



# Autoinflammatory syndromes for the dermatologist

Paula Dávila-Seijo, MD, Angela Hernández-Martín, MD, Antonio Torrelo, MD\*

Department of Dermatology, Hospital del Niño Jesús, Menéndez Pelayo 65, 28009 Madrid, Spain

**Abstract** While autoimmunity as cause of disease is well-established, other categories of immune-mediated diseases that are not produced by targeting of self-antigens by antibodies is in the process of being described. These so-called autoinflammatory diseases arise when an inappropriate activation of antigen-independent mechanisms occurs.

Autoinflammatory diseases course with recurrent attacks of fever and multisystemic inflammation; however, the skin may also be affected by a variety of inflammatory manifestations that often alert the clinician about the presence of an autoinflammatory disease. Recognizing the cutaneous features of these syndromes will aid for prompt diagnosis and early treatment that is key for the quality of life and survival of the affected patients.

In this paper, we focus on the skin manifestations of autoinflammatory diseases in children, which is the usual period of appearing of the first symptoms and signs.

© 2014 Elsevier Inc. All rights reserved.

## Introduction

The primitive arm of the immune response, the innate immune system, constitutes the first line of defense against pathogens and harmful stimuli. The innate immune system is antigen-independent; activity is based on recognition of molecular markers of infection or injury by the so-called “pattern recognition receptors,” which activate multiple inflammatory signaling cascades and the main cellular effectors of innate immunity: macrophages, neutrophils, mast cells, and natural killer cells. When inappropriate activation of the innate immune system appears it may produce an autoinflammatory disease, in contrast to the well-known phenomenon of autoimmune diseases caused by aberrations in the adaptative immune system.<sup>1–3</sup>

The best described autoinflammatory diseases (see Table 1) are the “autoinflammatory syndromes,” a group of rare conditions produced by mutations in single genes that codify proteins playing a crucial role in different inflammation

pathways of the innate immune system.<sup>1</sup> These syndromes have in common the presence of: (1) recurrent systemic inflammation signs and symptoms that appear early in life, usually during childhood; (2) genetic transmission in most cases; and (3) the presence of different skin manifestations that constitute a characteristic part of the clinical spectrum. Pediatricians, dermatologists, and pediatric dermatologists play an important role in the recognition of these rare but characteristic diseases.

In this paper, we have tried to give an overall updated vision of all autoinflammatory syndromes with dermatologic features that have been previously reported in the literature, focusing on etiopathogenesis, genetics advances, and clinical manifestations, with a particular emphasis on the features.

## Hereditary periodic fever syndromes (HPFS)

HPFS include a few autoinflammatory disorders characterized by recurrent episodes of fever, appearing at variable intervals from days to weeks, in conjunction with several

\* Corresponding author. Tel.: + 34 91 5035900; fax: + 34 91 5744669.  
E-mail address: atorrelo@aedv.es (A. Torrelo).

clinical manifestations of systemic inflammation caused by mutations in single genes that encode proteins with major roles in the innate immune system.

### Familial Mediterranean fever (FMF)

FMF, the paradigm of the periodic fever syndromes, is an autosomal recessive (AR) disorder, common among Armenians, Italians, North Africans, Sephardic Jews, and Turks, having been less commonly reported in a variety of other ethnicities.<sup>4</sup> There is an extraordinary high number of FMF carriers in Middle Eastern populations, suggesting some kind of advantage to individuals who are heterozygotes.<sup>5</sup>

The FMF gene, called MEFV (standing for MEditerranean FeVer), is located at chromosome 16 p and encodes a protein named pyrin (marenostriin) expressed in the cytoplasm of myeloid-derived circulating cells, synovial fibroblasts, and dendritic cells.<sup>6,7</sup> Pyrin plays a major role in the innate immune system as a main regulatory component of the NLRP3 inflammasome, a large protein complex composed of pyrin, ASC (apoptosis-associated specklike protein with a CARD), caspase 1, and cryopyrin. The inflammasomes take part in multiple inflammation signaling pathways such as the NF $\kappa$ B and IL-1  $\beta$  pathways.<sup>8</sup>

Eighty percent of MEFV mutations are missense mutations, located at one of three sites encoded on exon 10.<sup>9</sup> Others mutations are located at exon 2 of chromosome 16.<sup>5</sup> The 694 and 726 position mutation sites are the most widely distributed. M694V mutation is by far the most frequent in FMF and is associated with early onset, arthritis, erysipeloid-like skin lesions, oral lesions, splenomegaly, renal amyloidosis, higher fever, and more frequent attacks. Patients with these mutations usually require higher doses of treatment to prevent attacks.<sup>10–12</sup> The second most frequent mutation is V726A. There are a proportion of patients (up to 25%) who have a single MEFV mutation and who present clinical manifestations identical to homozygous patients, but usually in a milder form.<sup>13,14</sup>

Incomplete penetrance and variable clinical expression is seen among FMF patients, even in those who have the same mutation. This suggests the role of some mitigating environmental or genetic factors, which could modify the expression of systemic manifestations of FMF.<sup>15</sup> One such factor is the presence of major histocompatibility class I (MHC Class I) chain-related gene A alleles, which are associated with different clinical manifestations in FMF patients. For example, the A9 allele is related to early onset and A4 with lower frequency of attacks.<sup>16</sup>

It seems that neutrophils are the effector cells in serosal inflammation. They appear in high number in serosal fluids during attacks and express pyrin in their cytoplasm; colchicine, a neutrophil suppressor, has proven effective in preventing the attacks.<sup>9</sup> Deficit of the C5a/IL8 inhibitors may also play a role in FMF pathogenesis. This serin protease, which blocks C5a and IL-8, two potent neutrophil

chemotactic factors, has been found in low levels in serous fluids among FMF patients.<sup>17,18</sup>

The hallmark of FMF are episodic attacks of fever, that typically last less than 72 hours, together with abdominal pain (95%), pleurisy (30%), mono or oligoarticular arthritis (75%), and/ or arthralgias.<sup>19</sup> The arthritis may appear independently of the other clinical manifestations and it may last even months. Pericarditis or acute scrotal pain and swelling may be present but only rarely.<sup>5,20</sup> Attacks are self-limited and between them the patient remains asymptomatic. The lapse between attacks is very variable. Possible attacks triggers are vigorous exercise, emotional stress, exposure to extreme temperatures, and hormonal changes.<sup>19</sup> FMF begins

**Table 1** Autoinflammatory diseases with dermatologic manifestations

- Periodic fever syndromes (PFS):
  - Familial Mediterranean fever (FMF)
  - Tumor necrosis factor receptor-associated periodic syndrome (TRAPS)
  - Hyperimmunoglobulinemia D syndrome (HIDS)
  - Periodic fever with aphthous stomatitis, pharyngitis, and adenitis syndrome (PFAPA)
- Cryopyrin-associated periodic syndromes (CAPS):
  - Familial cold autoinflammatory syndrome (FCAS)
  - Muckle-Wells syndrome (MWS)
  - Neonatal onset multisystemic inflammatory disorder (NOMID)
- Generalized pustular syndromes:
  - Deficiency of the interleukin-1-receptor antagonist syndrome (DIRA)
  - Deficiency of interleukin thirty-six-receptor antagonist syndrome (DITRA)
- Other autoinflammatory syndromes:
  - Pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA)
  - NOD2-associated pediatric granulomatous arthritis (PGA): Blau syndrome/early-onset sarcoidosis.
  - Majeed syndrome
  - Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome and other proteasome related diseases
- Beçet syndrome
- Schnitzler syndrome
- SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome
- Chronic recurrent multifocal osteomyelitis (CRMO) sporadic form
- Systemic juvenile idiopathic arthritis (Still disease) and adult onset
- Pyoderma gangrenosum, acne, and suppurative hidradenitis (PASH)
- Possible autoinflammatory diseases:
  - Inflammatory bowel disease
  - Sweet syndrome, pyoderma gangrenosum, and other neutrophilic dermatoses

typically in childhood. In 65% of patients the first attack occurs before 10 years of age and 90% appears before 20.<sup>21</sup>

AA amyloidosis, caused by a deposit of serum amyloid A protein, is a severe complication that could appear in untreated patients and could produce renal and hepatic dysfunction. Amyloidosis is not always correlated with the frequency or intensity of attacks and evidenced inflammation. This observation suggests that there would be other factors, including some mutations, that increase or decrease the risk of developing amyloidosis.<sup>15</sup> During acute attacks there appears an elevation of many of the serum markers of systemic inflammation, such as erythrocyte sedimentation rate (ESR), beta-2 microglobulin, C-reactive protein (CRP), serum amyloid protein (SAA), fibrinogen and leukocytosis with a predominance of neutrophils is common.<sup>19</sup>

