mediterranean basin and along the Silk Road.

### Clinical Features and Genotype–Phenotype Correlations

Most patients begin to suffer fever attacks during childhood; in 25% to 60% of patients, disease onset occurs before 10 years of age and in 64% to 90% before 20 years [3, 4]. In any case, a relevant delay in the diagnosis is usually reported with a mean period of about 7 years [3]. The clinical manifestations associated with fever episodes during childhood do not present major differences with respect to those observed in the adult population.

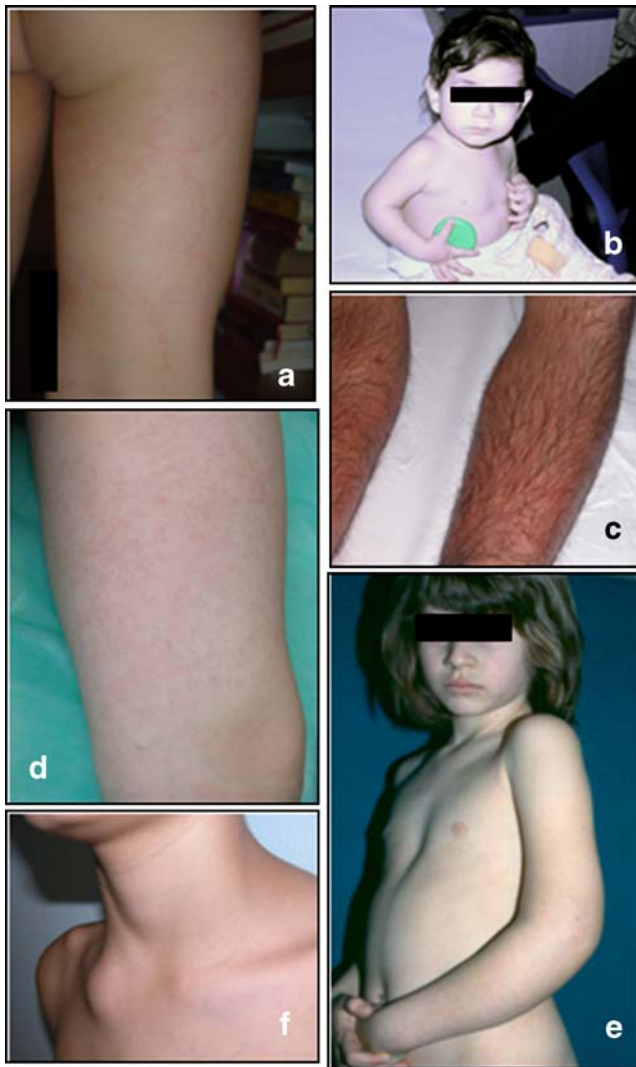
Fever episodes have a short duration (1–3 days) and are frequently associated (89–96% of the cases) with abdom-

inal pain because of aseptic peritonitis. Chest pain because of pleuritic involvement occurs in 33–53% of patients. Joint involvement is frequent and characterized by an asymmetrical and nondestructive oligoarthritis or monoarthritis that most commonly involves the hip, knee, or ankle. An erysipelas-like erythema on the lower part of the legs (ankle and the dorsum of the foot) is not frequent but is highly suggestive for the disease. However, a number of other different cutaneous manifestations could be also present during fever episodes (Fig. 1a). Myalgia may be observed during fever episodes. Some patients may experience prolonged episodes of protracted myalgia of the upper and lower extremities accompanied by fever and lasting up to 6 weeks. Splenomegaly may be present with a variable prevalence among different populations. Even if up to 15% of adult FMF patients refer headache during fever episodes, neurological manifestations are relatively uncommon in childhood. Neutrophilia and elevated erythrocyte sedimentation rate are typically associated with fever attacks.

Amyloid A (AA) type amyloidosis is the most severe long-term complication of FMF. This protein is a cleavage product of serum amyloid A (SAA), an acute phase reactant produced by the liver. The most common clinical manifestation of amyloidosis is the development of proteinuria and may lead to renal failure. Renal involvement is usually observed after a variable time from disease onset (phenotype-I). In some rare patients (less than 1%), renal amyloidosis may represent the first manifestation of the disease (phenotype-II). In the precolchicine era, the prevalence of amyloidosis among FMF patients was high, ranging from 60% to 80%. Untreated children may rapidly progress toward renal amyloidosis with a mean interval from disease onset of 6.4 years (range 1 to 19 year). Some of them may also develop renal failure despite colchicine treatment. IgA nephropathy, focal and diffuse proliferative glomerulonephritis, and rapidly progressive glomerulonephritis have been also reported in patients with FMF.