Erysipeloid-like lesions, which appear in 15% to 20% of children, are the distinctive cutaneous manifestation of FMF.<sup>22–24</sup> They are usually present in the lower extremities, on the anterior surface of the leg, below the knee, and the dorsum of foot. They appear as well-circumscribed edematous and erythematous plaques, bilateral or isolated, no larger than 15 cm in diameter. Pathologic studies of these lesions have revealed a predominantly neutrophilic infiltrate with nuclear dust.<sup>25</sup> Purpuric lesions on the face, trunk, and extremities have also been reported in children. Henoch-Schönlein purpura (5% of children) and polyarteritis nodosa are present with higher frequency in FMF patients.<sup>26–29</sup>

Colchicine, a neutrophil suppressor of choice is the elective drug in FMF patients. There is good evidence that the use of colchicine continuously reduces the frequency, the intensity and the duration of the attacks and also decreases the risk of developing amyloidosis. Colchicine could also abort an attack if it is taken during the prodromal phase. Colchicine is safe in long-term therapy in children. The initial and the maintenance dose vary with age and the needs to control symptoms, but usually they are between 0.5 to 1.8 mg/day. Colchicine should be introduced after a diagnosis of FMF is made and it should be maintained for life.<sup>30</sup>

In patients who do not respond to colchicine, it is important to verify the compliance with therapy. Intravenous colchicine could be tried as some of these not-responders do respond to this regime. There are isolated reported cases of truly colchicine-resistant patients that responded to thalidomide, to anti-TNF $\alpha$  agents such as etanercept and infliximab, and to the recombinant IL-1 receptor antagonist anakinra.<sup>31,32</sup>

### Tumor necrosis factor receptor-associated periodic syndrome (TRAPS)

TRAPS, also known as familial Hibernian fever (because it was firstly described in an Irish family), is a rare autosomal dominant (AD) disease that causes fever and local inflammation that typically last between 7 to 21 days.<sup>33,34</sup>

TRAPS is caused by a genetic mutation in the gene TNFR superfamily IA, localized in the short arm of chromosome 12

p13.<sup>35,36</sup> Its product, the tumor necrosis factor receptor (TNFR), is a 55 kDa protein that serves as an antagonist to circulating TNF and plays a role in cellular functions related to pyrexia, cachexia, cytokine production, leukocyte activation, expression of adhesion molecules, and resistance to cellular pathogens. To date more than 50 mutations have been reported.<sup>5</sup>

Clinically, TRAPS patients have recurrent episodes, usually lasting longer than 5 days but less than 1 month, of fever, myalgia with a characteristic distal migration (seen in 80% of patients), arthralgias, severe abdominal pain usually associated with gastrointestinal symptoms and conjunctivitis.<sup>5,33</sup> There are also reported cases without fever.<sup>37</sup> Systemic AA amyloidosis develops in 8% to 25% of the affected leading to impaired renal and/or hepatic function. It seems that patients with mutations involving the aminoacid cysteine and the T50 M mutation of TNFRSF1 A have an increased risk of developing AA amyloidosis.<sup>38</sup> The age of TRAPS onset is variable and ranges from 2 weeks to 53 years.<sup>39</sup>

Laboratory analyses show an elevation of inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), especially during attacks. Antinuclear antibodies (ANA) and rheumatoid factor are rarely present.<sup>33</sup>

Patients who present with cutaneous lesions are 69% to 87%. The most frequent skin lesion (seen in 40%) is a centrifugal migratory, erythematous patch overlying the area with myalgia, also called “painful erythema.” Typically, these lesions move from proximal to distal site over a period of minutes to several days. Frequently, the erythematous patch is associated with an underlying myalgia that also migrates concomitantly. Other lesions consist in urticarial-like plaques and generalized erythematous macular and papular lesions that, over time, coalesce in larger annular or serpiginous patches and plaques. Thirty-six percent of skin lesions resolve with an ecchymotic appearance.

Pathological examination reveals perivascular and interstitial infiltrate of mononuclear cells. Immunofluorescence studies of cutaneous lesions show IgM and C3 deposits at dermal-epidermal junction or diffuse IgA, IgG, and C3 deposition. Small vessel vasculitis and recurrent panniculitis have rarely been associated with TRAPS.<sup>34</sup>

TRAPS responds to treatment with oral corticosteroids. Unfortunately, colchicine has no therapeutic effect. Etanercept, a soluble p75 TNFR-Fc fusion protein, can decrease but not eliminate the symptoms. The hypothesis that a defective shedding of surface TNFR in TRAPS causes a continuous activation signal would explain the results of anti-TNF drugs in treating TRAPS. Treatment with other anti-TNF drugs, such as infliximab, can precipitate paradoxical attacks. Better results are obtained with anakinra, raising a new hypothesis in which intracellular aggregation of misfolded TNFR1 causes hyperimmune responses that is independent of TNF and mediated by enhanced production of mitochondrial-derived oxygen reactive species that disturb intracellular homeostasis.<sup>40</sup>

## Hyperimmunoglobulinemia D syndrome (HIDS)

HIDS is an AR disease characterized by recurrent episodes of fever associated with lymphadenopathy, gastrointestinal symptoms, and elevated levels of Ig D. About 50% of patients with HIDS are of Dutch ancestry.<sup>41,42</sup>

HIDS can be divided into two forms: classic and variant form. Classic HIDS includes cases in which the genetic mutation is known (about 75% of all HIDS cases). In variant HIDS, the clinical picture is the same as in classic HIDS, but the genetic bases are still unknown.<sup>43</sup>

The gene for classic HIDS is the mevalonate kinase (MVK) gene located in chromosome 12 q24.<sup>44</sup> Most patients are heterozygous for two different mutations in MVK gene: one of these mutations, when present in a homozygous state, causes mevalonic aciduria but the mutation in the other allele in HIDS is not typical for mevalonic aciduria. The most frequent mutation in homozygous HIDS patients is the V377I that appears in 50% of cases.<sup>45</sup> MVK is an enzyme that plays a role in the synthesis of the cholesterol/isoprenoids pathway. In HIDS there is a remaining activity of MVK, something that differentiates HIDS from mevalonic aciduria where the MVK function is completely absent. The gene defects associated with HIDS produce a temperature-dependant MVK, the activity of which is impaired by increasing temperature at a greater rate than normal MVK enzyme. In mevalonic aciduria the MVK activity is not temperature dependant.<sup>46,47</sup>

Although IgD levels are typically, but not always, elevated in HIDS they do not seem to be responsible of the clinical manifestations of HIDS because the levels do not correlate with the severity for frequency of the attacks. There is no clarity regarding what role IgD plays in HIDS pathophysiology, but the latest theories indicate that this elevation is a secondary phenomenon due to systemic inflammation.<sup>48</sup>

It is hypothesized that HIDS attacks start with a trigger (such as trauma, vaccinations, or stress) capable of inducing elevation in body temperature. Due to the heat-sensitivity of

MVK in HIDS, a decreased activity in the enzyme activity would lead to downstream of nonsteroid isoprenoids producing a proinflammatory state with further aggravation of fever and inflammatory symptoms. Eventually, the homeostasis is restored and the attack ends.<sup>49</sup>

Clinical manifestations in HIDS begin during the first year of life. They are characterized by episodic attacks of fever (usually more than 38.5 °C) that last from 4 to 7 days. Some patients describe prodromal symptoms such as headache, fatigue, and nasal congestion. During the attacks other clinical symptoms noted include (1) localized or generalized tender lymphadenopathy (90% of patients), (2) abdominal pain that can mimic acute abdomen (almost 100% of patients), (3) palpable splenomegaly (50%), and/or (4) polyarticular joint involvement (80%), with arthralgia and/or arthritis that is usually symmetric with a predilection for the large joints. Joint affection may last longer than febrile attacks, but there has never been reported any long-term joint destruction.<sup>48</sup>

Seroritis, orbital tendonitis with tendomyositis, may occur, but rarely.<sup>50</sup> One case of nummular keratopathy was reported, as well.<sup>51</sup> Amyloidosis is an infrequent serious complication of HIDS.<sup>52</sup>

The periodicity of attacks is variable (4 to 8 weeks), but in children and adolescents the periods between attacks are shorter than adults. HIDS patients remain asymptomatic in these interval periods with the exception of joint and skin manifestations that may last longer.<sup>5,49</sup>

In the HIDS variant, the clinical manifestation of HIDS may appear later in life, even in adulthood. The periodicity of attacks is more variable than in classic HIDS.<sup>49</sup>

Laboratory analyses frequently show a polyclonal IgD elevation (>14 mg/dL), but normal levels are also possible.<sup>48,53</sup> IgA elevation (greater than 260 mg/dL) is also seen in 80% of the affected. Other inflammatory markers are elevated as well.<sup>48</sup>

### Cutaneous manifestations

Heterogeneous skin lesions appear up to the 80% of the patients with HIDS. They usually consist in macular erythematous eruption composed of solitary lesions that may coalesce. They favor the acral parts over the trunk. Other skin lesions that may be present in HIDS are papules, erythematous nodules, urticarial lesions, and petechiae. Microscopic examination usually shows endothelial swelling and perivascular inflammatory infiltrates. Henoch-Schönlein purpura, erythema elevatum diutinumlike, sweetlike, cellulitislike lesions and deep vasculitis have also been reported in HIDS.<sup>5,48,54</sup>

### Therapy

The mainstream HIDS management is symptomatic therapy during attacks. The most used drugs are nonsteroidal antiinflammatory drugs (NSAIDs). There is no predilection agent. NSAIDs can be started during the prodromal phase and maintained until the episode ends. In patients who do not



**Fig. 1** NOMID syndrome. Hypertelorism, frontal bossing, and urticarial lesions.

respond to NSAIDs a short course of oral corticosteroids may be used. Doses vary from a single pulse dose at the beginning of symptoms to 1 mg/kg of prednisone or prednisolone daily for 4 to 7 days or even 2 weeks to alleviate the joint symptoms.