Diagnostic criteria have been proposed in adults [5], but have not been validated in children. These criteria displayed a high sensitivity and specificity in the context of the populations with a high prevalence of the disease [5]. In our recent experience on 228 children with periodic fever of prevalent Italian origin, Livneh's criteria confirmed a very high sensitivity (100%) in detecting those patients carrying a definitive FMF genotype (homozygous or compound heterozygous), but a much lower specificity as a relevant number of positive patients turned out to have other autoinflammatory diseases (i.e., MKD and TRAPS) (Gattorno et al., Arthritis and Rheumatism, in press).

Current studies suggest a limited phenotype–genotype correlation. The *MEFV* gene consists of 10 exons spanning approximately 15 kb. To date, more than 70 *MEFV* mutations have been recorded (<http://fmf.igh.cnrs.fr/infevers/>) [6]. In the



**Fig. 1** Clinical features of the autoinflammatory diseases. **a** Erythema marginatum-like manifestations during fever attacks in a pediatric FMF patient homozygous for the M694V *MEFV* mutation. **b** Patients homozygous for H20Q mutation of the *MVK* gene. The enzymatic activity of the patient was low and associated with an intermediate phenotype characterized by mild mental retardation, recurrent fever attacks, and chronic arthritis of the right elbow. **c** Erythematous patches overlying an area of myalgia in an 18-year-old TRAPS patient with monocytic fasciitis at legs. **d** The typical tan-colored, scaly, ichthyosiform rash observed in a 5-years-old patient affected with Blau's disease. **e** Septic-like appearance of the arthritis of the right elbow in a PAPA patient. **f** Classical bone deformity of the right clavicle in a boy with sporadic chronic recurrent multifocal osteomyelitis

ethnic groups in which FMF is endemic, 80–90% of the mutations are localised in exon 10. In particular, five founder molecular alterations, V726A, M694V, M694I, and M608I in exon 10 and E148Q in exon 2, account for 70–80% of cases.

The presence of M694V mutation has been associated with more severe disease and, in particular, with the development of amyloidosis. However, as observed in a

large Turkish multicenter study, this association is not present in all populations [3]. On the other hand, a number of observations have raised the question whether besides genetic predisposing factors, environmental factors may play a crucial role in the development of amyloidosis in FMF patients. In a recent large multicenter international study, the country of residence, rather than *MEFV* genotype, has been observed to represent the leading risk factor for the development of this severe complication [7].

#### Treatment

Colchicine is the treatment of choice for FMF [8]. The adult dose is 1 mg/day, and in nonresponsive patients, it can be increased to 2 mg. In children, the starting dose should be  $\leq 0.5$  mg/day for children below 5 years of age, 1 mg/day for children 5–10 years, and 1.5 mg/day for children above 10 years. Dosage can be increased in a stepwise fashion up to a maximum of 2 mg/day [9].

About 65% of patients show complete remission of fever episodes and 20–30% experience significant improvement with a reduction in the number and severity of fever attacks. Of the patients, 5% to 10% are nonresponders. The use of colchicine has dramatically reduced the incidence of amyloidosis. However, poor compliance to treatment (mainly because of gastrointestinal side effects, such as nausea and diarrhea) is one of the major causes of treatment failure.

The therapeutic margin of colchicine is quite narrow. In fact, colchicine is effective in a dose of 0.015 mg/kg, toxic (acute myopathy, bone marrow hypoplasia) in doses greater than 0.1 mg/kg, and lethal (acute multiorgan failure) in a dose of 0.8 mg/kg. Prolonged colchicine exposure seems to have no effects on male or female fertility, pregnancy outcomes, fetal development, or development after birth. Biologic treatments, especially IL-1 inhibitors, have been proposed as possible effective alternative treatments in colchicine-resistant FMF patients [10].

#### Periodic Fever Associated with Mevalonate Kinase Deficiency

Periodic fever associated with MKD was originally identified in 1984 in six patients of Dutch ancestry with a long history of recurrent attacks of fever of unknown cause and a high serum IgD level [11]. For this reason, this disorder has also been named *hyper IgD syndrome* or *Dutch fever*.