Other agents such as colchicine, cyclosporin, intravenous immunoglobulin G, statins, and thalidomide showed no beneficial effects in HIDS. Etanercept was used in several cases with variable results, but it seems to have some benefit in the rare cases with syndrome-overlap with TRAPS. So far, there are only a few reported cases of HIDS patients treated successfully with anakinra.<sup>55</sup>

### Periodic fever with aphthous stomatitis, pharyngitis, and adenitis syndrome (PFAPA)

PFAPA is the most common of all periodic fever syndromes, and unlike the others it is a sporadic condition in which familial cases are sparse.<sup>56</sup> Characteristically it begins during childhood, commonly between 2 and 5 years of age and resolved before the end of first decade. There is a mild male predominance and PFAPA does not show higher incidence in any ethnicity.<sup>57,58</sup>

#### Etiology

To date there are no identified mutations in PFAPA and the etiology remains unknown. There is an altered inflammatory cytokine profile during attacks in PFAPA and the cellular immune response is different from what is seen in infections. In addition, there is an activation of the innate immunity and an elevation of IL-1 beta secretion that might precipitate the attack.<sup>58,59</sup> The similarities between PFAPA and cyclic neutropenia prompt the idea of common pathways of immune dysfunction. They are truly periodic fever syndromes with a cyclic occurrence of episodes, but in PFAPA syndrome neutropenia is not found.<sup>60</sup>

The carrier state of MEVF, the familial Mediterranean fever gene, seems to act as a gene modifier of PFAPA associated with shorter duration of attacks, longer duration of attacks-free periods, and less oral lesions.<sup>61</sup>

#### Clinical manifestations

Patients present abrupt episodes of fever that last 3 to 6 days and recur every 3 to 4 weeks, and may associate one or more of the following symptoms: aphthous stomatitis, exudative or nonexudative pharyngitis, tender cervical lymphadenopathy, and mild abdominal pain. Other less specific symptoms are fatigue, myalgias and headache.<sup>57</sup>

Laboratory analyses during the attacks show moderate leukocytosis and elevation of ESR and CRP that return to normal once the attack ends.

#### Cutaneous manifestations

Aphthous ulcers occur in 40% to 70% of PFAPA patients. They are usually small, appear in low number on the lips or



**Fig. 2** Arthropathy in NOMID syndrome: Knee swellings and urticarial lesions.

oral mucosa and heal without scarring. A nonspecific skin rash was rarely reported during attacks.<sup>60</sup>

#### Therapy

PFAPA is a self healing condition, which usually disappears with age. Growth and development are preserved and no long-term sequelae are seen. Treatment is an option in which benefits need to be pondered against risks.

Antipyretics and NSAIDs are only effective for fever. Systemic corticosteroids, such as prednisone in doses of 1 or 2 mg/kg/day, lead to a dramatic relief of fever and pharyngitis in a couple of hours, but neither the aphthae nor the lymphadenopathy tend to improve. Up to 25% of affected children who are treated with corticosteroids present an increased frequency of febrile attacks, even weekly, as a side effect. This may limit the use of steroids as therapy in such cases. The most common dosage is one single dose of 2 mg/kg of prednisone at the beginning of fever; if there is no recurrence at 48 to 72 hours, the dose could be decreased to 1 mg/kg for 2 days and then to .5 mg/kg for another 2 days. Lower single doses of prednisone (.5 to 1.5 mg/kg/day) also showed good results in aborting the attack in several uncontrolled series.

Cimetidine use (20 to 40 mg/kg/day in divided doses) has been reported to be beneficial in reducing or eliminating the recurrence of episodes in small case series. In three cases, the response was maintained once drug was discontinued after 6 months.

Prophylaxis with colchicine (.5 to 1 mg/day) may induce a longer episode-free interval, but results are inconsistent and it is not routinely recommended.

Tonsillectomy shows beneficial effect in most but not all PFAPA patients, but recurrence appears in up to one third of treated patients. Taking into account that PFAPA is a benign condition tonsillectomy does not seem an adequate first-therapy option.<sup>60</sup>

## Cryopyrin-associated periodic syndromes (CAPS)

The CAPS, also called cryopyrinopathies, are a group of three rare, overlapping autoinflammatory syndromes that share a common etiology: all are due to different mutations in the NLRP3 gene (also called CIAS1) localized at chromosome 1 q44. All of them are autosomal dominant diseases with variable penetrance. NLRP3 product is the protein called cryopyrin (NALP3 or PYPAF1). Cryopyrin is part of a multiprotein inflammasome complex (the NLRP3 inflammasome), which in response to certain stimuli activates a cascade of interactions through caspase 1 that ends in production of potent proinflammatory cytokines, mainly IL-1 $\beta$  and IL-18.<sup>62</sup>

Cryopyrin activation is mediated by PAMPs (pathogen-associated molecular patterns, such as muramyl dipeptides, bacterial or viral RNA), DAMPs (danger-associated molecular patterns, such as uric acid crystals, skin irritants or ultraviolet B radiation), and maybe alum, used as a vaccine adjuvant.<sup>63–65</sup> Different self-activating mutations in the NLRP3 gene cause constitutive activation of inflammasome complex and production of proinflammatory IL-1 $\beta$ . The different clinical manifestations between CAPS reflect the way different mutations affect the activity of the inflammasome; however, these differences are not really marked and overlapping cases are commonly seen.<sup>65</sup>

## Familial cold autoinflammatory syndrome (FCAS)

FCAS or familial cold urticaria is the mildest of all CAPS. It is characterized by a constellation of clinical manifestation after generalized exposure to cold air. Usually it starts during the first year of age, even after delivery when the newborn is exposed to a cold maternity room.

### Clinical manifestations

Symptoms begin between 2 to 7 hours after generalized cold exposure and are characterized by an urticarialike skin



**Fig. 3** Urticarial lesions in NOMID syndrome.

rash associated with fever, chills, conjunctival injection, and arthralgias. The episode usually resolves in less than 12 hours (rarely last 24 hours). Other clinical manifestations include fatigue, headache, and myalgias. In laboratory analysis appears a marked leukocytosis 10 hours after cold exposure and starts to diminish 12 to 14 hours later. Amyloidosis is a very rare complication of FCAS.<sup>66,67</sup>

### Cutaneous manifestations

The skin eruption consists of erythematous-edematous, urticarialike papules, and plaques that develop after cold exposure. The contact with a cold object does not induce the rash. The lesions may be itchy but more often are burning or stinging and usually display a more symmetrical pattern that appears in true urticaria.

Histologic examinations reveals a predominant perivascular neutrophilic infiltrate without vasculitis, and dermal edema.<sup>5,66,68</sup>

## Muckle-Wells syndrome (MWS)

MWS, also known as urticaria-deafness-amyloidosis syndrome, is a rare condition similar to FCAS but with more severe manifestations. The episodes usually begin early during childhood, although the age of onset is variable. There are multiple triggers, but these cannot always be identified. The most common precipitating factors are exposure to heat and cold.<sup>65,69,70</sup>

### Clinical manifestations

They consist of intermittent febrile episodes together with headache, conjunctivitis skin rash, and joint manifestations (arthritis or arthralgia), that are similar to those in FCAS, but last longer in MWS (12 to 36 hours) and the intervals between episodes are not as regular as in FCAS.<sup>69,71</sup>

Patients with MWS characteristically present a progressive sensorineural hearing loss that starts in childhood and it may evolve into complete deafness. This hearing loss is thought to be secondary to cochlear or leptomeningeal inflammation.

Secondary amyloidosis is a complication of MWS in up to a quarter of patients. Nephropathy may identify in 35% of MWS caused mostly by renal amyloidosis.<sup>69,71</sup>

Abnormalities in laboratory analysis express the high level of inflammation that appears in MWS, with an elevation of inflammatory markers and leukocytosis during attacks.

### Cutaneous manifestations

An urticarial-like rash, similar to that in FCAS, appears in MWS. The histologic features are similar to FCAS as well.<sup>5</sup>

## Neonatal onset multisystemic inflammatory disorder (NOMID)

NOMID, also named as chronic infantile neurological cutaneous and articular (CINCA) syndrome, is the most



**Fig. 4** The papular eruption of Blau syndrome.

severe of the cryopyrinopathies. Most of the cases are sporadic and only a few present an autosomal-dominant transmission. The same as other CAPS, symptoms appear shortly after birth, usually before 6 months of age. The triad of skin rash, severe arthropathy, and central nervous system disorders characterizes NOMID.<sup>65,72</sup>

### Clinical manifestations

Recurrent short episodes of fever are common in NOMID. Patients show abnormal facial features (Figure 1), generally developed at birth or nearly after, such as flattening of the nasal bridge, macrocephaly, frontal bossing, and protruding eyes.<sup>73</sup> They usually present a constellation of neurological manifestation-like chronic aseptic meningitis, cerebral atrophy, sensorineural hearing loss, early-morning headaches related with increased intracranial pressure, and developmental delay. Eye manifestations, including anterior uveitis, papilledema or blindness, are also part of NOMID systemic manifestations.<sup>74</sup>

Even though arthropathy is present in variable degrees of severity, 50% of patients have severe arthropathy before 12 months of age (Figure 2). In mild cases, there is only some pain and joint effusion. In most severe forms, exuberant cartilaginous proliferations with secondary ossification resembling tumors are seen at growth plates and epiphyses in radiologic studies.<sup>75</sup> Other features include lymphadenopathy and hepatosplenomegaly. Secondary amyloidosis may appear due to chronic inflammation.<sup>1,5</sup>

Laboratory findings include acute-phase reactants elevation, leukocytosis, thrombocytosis and eosinophilia, and serum hyperglobulinemia.

### Cutaneous manifestations

A migratory, nonpruritic, erythematous skin eruption resembling urticaria appears in most cases before 6 months of age (Figure 3); two-thirds of newborns have skin lesions at birth. The rash persists during the whole life of patients. Histologic features are superficial and deep perivascular infiltrates composed mainly of lymphocytes, neutrophils, and some eosinophils. Mast cells are absent and epidermis is preserved.<sup>76</sup> Neutrophilic eccrine hidradenitis has been reported as well in NOMID.<sup>77</sup>

### Therapy of CAPS

Anakinra, the IL-1 receptor antagonist, given in daily subcutaneous injections, has shown marked capacity in preventing attacks and reducing inflammation manifestations in FCAS and MWS, reducing the risk of developing secondary amyloidosis also. The role of anakinra in preventing hearing loss is not clear in MWS, but some partial recovery has been reported in several cases. Anakinra seems also effective in reducing inflammation in some cases of NOMID, but not all patients respond and apparently it does not play an important role in decreasing joint and bone alterations.<sup>78</sup>

Rilonacept, an IL-1 trap given subcutaneous on weekly basis, appears as an effective agent in decreasing signs and symptoms of inflammation in FCAS and MWS without severe adverse effects.<sup>78</sup>

Treatment with canakinumab, a human anti-IL-1 $\beta$  monoclonal antibody, showed complete and sustained responses in almost all cases of CAPS in a randomized placebo-controlled trial. A significant increase in the incidence of suspected infections appeared in the canakinumab group.<sup>78</sup>

### Deficiency of the interleukin-1-receptor antagonist syndrome (DIRA)

DIRA is a rare autosomal recessive autoinflammatory syndrome due to deficiency of the interleukin-1-receptor antagonist (IL1RN).

### Etiology

DIRA share etiopathogenic features with CAPS but clinical manifestations differ from them. The deficiency of interleukin-1-receptor is secondary to homozygous germ line mutations in IL1RN (single point mutations, deletions, and microdeletions have been reported).<sup>79–82</sup> These mutations produce a protein, which lacks antagonistic activity of IL-1

receptor leading to a continuous activation of inflammatory pathways through IL-1. Heterozygous carriers are usually asymptomatic or may have mild manifestations.

### Clinical manifestations

Characteristically, DIRA patients present chronic recurrent episodes of multifocal aseptic osteomyelitis and periostitis at birth or within 2 months postpartum. Recently, a case of a fetus with clinical manifestation of DIRA has been reported.<sup>83</sup> Other skeletal manifestations include osteopenia, periarticular swelling secondary to long-bone epiphyseal overgrowth, cervical vertebral fusion, and widening of clavicle and anterior rib ends. Fever and failure to thrive are present commonly in DIRA. Other clinical manifestations in DIRA are respiratory distress, pulmonary infiltrates, thrombotic episodes, and vasculitis. Laboratory analyses show an increase in acute-phase reactants, mild anemia, and blood leukocytosis with neutrophilia.<sup>79,80,84</sup>

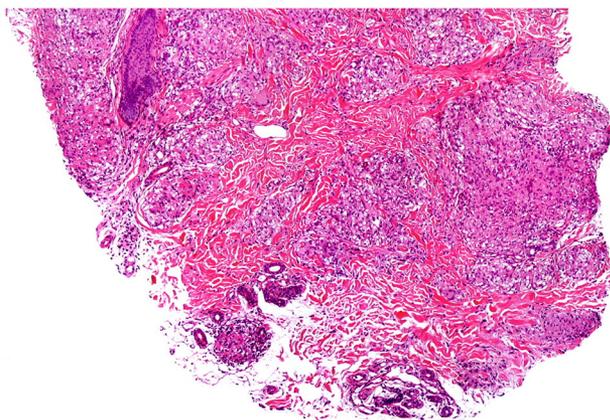
### Cutaneous manifestations

Generalized erythematous plaques with overlying pustules, simulating generalized pustular psoriasis, appear at birth or during the first 2 months of age. This severe pustular skin rash, that usually respects palms and soles, may result in diffuse desquamation. Nail changes (mostly pitting but also onychia) are common in DIRA. Mucous lesions, mostly in the form of a vesicular stomatitis or mouth ulcers, are also described. Pathergy reaction has been reported.<sup>79,80,84</sup>

Skin lesion biopsies show epidermal parakeratosis with subcorneal acantholytic or spongiform neutrophilic pustules, dermal neutrophilic infiltrates with concomitant superficial folliculitis and/or neutrophilic eccrine hidradenitis. Immunofluorescence studies are negative.<sup>79,80,84</sup>

### Therapy

Daily subcutaneous injections with anakinra, the recombinant analogue of IL1RN, 1 to 5 mg/kg, has led to



**Fig. 5** Sarcoid-like granulomas in Blau syndrome.

complete clinical resolution of cutaneous and osteoarticular manifestations in most patients with DIRA and partial resolution in some of them. This variable response to treatment with anakinra seems to have a genetic relation with mutations that lead to a more severe or unresponsive disease. Treatment with NSAIDs, corticosteroids, and other immunomodulatory drugs was either noneffective or only partially effective.<sup>79–82,84</sup>

### Other pustular autoinflammatory syndromes

#### Deficiency of interleukin thirty-six-receptor antagonist syndrome (DITRA)

Recently, mutations in the IL-36 receptor antagonist (IL36RN) were identified as the cause of some familial and sporadic cases of generalized pustular psoriasis (GPP).<sup>85,86</sup> The new disorder of IL-36-receptor antagonist associated GPP has been named DITRA syndrome.<sup>86</sup>

#### Etiology

Loss-of-function homozygous mutations in IL36RN gene were shown to be the cause of familial and sporadic cases of DITRA. In familial cases the disorder has an autosomal recessive inheritance. IL36RN is a protein of the IL-1 cytokine family, which is abundantly expressed in the skin and that has an important role in inflammatory pathways, such as the NF- $\kappa$ B, blocking the recruitment of interleukin-1 receptorlike 2 (IL-1 RL2) receptor through its inhibition of IL-36  $\alpha$  and IL-36  $\gamma$ , which has been found in higher levels in skin lesions in DITRA patients in response to IL-1  $\beta$  and polyosinic-polycytidylic acid stimuli.<sup>85–87</sup>

#### Clinical manifestations

DITRA is characterized by sudden and recurrent episodes of skin eruption together with fever, malaise, and asthenia without involvement of other organs. There is an increased risk of death due to sepsis during the flares. The frequency of episodes is variable. They usually begin during the childhood but some adult onset cases were reported as well. Some reported triggers have been bacterial and viral infections, menstruation, pregnancy or drugs.<sup>85,86</sup>

#### Cutaneous manifestations

The skin lesions in DITRA resemble GPP: a rapid onset of generalized pustular eruption over erythematous skin. Psoriasis vulgaris lesions and acral pustular lesions with nail destruction are also found in some patients. Interestingly, palmoplantar pustulosis seems to not be part of the clinical spectrum of DIRA syndrome. The histologic studies show the typical features of pustular psoriasis: spongiform pustules, psoriasiform acanthosis, and parakeratosis in the stratum corneum.<sup>86</sup>

#### Therapy

Anakinra, the recombinant IL-1 receptor antagonist has been reported to be effective in some cases of GPP.<sup>88</sup>

## Other autoinflammatory syndromes

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

PAPA, also named familial recurrent arthritis, is a very uncommon autosomal-dominant disease characterized by the presence of pyogenic arthritis, pyoderma gangrenosum, and cystic acne.<sup>89</sup>

#### Etiology

The gene found to be responsible for this syndrome is the proline/serine/threonine phosphatase-interacting protein 1 (PSTPIP1; also known as CD2 antigen-binding protein 1 [CD2BP1]) localized on chromosome 15 q24-25.1. Its product, PSTPIP1, is a cytoskeletal protein expressed predominantly in hematopoietic cells that modulates T cell activation, cytoskeletal organization, and interleukin-1  $\beta$  (IL-1  $\beta$ ) release. When it is mutated there is a disruption of PSTPIP1 with protein tyrosine phosphatase-PEST that increases its avidity for pyrin that causes overproduction of IL-1  $\beta$ .<sup>89,90</sup> A recent report showed a PAPA case without PSTPIP1 mutation.<sup>91</sup>

#### Clinical manifestations

Recurrent episodes of sterile arthritis, spontaneous or following minor trauma, leading to joint destruction that appear during childhood are the hallmark of PAPA. They usually tend to decrease its frequency after puberty. Other less frequent clinical manifestations are recurrent otitis, pharyngeal papillomatosis, lymphadenopathy, splenomegaly, thrombocytopenia, hypergammaglobulinemia, hemolytic anemia, and T cell large granular lymphocytosis.<sup>92,93</sup>

#### Cutaneous manifestations

Usually skin lesions begin during childhood but they become worse at puberty. They consist essentially of severe cystic acne, pathergy phenomenon and recurrent sterile ulcers with peripheral undermined borders, and cribriform scarring similar to those seen in pyoderma gangrenosum.