High IgD plasma levels have been used as a diagnostic hallmark until when mutations in the mevalonate kinase (*MVK*) gene, encoded on chromosome 12q24, were identified as the cause of the disease [12]. The complete deficiency of this enzyme causes a distinct syndrome called



mevalonic aciduria (MA; MIM 251170), which is clinically characterized by severe mental retardation, ataxia, failure to thrive, myopathy, and cataracts; notably, these patients also suffer from recurrent fever attacks [13]. MVK is an essential enzyme in the isoprenoid biosynthesis pathway which produces several biomolecules involved in different cellular processes. Cells from patients with the MKD phenotype still contain residual MVK enzyme activities (from 1% to 8% of the activities of control cells), whereas in cells from patients with the MA phenotype, the MVK enzyme activity is below the detection level (approximately 0.1% of the normal) [13].

Although the dysregulation of this biochemical pathway seems to play a pivotal role in the development of fever, at present, the pathogenetic mechanisms leading to the auto-inflammatory disease remain still poorly understood. Recent *in vitro* studies have shown that a shortage of geranylgeranylated proteins (a metabolic compound downstream to MVK), rather than an excess of mevalonate, is likely to cause increased IL-1 $\beta$  secretion by PBMCs of patients with MKD.

After the identification of the molecular defect, it became clear that the distribution of MKD is not limited to Northern European populations. In fact, a relevant number of patients have been observed also among populations living around the Mediterranean basin and Asia.

#### Clinical Features and Genotype–Phenotype Correlations

MKD is essentially a pediatric disease. Disease onset occurs very early in life, most often in infancy; almost all patients have developed the disease during the first decade of life. Fever attacks have an abrupt onset and last 4–6 days. Irritability is quite common. Severe abdominal pain often accompanied by vomiting and/or diarrhea are frequently associated with fever attacks. Cervical lymphadenopathy is common; axillary, inguinal, and intraabdominal lymph node enlargement may also be present. Splenomegaly is observed during fever attacks in about half of patients. Mucocutaneous manifestations are frequent and include erythematous macules, urticaria-like lesions and, less commonly, oral aphthous lesions. Articular involvement occurs in the majority of patients as arthralgia or as an oligoarticular, usually symmetric, arthritis [14, 15].

The symptoms of MKD persist for years but usually tend to become less prominent with time. However, in some patients, the disease may progress toward adulthood. Even if amyloidosis was not considered as a possible long-term complication of MKD, it has been recently described in rare patients [15].

Neutrophilia and elevated acute phase reactants are present during fever attacks. Increased plasma levels of

IgD (>100 UI/ml) during fever episodes and in basal conditions have been considered in the past as a hallmark of the disease. However, the specificity of this finding is low [15]. Concomitant elevation of IgA has been also reported [15]. An increased urine excretion of mevalonic acid is observed during fever spikes and decreased MVK activity may also orientate toward the diagnosis. However, the abovementioned determinations need a highly specialized laboratory and, therefore, are often difficult to perform as a screening test. Thus, the decision to undergo molecular analysis of the *MVK* gene in children with periodic fever is usually taken on the clinical ground.

MKD is an autosomal recessive disease. So far, more than 100 substitutions or deletions of the *MVK* gene have been reported (<http://fmf.igh.cnrs.fr/infevers/>) [6]. Some variants (i.e., V310M, A334T) are strongly associated with a severe MA phenotype and a severely impaired cellular MVK activity.

The most common mutation in the *MVK* gene is the V377I variant, which is exclusively associated with the mild phenotype of MKD and with a residual MVK activity [12]. In fact, it is found in compound heterozygous state in the vast majority of patients with the periodic fever associated to MKD [15].

Other mutations, such as H20P and I268T, have been also associated either with the MA or the MKD phenotype (<http://fmf.igh.cnrs.fr/infevers/>). It is, therefore, conceivable that some patients may also present an intermediate phenotype characterized by the typical fever attacks associated with some neurological manifestations (mental retardation, cerebellar ataxia) of variable severity [16] (Fig. 1b). It is, therefore, clear that mevalonic aciduria and periodic fever associated with MKD represent the two extremities of a wide clinical spectrum.