Patients with milder skin manifestations similar to psoriasis and rosacea have also been reported.<sup>92,93</sup>

#### Therapy

Antitumor necrosis factor (TNF) drugs, infliximab, adalimumab, and etanercept, appear to be the most effective therapy in PAPA syndrome, but not all patients respond. Anakinra was used in PAPA with variable results: some patients showed marked improvement whereas others only obtained a partial benefit. Corticosteroids seem to be effective for arthritis, but less beneficial in treating pyoderma gangrenosum lesions. Other immunosuppressants are partially or noneffective, although the combination of sulfasalazine and leflunomide induced remission in one reported case.<sup>93,94</sup>

### NOD2-associated pediatric granulomatous arthritis (PGA): Blau syndrome/early-onset sarcoidosis

Under the name of PGE there are two diseases with an identical phenotype: One autosomal-dominant disease, also known as Blau syndrome, and one sporadic condition or early-onset sarcoidosis. Thanks to genetic analyses, we now know that there are common mutations in the NOD2 gene (also known as CARD15) in all patients with Blau syndrome and most of patients with early-onset sarcoidosis confirming the same etiology of both conditions and supporting the notion that they are, in fact, the same disease.<sup>95-97</sup> That is why the common denomination of NOD2-associated PGA may be preferable, reserving the denomination of early-onset sarcoidosis for those patients who have similar phenotype without identifiable mutation in the NOD2 gene.<sup>98,99</sup>

#### Etiology

The NOD2 gene is mapped to chromosome 16 q12-21. Mutations in the NOD2 gene are also related with Crohn's disease but they differ from those found in NOD2-associated PGA. Mutations in NOD2 identified in NOD-associated PGA are missense mutations resulting in constitutive self-activation of NOD2, thus leading to increased basal NF $\kappa$ B activation. In contrast, NOD2 mutations associated with Crohn's disease produce a decrease in NOD2 function, and, hence, in the NF $\kappa$ B pathway. NOD2 protein, mostly expressed in the cytoplasm of hematopoietic cells and in the epithelium of the small intestine, has a role in the innate response to microorganisms recognizing components of bacterial wall muramyl dipeptide that leads to activation of NF $\kappa$ B.<sup>100</sup>

#### Clinical manifestations

Classic clinical manifestations are characterized by the triad of early-onset of polyarticular boggy synovitis,



**Fig. 6** Panniculitis as a sign of Blau syndrome.



**Fig. 7** CANDLE syndrome: Annular purpuric plaques.

granulomatous acute anterior uveitis, and skin rash.<sup>101</sup> The joint manifestations begin before the age of 10 as painless, cystic lesions on feet and wrists together with mild boutonniere deformities of the fingers. With time, they develop camptodactily with cystic swelling of the wrists, ankles, knees, and elbows. These joint anomalies are slowly progressive and they do not limit mobility until several decades after beginning. In histologic studies of synovial membrane appears granulomatous inflammation with giant multinucleated cells.<sup>102</sup>

Eye involvement, with recurrent episodes of anterior uveitis that may progress to posterior involvement, can lead to cataracts, glaucoma, and even blindness years after initial symptoms, which may start early in childhood or during adulthood.

Other nonclassic manifestations described in NOD2-associated PGA are mild to moderate nonperiodic fever, granulomatous lymphadenopathy, multiple asymptomatic hepatic epithelioid granulomas, hepatosplenomegaly, granulomatous infiltration of salivary glands, pneumonitis, granulomatous glomerulonephritis, and interstitial nephritis and cranial neuropathy.<sup>102</sup>

### Cutaneous manifestations

Characteristic skin lesions are one of the three main features of classic NOD2-associated PGA. These lesions are usually observed in early childhood and consist in asymptomatic tiny red or tan, sometimes lichenoid papules that may be localized or generalized in trunk and extremities sparing the palms and soles (Figure 4). The skin lesions can be so inconspicuous that may be missed. Histological examinations show noncaseating granulomas in dermis with multiple epithelioid and multinucleated giant cells indistinguishable from sarcoidosis (Figure 5). Electron microscopy may show the characteristic “comma-shaped bodies” inside epithelioid cells, but they are not always present.<sup>98,99,101,102</sup>

Other cutaneous manifestations described in NOD2-associated PGA have been panniculitis related with febrile episodes clinically resembling erythema nodosum (Figure 6)

and leukocytoclastic vasculitis with maculopapular and urticarial rash.<sup>98</sup>

### Therapy

Cutaneous lesions may respond to chronic therapy with erythromycin. NSAIDs, corticosteroids, methotrexate, and anti-TNF drugs are the usual therapies for extracutaneous manifestations. Thalidomide has been reported to show good efficacy in this disorder. There are occasional reports of the response with the use of anakinra.<sup>103</sup>

### Majeed syndrome

The hallmark of this disorder is the presence of a chronic recurrent multifocal osteomyelitis (CRMO) and congenital dyserythropoietic anemia (CDA) with microcytosis, sometimes associated with inflammatory dermatosis.<sup>104,105</sup>

The disease usually starts during the first year of age but no later than the age of two and presents clinical exacerbations and remissions.

### Etiology

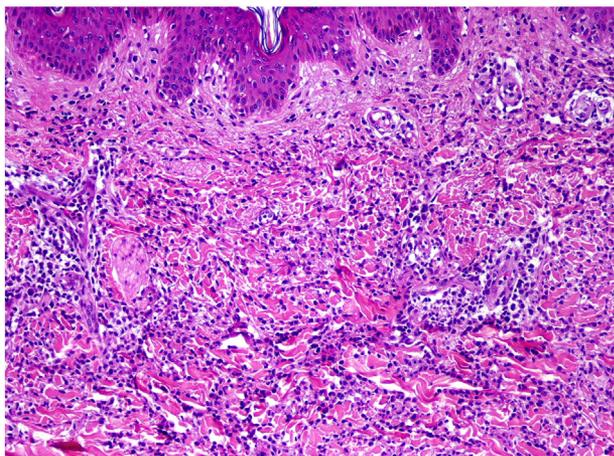
Different homozygous mutations in LPIN2 gene have been found in Majeed patients.<sup>106–108</sup> LPIN2 is a protein that shares the lipin domain with LPIN1 and LPIN3, all these are phosphatidate phosphatase (PAPs). PAPs play an important role in glycerolipid biosynthesis and act as transcription coactivators regulating lipid metabolism genes. The mutations reported in Majeed syndrome appear to abolish the PAPs function. Also, LPIN2 may be increased in response to oxidative stress and play a role in mitoses. Although, the mechanism by which mutations in LPIN2 cause Majeed syndrome is unclear it seems that IL-1 may be important in pathogenesis due to the good response to therapy with an IL-1 receptor antagonist.

### Clinical manifestations

Onset of CRMO in Majeed syndrome begins earlier (3 weeks to 2 years) than in the isolated form of CRMO (4 to 15 years of age), and also shows shorter remissions, an increased number of exacerbations and a prolonged course with poor tendency to autoresolution.<sup>105</sup>

Each exacerbation consists of high fever, pain, and swelling, mainly around large joints. As a consequence, growth delay and permanent flexion contractures may ensue. Radiological studies have shown that changes resemble bacterial osteomyelitis: osteolytic lesions with surrounding sclerosis. Biopsy of bone lesions shows nonspecific inflammatory changes.<sup>109</sup>

CDA usually presents during the first year of life as hypochromic, microcytic anemia and its severity is variable. Bone marrow examination evidences increased erythropoiesis associated with dyserythropoiesis including binucleated and trinucleated normoblasts.<sup>109</sup>



**Fig. 8** CANDLE syndrome: Mononuclear infiltrate of the skin with bizarre nuclei.

Individuals with Majeed syndrome have also growth retardation with short stature.<sup>105</sup>

#### Cutaneous manifestations

The inflammatory dermatosis is not a consistent phenotypic component of Majeed syndrome. To date, two patients had Sweet syndrome, another one showed a “cutaneous pustulosis,” and a heterozygous carrier was affected with psoriasis.<sup>109</sup>

#### Therapy

The main therapy of CRMO is NSAIDs, which provide moderate improvement. Corticosteroids are also useful in controlling CRMO and skin manifestations. Recently there were reported two cases of Majeed syndrome with no response to corticosteroids and etanercept that showed a complete and maintained response to anakinra and canakinumab (anti-IL-1  $\beta$  antibody).<sup>107</sup>

### Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome

CANDLE syndrome is a recently described entity characterized by recurrent episodes of fever, cutaneous lesions, lipodystrophy, and visceral inflammatory manifestations.<sup>110</sup> The clinical manifestations begin during the first year of age, generally during the first weeks, and show no tendency to autoresolution.