#### Treatment

Fever attacks usually respond dramatically to the administration of steroids (prednisone 1 mg/day in a single dose). However, because of the high frequency of the fever episodes, some patients may need almost continuous treatment. Thalidomide has been proven to be ineffective.

The use of biologic treatments is largely anecdotal and sometime controversial. Anti-TNF therapy has been found to reduce the frequency and intensity of fever attacks in some patients [17], but not in others [18]. Recently, the use of the IL-1 receptor antagonist (anakinra) was found to be effective in a patient [19]. However, these observations deserve confirmation in large multicenter therapeutic trials.

Other authors have reported the positive response to simvastatin treatment in six adult patients with MKD [20]. This preliminary experience has not been confirmed so far but suggests the possibility that a “metabolic” intervention

could represent an alternative therapeutic strategy for MKD.

### The TNF Receptor-associated Autoinflammatory Syndrome (TRAPS)

TRAPS was formerly known as familial Hibernian fever, as was initially described in a kindred of Irish–Scottish descent in 1982 [21]. It is a dominantly inherited disorder caused by mutations in the p55 TNF receptor (or TNFR1) encoded by the TNF super family receptor 1A gene (*TNFRSF1A*) [22]. Less than 200 families have been reported worldwide, but this number is likely to be underestimated.

The disease mainly affects people of Northern European ancestry, but has been described in almost all ethnic groups, including those living in the Mediterranean countries and Asia.

A total of 80 sequence variants of the *TNFRSF1A* have been recorded so far, among which 64 were found in patients with TRAPS phenotype (<http://fmf.igh.cnrs.fr/infervers/>) [6]. Most of them are missense substitutions. Approximately half of these TRAPS-related mutations result in single amino acid substitutions in the cysteine-rich domains (CRD), CRD1, CRD2, or CRD3 of the ectodomain of the mature TNFR1 (also called p55 TNFR) protein [22]. These CRDs are involved in disulfide bond formation and in the folding of the extracellular portion of the protein. Notably, mutations that result in cysteine substitutions demonstrate a higher penetrance of the clinical phenotype and, as reported below, are usually associated with a more aggressive phenotype.

#### Clinical Features and Genotype–Phenotype Correlations

Disease onset is usually reported during the pediatric age, but is often misdiagnosed. Fever attacks last from 1 to 3 weeks and are spaced by variable intervals of complete well-being. No clear periodicity is usually observed [23, 24].

Abdominal and chest pain are frequently observed and are caused by acute peritoneal inflammation or pleurisy. The cutaneous manifestations associated with TRAPS consist of a migratory, macular rash that occurs on the extremities and/or torso. These cutaneous lesions are usually warm and tender and are histologically characterized by deep perivascular infiltrates of mononuclear cells. When lesions occur on the limbs or arms, they may be associated with myalgia because of an underlying monocytic fasciitis (Fig. 1c). Other skin rashes, such as generalized serpiginous plaques or annular patches may be also observed. Arthralgia is more prominent than arthritis and it generally involves large joints (hips, knees, ankles). Ocular involvement,

characterized by periorbital edema and conjunctivitis is frequent.

Attacks are associated with important rise in acute phase reactants (ESR, CRP), increased neutrophils count, and variable degree of hypochromic anemia.

In adulthood, fever episodes may become less frequent and patients may experience a subchronic disease course characterized by flares of abdominal pain, arthromyalgia, and ocular manifestations and by a slight but persistent elevation of acute phase reactants, including SAA. Renal AA amyloidosis represents the most serious long-term complication with a prevalence ranging from 14% to 25% [23, 25]. A central nervous involvement characterized by a demyelinating disorder has been described in few adult patients.

Mutations of the *TNFRSF1A* gene that result in cysteine substitutions demonstrate a higher penetrance of the clinical phenotype and are characterized by a severe disease course and by an increased probability of developing renal amyloidosis. In contrast, other low-penetrance mutations (such as the R92Q and P46L mutations) are usually associated with a more heterogeneous clinical presentation with a milder disease course and lower prevalence of amyloidosis [23].

This observation was confirmed also in our recent study on a pediatric population of 21 TRAPS patients [24]. In fact, patients with missense substitutions of cysteine residues had a more aggressive disease with longer duration of fever episodes (mean duration 23 days), higher steroid requirement, and higher incidence of amyloidosis. Conversely, children carrying a R92Q substitution displayed a milder disease course in terms of duration of flares (mean duration 4.1 days), intensity of disease-associated symptoms, and responsiveness to steroids treatment. In this study, the allele frequency in the normal population was 2.25%; moreover, in most of R92Q patients, the mutation was inherited from one asymptomatic parent, thus suggesting a reduced penetrance for this substitution [24].