#### Etiology

In a recent report, genetic analyses were performed on nine patients with clinical CANDLE syndrome, finding homozygous and compound heterozygous mutations in PSMB8, encoding the immunoproteasome subunit  $\beta 5$  i in most of them.<sup>111</sup> None of these were observed in healthy controls. All patients expressed high levels of interferon- $\gamma$

(IFN $\gamma$ )-inducible protein 10 (IP-10). CANDLE syndrome, caused by mutations in PSMB8, is allelic with “JMP” syndrome (joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced childhood-onset lipodystrophy) and a similar phenotype named the Nakajima-Nishimura syndrome in Japan. The proteasome/immunoproteasome are key cell structures to cleave and eliminate ubiquitinated proteins fated to be removed; in the absence of immunoproteasome assembly or decreased catalytic function, polyubiquitinated proteins accumulate in the cytoplasm of macrophages, leading to cellular stress; in turn, cellular stress activates JAK kinase and production of interferons, leading to more cellular stress and accumulation of stress proteins that cannot be adequately removed, thus leading to a circle of increasing cellular stress.<sup>111</sup>

#### Clinical manifestations

Daily or recurrent episodes of fever (higher than 38 °C) are characteristic in CANDLE syndrome. Low weight and height are always present. Hepatomegaly, splenomegaly, and arthralgia without arthritis are common features. A constellation of inflammatory manifestations were described in CANDLE patients, such as ear and nose chondritis, conjunctivitis and nodular episcleritis, epididimitis, nephritis, otitis, parotitis, aseptic meningitis, or lymphadenopathy. Laboratory analyses evidence chronic anemia, elevation of acute-phase reactants, and mild raise of liver enzymes.<sup>110</sup>

#### Cutaneous manifestations

Recurrent annular erythematous, edematous plaques with raised borders, are one of the hallmarks of CANDLE and they have been seen in all reported patients (Figure 7). These



**Fig. 9** Lipodystrophy in CANDLE syndrome.



**Fig. 10** Violaceous periorbital erythema in CANDLE syndrome.

lesions appear predominantly on the trunk but also on the face and limbs, especially over the interphalangeal joints. Usually, they spontaneously resolved leaving hyperpigmented or ecchymosislike residual lesions. New plaques are continuously appearing resulting in a chronic skin eruption. Histologic examination of these lesions shows dense dermal perivascular and interstitial infiltrates sometimes with subcutaneous involvement, composed of mononuclear myeloid cells with atypical features resembling leukemia cutis, with increased number of mitotic figures (Figure 8). A variable number of neutrophils and eosinophils may be present mixed together with the atypical myeloid cells.<sup>110</sup>

Progressive lipodystrophy in the face, upper extremities, and trunk is a consistent clinical manifestation as well (Figure 9). Persistent purplish eyelid swelling and perioral swelling are quite common (Figure 10).

### Therapy

NSAIDs were used with partial control of fever. Corticosteroids are also only partially effective in controlling the symptoms. Other antiinflammatory drugs such colchicine, dapsone, cyclosporin, immunoglobulin infusions, and methotrexate were used with little or no improvement. Anti-TNF $\alpha$  drugs, such as etanercept and infliximab, were attempted with exacerbation of skin lesions and no improvement, respectively. Anakinra was also tried unsuccessfully.<sup>110</sup>

### References

- Nigrovic PA. Periodic fever syndromes and other autoinflammatory diseases: an overview. 2012. [UpToDate®].
- Lachmann HJ, Quartier P, So A, Hawkins PN. The emerging role of interleukin-1 beta in autoinflammatory diseases. *Arthritis Rheum.* 2011;63:314-324.
- Heymann WR. The interplay of innate immunity, adaptive immunity, and autoimmunity. *J Am Acad Dermatol.* 2007;57:700-701.
- Ben-Chetrit E, Touitou I. Familial mediterranean Fever in the world. *Arthritis Rheum.* 2009;61:1447-1453.
- Farasat S, Aksentijevich I, Toro JR. Autoinflammatory diseases: clinical and genetic advances. *Arch Dermatol.* 2008;144:392-402.
- The International FMF Consortium. Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. *Cell.* 1997;90:797-807.
- French FMF Consortium. A candidate gene for familial Mediterranean fever. *Nat Genet.* 1997;17:25-31.
- Shinkai K, Kilcline C, Connolly MK, Frieden IJ. The pyrin family of fever genes: unmasking genetic determinants of autoinflammatory disease. *Arch Dermatol.* 2005;141:242-247.
- Peter M, Rosenberg SEG. Pathophysiology of familial Mediterranean fever. © 2013. 2012. [UpToDate].
- Grateau G. The relation between familial Mediterranean fever and amyloidosis. *Curr Opin Rheumatol.* 2000;12:61-64.
- Shinar Y, Livneh A, Langevitz P, et al. Genotype-phenotype assessment of common genotypes among patients with familial Mediterranean fever. *J Rheumatol.* 2000;27:1703-1707.
- Kone Paut I, Dubuc M, Sportouch J, Minodier P, Garnier JM, Touitou I. Phenotype-genotype correlation in 91 patients with familial Mediterranean fever reveals a high frequency of cutaneous mucous features. *Rheumatology (Oxford).* 2000;39:1275-1279.
- Marek-Yagel D, Berkun Y, Padeh S, et al. Clinical disease among patients heterozygous for familial Mediterranean fever. *Arthritis Rheum.* 2009;60:1862-1866.
- Booty MG, Chae JJ, Masters SL, et al. Familial Mediterranean fever with a single MEFV mutation: where is the second hit? *Arthritis Rheum.* 2009;60:1851-1861.
- Pras M. Amyloidosis of familial mediterranean fever and the MEFV gene. *Amyloid.* 2000;7:289-293.
- Touitou I, Picot MC, Domingo C, et al. The MICA region determines the first modifier locus in familial Mediterranean fever. *Arthritis Rheum.* 2001;44:163-169.
- Matzner Y, Partridge RE, Levy M, Babior BM. Diminished activity of a chemotactic inhibitor in synovial fluids from patients with familial Mediterranean fever. *Blood.* 1984;63:629-633.
- Matzner Y, Brzezinski A. C5 a-inhibitor deficiency in peritoneal fluids from patients with familial Mediterranean fever. *N Engl J Med.* 1984;311:287-290.
- Peter M, Rosenberg SEG. Clinical manifestations and diagnosis of familial Mediterranean fever. © 2013. 2011. [UpToDate].
- Kees S, Langevitz P, Zemer D, Padeh S, Pras M, Livneh A. Attacks of pericarditis as a manifestation of familial Mediterranean fever (FMF). *Q J Med.* 1997;90:643-647.
- Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and review of the literature. *Am J Med.* 1967;43:227-253.
- Majeed HA, Quabazard Z, Hijazi Z, Farwana S, Harshani F. The cutaneous manifestations in children with familial Mediterranean fever (recurrent hereditary polyserositis). A six-year study. *Q J Med.* 1990;75:607-616.
- Gedalia A, Adar A, Gorodischer R. Familial Mediterranean fever in children. *J Rheumatol Suppl.* 1992;35:1-9.
- Rawashdeh MO, Majeed HA. Familial mediterranean fever in Arab children: the high prevalence and gene frequency. *Eur J Pediatr.* 1996;155:540-544.
- Barzilai A, Langevitz P, Goldberg I, et al. Erysipelas-like erythema of familial Mediterranean fever: clinicopathologic correlation. *J Am Acad Dermatol.* 2000;42:791-795.
- Ozen S, Ben-Chetrit E, Bakkaloglu A, et al. Polyarteritis nodosa in patients with familial Mediterranean fever (FMF): a concomitant disease or a feature of FMF? *Semin Arthritis Rheum.* 2001;30:281-287.
- Ozdogan H, Arisoy N, Kasapcapur O, et al. Vasculitis in familial Mediterranean fever. *J Rheumatol.* 1997;24:323-327.
- Bosacki C, Richard O, Freycon F, Mosnier JF, Cathebras P. The association of polyarteritis nodosa and familial Mediterranean fever. *Presse Med.* 2003;32:24-26.
- Tinaztepe K, Gucer S, Bakkaloglu A, Tinaztepe B. Familial Mediterranean fever and polyarteritis nodosa: experience of five