#### Treatment

Fever episodes usually respond to steroid treatment. However, because of the possible long duration of fever attacks and the tendency to a chronic course, patients may become steroid-dependent.

The use of immunosuppressive drugs has been reported to be ineffective in TRAPS patients in reducing the frequency and the intensity of the inflammatory episodes and/or in preventing the development of amyloidosis [25]. Because of the observation that the molecular defect of p55 TNFR is associated with an impaired shedding of the receptor from the membrane surface, the use of anti-TNF treatment has been proposed [22]. After some initial

anecdotal evidence on the efficacy of etanercept in the prevention of disease flares and in the treatment of long-term renal complications [25], it has been shown that anti-TNF therapy is ineffective in some patients and unable to completely control inflammation in others.

An excellent short-term response to treatment with the recombinant receptor antagonist for IL-1 (IL-1Ra, anakinra) has been observed in one TRAPS patient, suggesting that IL-1 blockade may represent a possible alternative strategy, as already observed for other monogenic autoinflammatory diseases. In a recent study, we described the long-term efficacy and safety of anakinra treatment in five TRAPS patients with a severe disease course (Gattorno et al., *Arthritis and Rheumatism*, in press).

### The Cryopyrinopathies

FCAS (MIM 120100), MWS (MIM 191900), and CINCA (MIM 607115) represent autosomal-dominant disorders characterized by different mutations in a single gene, *CIAS1* (cold-induced autoinflammatory syndrome 1, also known as *NALP-3* or *PYPAFI*), encoding a protein called cryopyrin.

FCAS, also named familial cold urticaria, familial polymorphous cold eruption, and cold hypersensitivity, was first described in 1940 as a rare autosomal-dominant disorder characterized by intermittent episodes of rash, fever, and arthralgia secondary to exposure to cold [26].

MWS was first described in 1962 in a British family with recurrent episodes of urticaria-like eruptions, fever, chills, malaise, and limb pain since childhood associated with the late development of sensorineural hearing loss and amyloidosis [27].

In 1981, Prieur and Griscelli described three unrelated children that presented since birth a syndrome characterized by a permanent skin rash fever, lymphadenopathy, severe central nervous system (CNS) involvement (mental retardation, sensorineural hearing loss, and chronic aseptic meningitis), chronic arthropathy, and peculiar facial and dysmorphic features [28]. They defined this syndrome as CINCA (MIM 607115), whereas American authors defined the same entity as neonatal onset multisystemic inflammatory disease (NOMID).

In 2001, the gene responsible for FCAS and MWS was identified and named *cold-induced autoinflammatory syndrome 1* (*CIAS1*), and the encoded protein was named cryopyrin [29]. Mutations of the same gene were found in almost 60% of patients with the more severe CINCA phenotype.

Cryopyrin is a member of the NALP/PYPAF subfamily of the CATERPILLER cytoplasmic protein family. Cryopyrin is a key protein of a multiprotein cytoplasmic complex named *inflammasome*. In the presence of a

number of stimuli, cryopyrin oligomerizes and binds the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD). This association activates directly the IL-converting enzyme (ICE)/caspase-1, which, in turn, converts pro-IL-1 $\beta$  to the mature, active 17 kDa form. Therefore, activated cryopyrin induces the release of the active form IL-1 $\beta$ . Monocytes from patients carrying *CIAS-1* mutations display in fact, with respect to healthy donors, a massive secretion of IL-1 $\beta$  [30].