- paediatric cases. A causal relationship or coincidence? *Eur J Pediatr.* 1997;156:505-506.
30. Peter M, Rosenberg SEG. Management of familial Mediterranean fever. © 2013. 2010. [UpToDate].
  31. Seyahi E, Ozdogan H, Celik S, Ugurlu S, Yazici H. Treatment options in colchicine resistant familial Mediterranean fever patients: thalidomide and etanercept as adjunctive agents. *Clin Exp Rheumatol.* 2006;24:S99-S103.
  32. Calligaris L, Marchetti F, Tommasini A, Ventura A. The efficacy of anakinra in an adolescent with colchicine-resistant familial Mediterranean fever. *Eur J Pediatr.* 2008;167:695-696.
  33. Hull KM, Drewe E, Aksentjevich I, et al. The TNF receptor-associated periodic syndrome (TRAPS): emerging concepts of an autoinflammatory disorder. *Medicine (Baltimore).* 2002;81:349-368.
  34. Toro JR, Aksentjevich I, Hull K, Dean J, Kastner DL. Tumor necrosis factor receptor-associated periodic syndrome: a novel syndrome with cutaneous manifestations. *Arch Dermatol.* 2000;136:1487-1494.
  35. McDermott MF, Ogunkolade BW, McDermott EM, et al. Linkage of familial Hibernian fever to chromosome 12 p13. *Am J Hum Genet.* 1998;62:1446-1451.
  36. Mulley J, Saar K, Hewitt G, et al. Gene localization for an autosomal dominant familial periodic fever to 12 p13. *Am J Hum Genet.* 1998;62:884-889.
  37. Kallinich T, Haffner D, Rudolph B, et al. "Periodic fever" without fever: two cases of non-febrile TRAPS with mutations in the TNFRSF1 A gene presenting with episodes of inflammation or monosymptomatic amyloidosis. *Ann Rheum Dis.* 2006;65:958-960.
  38. Kallinich T, Briese S, Roesler J, et al. Two familial cases with tumor necrosis factor receptor-associated periodic syndrome caused by a non-cysteine mutation (T50 M) in the TNFRSF1 A gene associated with severe multiorganic amyloidosis. *J Rheumatol.* 2004;31:2519-2522.
  39. Kanazawa N, Furukawa F. Autoinflammatory syndromes with a dermatological perspective. *J Dermatol.* 2007;34:601-608.
  40. Nigrovic PA. Tumor necrosis factor receptor-1 associated periodic syndrome (TRAPS). © 2013. 2012. [UpToDate].
  41. Grose C, Renee Schnetzer J, Ferrante A, Vladutiu AO. Children with hyperimmunoglobulinemia D and periodic fever syndrome. *Pediatr Infect Dis J.* 1996;15:72-77.
  42. Drenth JPH, Haagsma CJ, Van der Meer JWM, et al. Hyperimmunoglobulinemia D and periodic fever syndrome. The clinical spectrum in a series of 50 patients. *Medicine.* 1994;73:133-144.
  43. Simon A, Cuisset L, Vincent MF, et al. Molecular analysis of the mevalonate kinase gene in a cohort of patients with the hyper-igd and periodic fever syndrome: its application as a diagnostic tool. *Ann Intern Med.* 2001;135:338-343.
  44. Houten SM, Koster J, Romeijn GJ, et al. Organization of the mevalonate kinase (MVK) gene and identification of novel mutations causing mevalonic aciduria and hyperimmunoglobulinaemia D and periodic fever syndrome. *Eur J Hum Genet.* 2001;9:253-259.
  45. Houten SM, van Woerden CS, Wijburg FA, Wanders RJ, Waterham HR. Carrier frequency of the V377 I (1129 G>A) MVK mutation, associated with Hyper-IgD and periodic fever syndrome, in the Netherlands. *Eur J Hum Genet.* 2003;11:196-200.
  46. Drenth JP, Cuisset L, Grateau G, et al. Mutations in the gene encoding mevalonate kinase cause hyper-IgD and periodic fever syndrome. International Hyper-IgD Study Group. *Nat Genet.* 1999; 22:178-181.
  47. Houten SM, Frenkel J, Rijkers GT, Wanders RJ, Kuis W, Waterham HR. Temperature dependence of mutant mevalonate kinase activity as a pathogenic factor in hyper-IgD and periodic fever syndrome. *Hum Mol Genet.* 2002;11:3115-3124.
  48. Drenth JP, Haagsma CJ, van der Meer JW. Hyperimmunoglobulinemia D and periodic fever syndrome. The clinical spectrum in a series of 50 patients. International Hyper-IgD Study Group. *Medicine (Baltimore).* 1994;73:133-144.
  49. Yoram C, Padeh AR. Hyperimmunoglobulin-D syndrome: pathophysiology. © 2013. 2012. [UpToDate].
  50. Armbrust S, Drenth JP, Schroder C, Domning E, Poeschl E, Wiersbitzky SK. Tendonitis in variant hyperimmunoglobulinaemia D and periodic fever syndrome—a rare disease with a new symptom. *Eur J Pediatr.* 2005;164:391-394.
  51. Kraus CL, Culican SM. Nummular keratopathy in a patient with Hyper-IgD Syndrome. *Pediatr Rheumatol Online J.* 2009;7:14.
  52. van der Hilst JC, Simon A, Drenth JP. Hereditary periodic fever and reactive amyloidosis. *Clin Exp Med.* 2005;5:87-98.
  53. Di Rocco M, Caruso U, Waterham HR, Picco P, Loy A, Wanders RJ. Mevalonate kinase deficiency in a child with periodic fever and without hyperimmunoglobulinaemia D. *J Inher Metab Dis.* 2001;24:411-412.
  54. Drenth JP, Boom BW, Toonstra J, Van der Meer JW. Cutaneous manifestations and histologic findings in the hyperimmunoglobulinemia D syndrome. International Hyper IgD Study Group. *Arch Dermatol.* 1994;130:59-65.
  55. Yoram C, Padeh AR. Hyperimmunoglobulin-D syndrome: management. © 2013. 2012. [UpToDate].
  56. Valenzuela PM, Majerson D, Tapia JL, Talesnik E. Syndrome of periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) in siblings. *Clin Rheumatol.* 2009;28:1235-1237.
  57. Padeh S, Brezniak N, Zemer D, et al. Periodic fever, aphthous stomatitis, pharyngitis, and adenopathy syndrome: clinical characteristics and outcome. *J Pediatr.* 1999;135:98-101.
  58. Thomas KT, Feder Jr HM, Lawton AR, Edwards KM. Periodic fever syndrome in children. *J Pediatr.* 1999;135:15-21.
  59. Stojanov S, Hoffmann F, Kery A, et al. Cytokine profile in PFAPA syndrome suggests continuous inflammation and reduced anti-inflammatory response. *Eur Cytokine Netw.* 2006;17:90-97.
  60. Padeh S. Periodic fever with aphthous stomatitis, pharyngitis and adenitis (PFAPA syndrome). © 2013. 2012. [UpToDate].
  61. Berkun Y, Levy R, Hurwitz A, et al. The familial Mediterranean fever gene as a modifier of periodic fever, aphthous stomatitis, pharyngitis, and adenopathy syndrome. *Semin Arthritis Rheum.* 2011;40:467-472.
  62. Neven B, Callebaut I, Prieur AM, et al. Molecular basis of the spectral expression of CIAS1 mutations associated with phagocytic cell-mediated autoinflammatory disorders CINCA/NOMID, MWS, and FCU. *Blood.* 2004;103:2809-2815.
  63. Neven B, Prieur AM, Quartier dit Maire P. Cryopyrinopathies: update on pathogenesis and treatment. *Nat Clin Pract Rheumatol.* 2008;4: 481-489.
  64. Eisenbarth SC, Colegio OR, O'Connor W, Sutterwala FS, Flavell RA. Crucial role for the Nalp3 inflammasome in the immunostimulatory properties of aluminium adjuvants. *Nature.* 2008;453:1122-1126.
  65. Aksentjevich I, C DP, Remmers EF, Mueller JL, et al. The clinical continuum of cryopyrinopathies: novel CIAS1 mutations in North American patients and a new cryopyrin model. *Arthritis Rheum.* 2007;56:1273-1285.
  66. Hoffman HM, Wanderer AA, Broide DH. Familial cold autoinflammatory syndrome: phenotype and genotype of an autosomal dominant periodic fever. *J Allergy Clin Immunol.* 2001;108:615-620.
  67. Doeglas HM, Bleumink E. Familial cold urticaria. Clinical findings. *Arch Dermatol.* 1974;110:382-388.
  68. Peroni A, Colato C, Zanoni G, Girolomoni G. Urticarial lesions: if not urticaria, what else? The differential diagnosis of urticaria: Part II. Systemic diseases. *J Am Acad Dermatol.* 2010;62:557-570. [quiz 71–72].
  69. Muckle TJ, Wells M. Urticaria, deafness, and amyloidosis: a new heredo-familial syndrome. *Q J Med.* 1962;31:235-248.
  70. Aganna E, Martinon F, Hawkins PN, et al. Association of mutations in the NALP3/CIAS1/PYPAF1 gene with a broad phenotype including recurrent fever, cold sensitivity, sensorineural deafness, and AA amyloidosis. *Arthritis Rheum.* 2002;46:2445-2452.
  71. Muckle TJ. The 'Muckle-Wells' syndrome. *Br J Dermatol.* 1979;100: 87-92.
  72. Aksentjevich I, Nowak M, Mallah M, et al. De novo CIAS1 mutations, cytokine activation, and evidence for genetic heterogeneity in patients with neonatal-onset multisystem inflammatory disease