### Clinical Features and Genotype–Phenotype Correlations

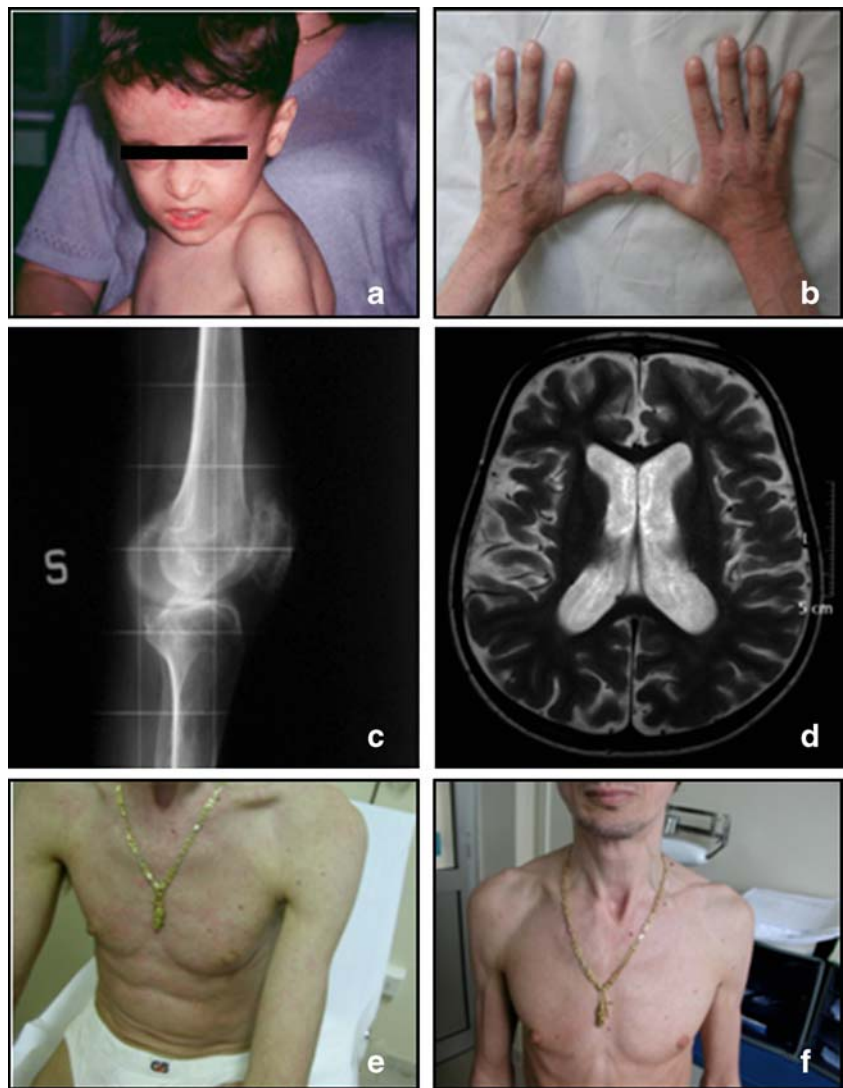
FCAS is characterized by urticarial rash and fever spikes of short duration (usually <24 h) induced by cold exposure. Arthralgia and conjunctivitis are also common. Other symptoms observed after cold exposure include profuse sweating, drowsiness, headache, extreme thirst, and nausea [31].

MWS is characterized by recurrent episodes of urticaria and fever that may develop in the early infancy. The fever episodes (usually below 38°C) can be associated with the same clinical manifestations observed in FCAS (arthralgia, conjunctivitis, drowsiness), but are usually not strictly evoked by cold exposure. Acute phase reactants are elevated during fever episodes and may also persist or slightly increase during free intervals. During the course of the disease, neurosensorial deafness and polyarthritides may develop. AA amyloidosis is a complication of the late stage of the disease [27, 32].

CINCA represents the more severe phenotype associated with mutations of the *cryopyrin* gene (Fig. 2). An urticaria-like rash may develop during the first weeks of life. Many affected individuals present a typical “facies” characterized by frontal bossing, saddle back nose, and midface hypoplasia, causing a sibling-like resemblance (Fig. 2a). Bone involvement is another characteristic hallmark of the disease. The most characteristic features are represented by bony overgrowth that predominantly involve the knees (including the patella) and the distal extremities of the hands and feet (Fig. 2b and c). Major alterations in the organization of the growth cartilage have been described in biopsy specimens. A chronic inflammatory polyarthritides may be also present, sometime leading to bone erosions. Central nervous system (CNS) manifestations include chronic aseptic meningitis, increased intracranial pressure, cerebral atrophy, ventriculomegaly (Fig. 2d), sensorineural hearing loss, and chronic papilledema with associated optic nerve atrophy and loss of vision. Mental retardation and seizures have also been reported. Patients display a persistent elevation of acute phase reactants, leukocytosis, and chronic anemia.