- (NOMID): a new member of the expanding family of pyrin-associated autoinflammatory diseases. *Arthritis Rheum.* 2002;46:3340-3348.
73. Goldfinger S. The inherited autoinflammatory syndrome: a decade of discovery. *Trans Am Clin Climatol Assoc.* 2009;120:413-418.
  74. Ahmadi N, Brewer CC, Zalewski C, et al. Cryopyrin-associated periodic syndromes: otolaryngologic and audiologic manifestations. *Otolaryngol Head Neck Surg.* 2011;145:295-302.
  75. Prieur AM. A recently recognised chronic inflammatory disease of early onset characterised by the triad of rash, central nervous system involvement and arthropathy. *Clin Exp Rheumatol.* 2001;19:103-106.
  76. Goldbach-Mansky R, Dailey NJ, Canna SW, et al. Neonatal-onset multisystem inflammatory disease responsive to interleukin-1(beta) inhibition. *N Engl J Med.* 2006;355:581-592.
  77. Huttenlocher A, Frieden IJ, Emery H. Neonatal onset multisystem inflammatory disease. *J Rheumatol.* 1995;22:1171-1173.
  78. Nigrovic PA. Cryopyrin-associated periodic syndromes and related disorders. © 2013. 2012. [UpToDate].
  79. Minkis K, Aksentijevich I, Goldbach-Mansky R, et al. Interleukin 1 receptor antagonist deficiency presenting as infantile pustulosis mimicking infantile pustular psoriasis. *Arch Dermatol.* 2012;148:747-752.
  80. Brau-Javier CN, Gonzales-Chavez J, Toro JR. Chronic cutaneous pustulosis due to a 175-kb deletion on chromosome 2 q13: excellent response to anakinra. *Arch Dermatol.* 2012;148:301-304.
  81. Reddy S, Jia S, Geoffrey R, et al. An autoinflammatory disease due to homozygous deletion of the IL1 RN locus. *N Engl J Med.* 2009;360:2438-2444.
  82. Aksentijevich I, Masters SL, Ferguson PJ, et al. An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist. *N Engl J Med.* 2009;360:2426-2437.
  83. Altiok E, Aksoy F, Perk Y, et al. A novel mutation in the interleukin-1 receptor antagonist associated with intrauterine disease onset. *Clin Immunol.* 2012;145:77-81.
  84. Jesus AA, Osman M, Silva CA, et al. A novel mutation of IL1 RN in the deficiency of interleukin-1 receptor antagonist syndrome: description of two unrelated cases from Brazil. *Arthritis Rheum.* 2011;63:4007-4017.
  85. Onoufriadis A, Simpson MA, Pink AE, et al. Mutations in IL36RN/IL1 F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis. *Am J Hum Genet.* 2011;89:432-437.
  86. Marrakchi S, Guigue P, Renshaw BR, et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. *N Engl J Med.* 2011;365:620-628.
  87. Cowen EW, Goldbach-Mansky R. DIRA, DITRA, and new insights into pathways of skin inflammation: what's in a name? *Arch Dermatol.* 2012;148:381-384.
  88. Viguier M, Guigue P, Pages C, Smahi A, Bachelez H. Successful treatment of generalized pustular psoriasis with the interleukin-1-receptor antagonist Anakinra: lack of correlation with IL1 RN mutations. *Ann Intern Med.* 2010;153:66-67.
  89. Lindor NM, Arsenaault TM, Solomon H, Seidman CE, McEvoy MT. A new autosomal dominant disorder of pyogenic sterile arthritis, pyoderma gangrenosum, and acne: PAPA syndrome. *Mayo Clin Proc.* 1997;72:611-615.
  90. Yeon HB, Lindor NM, Seidman JG, Seidman CE. Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome maps to chromosome 15 q. *Am J Hum Genet.* 2000;66:1443-1448.
  91. Hong JB, Su YN, Chiu HC. Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome (PAPA syndrome): report of a sporadic case without an identifiable mutation in the CD2 BP1 gene. *J Am Acad Dermatol.* 2009;61:533-535.
  92. Demidowich AP, Freeman AF, Kuhns DB, et al. Genotype, phenotype, and clinical course in five patients with PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum, and acne). *Arthritis Rheum.* 2012;64:2022-2027.
  93. Demidowich AP, Freeman AF, Kuhns DB, et al. Brief report: genotype, phenotype, and clinical course in five patients with PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum, and acne). *Arthritis Rheum.* 2012;64:2022-2027.
  94. Ter Haar N, Lachmann H, Ozen S, et al. Treatment of autoinflammatory diseases: results from the Eurofever Registry and a literature review. *Ann Rheum Dis.* 2012;72:678-685.
  95. Miceli-Richard C, Lesage S, Rybojad M, et al. CARD15 mutations in Blau syndrome. *Nat Genet.* 2001;29:19-20.
  96. Kanazawa N, Okafuji I, Kambe N, et al. Early-onset sarcoidosis and CARD15 mutations with constitutive nuclear factor-(kappa)B activation: common genetic etiology with Blau syndrome. *Blood.* 2005;105:1195-1197.
  97. Rose CD, Doyle TM, McIlvain-Simpson G, et al. Blau syndrome mutation of CARD15/NOD2 in sporadic early onset granulomatous arthritis. *J Rheumatol.* 2005;32:373-375.
  98. Rose CD, Arostegui JI, Martin TM, et al. NOD2-associated pediatric granulomatous arthritis, an expanding phenotype: study of an international registry and a national cohort in Spain. *Arthritis Rheum.* 2009;60:1797-1803.
  99. Rose CD, Wouters CH, Meiorin S, et al. Pediatric granulomatous arthritis: an international registry. *Arthritis Rheum.* 2006;54:3337-3344.
  100. Kambe N, Nishikomori R, Kanazawa N. The cytosolic pattern-recognition receptor Nod2 and inflammatory granulomatous disorders. *J Dermatol Sci.* 2005;39:71-80.
  101. Blau EB. Familial granulomatous arthritis, iritis, and rash. *J Pediatr.* 1985;107:689-693.
  102. Manouvrier-Hanu S, Puech B, Piette F, et al. Blau syndrome of granulomatous arthritis, iritis, and skin rash: a new family and review of the literature. *Am J Med Genet.* 1998;76:217-221.
  103. Arostegui JI, Arnal C, Merino R, et al. NOD2 gene-associated pediatric granulomatous arthritis: clinical diversity, novel and recurrent mutations, and evidence of clinical improvement with interleukin-1 blockade in a Spanish cohort. *Arthritis Rheum.* 2007;56:3805-3813.
  104. Majeed HA, El-Shanti H, Al-Rimawi H, Al-Masri N. On mice and men: an autosomal recessive syndrome of chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia. *J Pediatr.* 2000;137:441-442.
  105. Majeed HA, Al-Tarawna M, El-Shanti H, Kamel B, Al-Khalailah F. The syndrome of chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anaemia. Report of a new family and a review. *Eur J Pediatr.* 2001;160:705-710.
  106. Ferguson PJ, Chen S, Tayeh MK, et al. Homozygous mutations in LPIN2 are responsible for the syndrome of chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anaemia (Majeed syndrome). *J Med Genet.* 2005;42:551-557.
  107. Herlin T, Fiirgaard B, Bjerre M, et al. Efficacy of anti-IL-1 treatment in Majeed syndrome. *Ann Rheum Dis.* 2012;72:410-413.
  108. Al-Mosawi ZS, Al-Saad KK, Ijadi-Maghsoodi R, El-Shanti HI, Ferguson PJ. A splice site mutation confirms the role of LPIN2 in Majeed syndrome. *Arthritis Rheum.* 2007;56:960-964.
  109. El-Shanti H, Ferguson P. Majeed Syndrome. In: Pagon RA, Adam MP, Ardinger HH, Bird TD, Dolan CR, Fong CT, Smith RJH, Stephens K, eds. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2014. 2008 Sep 23 [updated 2013 Mar 14].
  110. Torrello A, Patel S, Colmenero I, et al. Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome. *J Am Acad Dermatol.* 2010;62:489-495.
  111. Liu Y, Ramot Y, Torrello A, et al. Mutations in proteasome subunit beta type 8 cause chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature with evidence of genetic and phenotypic heterogeneity. *Arthritis Rheum.* 2012;64:895-907.