So far, more than 80 different missense mutations have been associated with a phenotype consistent with a cryopyrinopathy (<http://fmf.igh.cnrs.fr/infevers/>) [6]. Almost all the observed mutations are found in the exon 3

**Fig. 2** The clinical picture of the CINCA/NOMID syndrome. **a** Typical “facies” characterized by frontal bossing, saddle back nose, and midface hypoplasia in a child carrying the N477K mutation of the *CIAS-1/NALP3* gene. **b** Digital clubbing observed in an adult CINCA patient. **c** Overgrowth of the patella at x-ray. **d** Cerebral atrophy and ventriculomegaly in a 17-year-old CINCA patient. **e** and **f** Urticaria-like skin rash in a CINCA patient the day before the beginning of treatment with anakinra (**e**) and complete resolution of the cutaneous manifestations the day after the first injection (**f**)



of the *CIAS-1* gene, coding for the NACHT domain of cryopyrin that plays a crucial role in the oligomerization of the protein.

#### Treatment

The pivotal role of cryopyrin in the control of caspase 1 activation and the massive secretion of active IL-1 $\beta$  observed in cryopyrin-mutated individuals, suggesting that anti-IL-1 treatment could represent an effective therapy. Initial isolated case reports suggested that the recombinant IL-1 receptor antagonist, anakinra, presents a dramatic effect in the control of rash and constitutional symptoms in Muckle–Wells patients [33]. These findings have recently been confirmed in a multicenter study performed on a large cohort of CINCA patients [34].

We have treated seven CINCA patients with anakinra at the starting dosage of 1 mg/kg s.c. [35]. All displayed a dramatic improvement of urticarial rash, arthritis, and fever

with complete resolution within 1 week from the beginning of the treatment (Fig. 2e and f). A rapid decrease of acute phase reactants was also observed in the first weeks of treatment with a complete normalization in the majority of the patients. Monitoring of the patients under anakinra treatment with a follow-up longer than 2 years revealed that all CINCA patients still displayed a complete control of the inflammatory symptoms with near complete normalization of the general conditions. In our experience, no significant improvement was so far observed in the visual and/or acoustic impairments present in these patients [35]. However a significant improvement of hearing loss has been described after anakinra treatment [34].

#### Blau's Syndrome

Blau syndrome or familial juvenile systemic granulomatosis is an autosomal-dominant, autoinflammatory disease



characterized by a noncaseating granulomatous inflammation affecting the joint, the skin, and the uveal tract (the triad of arthritis, dermatitis, and uveitis) [36]. The gene responsible for Blau syndrome, *NOD2/CARD15*, encodes a protein containing a NACHT domain [37]. To date, more than 10 different genetic mutations leading to substitutions in or near the NACHT domain of *NOD2/CARD15* have been documented in affected patients with either the familial or the sporadic presentation [37]. Notably, mutations of the LRR domain of the same gene are associated with another chronic granulomatous disease, such as Crohn's disease.

Disease onset is usually observed during the first years of life. Symmetrical polyarticular arthritis with a typical pattern of boggy synovitis is the typical joint manifestation. Eye involvement is characterized by intermediate uveitis or panuveitis. Of the patients with ocular involvement, 50% develop cataracts, and approximately one third may develop into secondary glaucoma. A typical tan-colored, scaly, ichthyosiform rash is seen in almost 90% of the affected individuals [38, 39] (Fig. 2d). Patients are treated with oral steroids and immunosuppressive drugs (methotrexate, cyclosporin A) with variable results. Recent anecdotal reports suggest a beneficial effect of anti-TNF (infliximab) [38] and anti-IL-1 treatment [39].

### PAPA Syndrome

PAPA (MIM 604416) is a disorder caused by mutations in the *CD2BP1* [40, 41]. The manifestations of this disorder are pyogenic gangrenosum, cystic acne, and pyogenic sterile arthritis, which represent the most common symptom of the disease. The arthritis usually has its onset in early childhood. It is pauciarticular in nature, affecting one to three joints at a time, and is characterized by recurring inflammatory episodes that resemble septic arthritis (Fig. 1f) and lead to accumulation of pyogenic, neutrophil-rich material within the affected joints, which ultimately results in significant synovial and cartilage destruction [40, 41]. Cultures of the skin and joints of these patients are sterile. Dermatologic manifestations are also episodic and recurrent with onset usually during the second decade of life and are characterized by debilitating, aggressive, and ulcerative skin lesions, usually of the lower extremities, undistinguishable from pyogenic gangrenosum. Sterile abscesses at injection sites may also be observed.

Genome-wide linkage scans localized a candidate region to 15q22–24 by Wise et al. Subsequent positional cloning identified two missense mutations within the *CD2BP1* (or *PSTPIP1*) gene of these families [41]. *CD2BP1* has been shown to bind pyrin. It is postulated that the increased pyrin binding seen with the PAPA mutations may alter inflammatory susceptibility.

PAPA syndrome has been reported to be generally responsive to oral glucocorticoids [40, 41]. Sustained remission in a steroid-resistant patient and dramatic amelioration of cutaneous manifestations have been reported after anti-TNF and anti-IL-1 treatment.

### Majeed's Syndrome

In 1989, three related Arab children presenting an association of chronic recurrent multifocal osteomyelitis (CRMO), congenital dyserythropoietic anemia, and inflammatory dermatosis were described by Majeed et al. [42].

Unlike isolated CRMO (Fig. 1f), bone manifestations has an earlier age at onset, more frequent episodes, shorter and less frequent remissions, and is probably life long. Congenital dyserythropoietic anemia is characterized by microcytosis both peripherally and in the bone marrow that may deserve repeated blood transfusions. Inflammatory dermatosis may vary from a Sweet syndrome to chronic pustulosis. Recurrent fever episodes and growth failure have also been reported [42, 43]. Nonsteroidal antiinflammatory drugs are moderately helpful, whereas short courses of oral steroids promptly control disease relapses, even if steroid dependence has been reported. Colchicine does not seem to be effective. Splenectomy was effective in controlling the hematological manifestations [43].

In 2005, a linkage analysis was performed on two new Jordan families allowing the identification of the *LPIN2* gene mapped on chromosome 18p [44].

The existence of a monogenic disease associated to CRMO has raised the hypothesis that sporadic CRMO could also be included in the group of autoinflammatory diseases. This hypothesis have been further supported by the recent identification on a chromosome 18 of a missense mutation in the *pstpip2* gene in a spontaneous murine model of autoinflammatory disorder characterized by chronic multifocal osteomyelitis [45].

### The Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis (PFAPA) Syndrome

Those children presenting with periodic fever attacks similar to those observed in monogenic periodic fevers but negative for mutations of known genes (*MEFV*, *MVK*, *TNFRS1A*) are often classified with this syndrome. In fact, although some anecdotic familial cases of PFAPA have been reported, it does not have a documented genetic basis.

PFAPA was first described by Marshall et al. in 1987 [46]. The disease usually develops before 5 years of age. It is characterized by fever spikes of abrupt onset lasting 3–6 days; fever recurs regularly every 2–6 weeks, although an

explanation for its clockwork periodicity is lacking. The fever flare-ups are usually heralded by chills; neither myalgia nor malaise is present during the acute phase. Children with PFAPA syndrome often appear in good conditions also during the fever spikes; this is a clinical feature that may help to distinguish PFAPA from the other form of periodic fever associated with genetic defect. The aphthous lesions observed in PFAPA are small and localized to labial gingival and are rapidly self-remitting. Cervical lymph node enlargement is frequent (and may be relevant); enlarged lymph nodes are tender and normalize with the resolution of the fever attack [47]. Acute phase reactants and neutrophils are elevated during attacks and completely normalize during the periods of complete well-being. The disease has a benign course and tends to spontaneously remit with time. Fever attacks respond to steroids.

The diagnosis of PFAPA is based on current diagnostic criteria [47]. In a recent study, we have shown the low specificity of these criteria. In fact, almost 50% of genetically positive children (especially MKD) also fulfill the PFAPA criteria [48], which, therefore, do not represent a specific tool to select patients with high probability to be negative at genetic testing. In this line, some clinical manifestations during fever attacks, such as abdominal and chest pain and gastrointestinal symptoms (vomiting and/or diarrhea) should be considered as evocative for a higher risk to carry mutations of known genes [48].

In conclusion, autoinflammatory diseases probably represent the tip of an iceberg of a much larger group of syndromes caused by still unknown genetically determined anomalies in the regulation of the inflammatory response, primarily involving cells of innate immunity. The study of the pathogenic mechanisms related to these diseases is certainly contributing to a better understanding of the pathogenesis of chronic inflammatory diseases.

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