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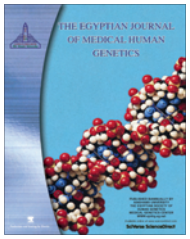

REVIEW

Hereditary periodic fever syndromes

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Abstract Hereditary periodic fever syndromes, comprise a group of hereditary disorders with similar clinical features of recurrent short episodes of fever associated with inflammatory manifestations. These are usually self-limited in nature and occur in the absence of infection or autoimmune reaction. Between attacks, patients feel well and regain their normal daily functions until the next episode occurs. The episodes are usually associated with elevated serum levels of acute-phase reactants (e.g., fibrinogen, serum amyloid A [SAA]), an elevated erythrocyte sedimentation rate (ESR), and leukocytosis. These illnesses represent inborn errors in the regulation of innate immunity thus substantiating the distinction from autoimmune disorders, which more directly affect the adaptive immune system. Each of these disorders has a distinct genetic defect. Most of these proteins are members of the Death Domain Superfamily and are involved in inflammation and apoptosis. These proteins mediate the regulation of nuclear factor-kB (NF-kB), cell apoptosis, and interleukin 1β (IL-1β) secretion through cross-regulated and common signaling pathways. Six periodic fever syndromes have been characterized. Genetic defects, pathogenesis, epidemiology and management of these fevers will be discussed.

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Contents

1. Background

Hereditary periodic fever syndromes (HPFSs) are rare and distinct heritable disorders characterized by short and recurrent attacks of fever and severe localized inflammation that occur periodically or irregularly and that are not explained by usual childhood infections. These attacks undergo spontaneous remission without antibiotic, anti-inflammatory, or immunosuppressive treatment. Between attacks, patients feel well and regain their normal daily functions until the next episode occurs. The episodes are usually associated with elevated serum levels of acute-phase reactants (e.g., fibrinogen, serum amyloid A [SAA]), an elevated erythrocyte sedimentation rate (ESR), and leukocytosis [1]. They were initially described as affecting primarily the serosal and synovial surfaces and the skin, but now recognized to include a somewhat broader distribution of affected tissues [2]. They differ from autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis in that they lack high-titer autoantibodies or antigen-specific T-cells. They are termed autoinflammatory diseases [3]. Advances in the genetics and molecular biology of the hereditary periodic fever syndromes have defined important new gene families and

Table 1 Summarizes the gene symbols, chromosomal loci, protein products, and modes of inheritance of these diseases [1].

Syndrome	Gene and Locus	Protein	Mode of Inheritance
FMF	*MEFV,* 16P13.3	Pyrin, marenostrin	Autosomal recessive
HIDS	*MVK,* 12q24	Mevalonate kinase (MK)	Autosomal recessive
TRAPS	*TNFRSF1,* 12p13	TNF-receptor type 1	Autosomal dominant
MWS	*NLRP3 (CIAS1),* 1q44	Cryopyrin (NALP3/ PYPAF1)	Autosomal dominant
FCAS	*NLRP3 (CIAS1),* 1q44	Cryopyrin (NALP3/ PYPAF1)	Autosomal dominant
CINCA	*NLRP3 (CIAS1),* 1q44	Cryopyrin (NALP3/ PYPAF1)	Autosomal dominant

pathways in the regulation of innate immunity, thus substantiating the distinction from autoimmune disorders, which more directly affect the adaptive immune system [4].

2. Types

Six periodic fever diseases have been well characterized over the last few years. They include familial mediterranean fever (FMF), followed by tumor necrosis factor (TNF)–receptor-associated periodic syndrome (TRAPS), and hyperimmunoglobulinemia D syndrome (HIDS). Additional syndromes include Muckle–Wells syndrome (MWS); familial cold urticaria (FCU), known also as familial cold autoinflammatory syndrome (FCAS); and chronic infantile neurological cutaneous and articular disease (CINCA), also known as neonatal onset multisystemic inflammatory disease (NOMID) [5–8], Table 1.

Another periodic fever syndrome is periodic fever, adenopathy, and pharyngitis with aphthous ulcerations (PFAPA), but it is not classified as a human autoinflammatory syndrome [9].

The differential diagnosis for periodic fever spectrum of diseases is wide and includes infectious, malignant, and autoimmune disorders, as well as factitious and iatrogenic fever. If these attacks persist for longer than 1 year and, especially if they are associated with a family history of periodic fever, the possibility of HPFS should be raised [1].

3. Genetic defects and general pathogenesis

Each of these disorders has a distinct genetic defect which leads to mutations in NAIP proteins. Most of these proteins are members of the Death Domains Superfamily and are involved in inflammation and apoptosis. These proteins mediate the regulation of nuclear factor-kB (NF-kB), cell apoptosis, and interleukin 1β (IL-1β) secretion through cross-regulated and common signaling pathways [9].

HPFs are Mendelian disorders associated with sequence variations in very few genes. These variations are mostly missense mutations with deleterious effects. The mutations involve NALP proteins, also known as NLRPs, belong to the CATERPILLER protein family, like Toll-like receptors, involved in the recognition of microbial molecules and the subsequent activation of inflammatory and immune responses [10].

3.1. Familial mediterranean fever (FMF)

FMF, also known as recurrent hereditary polyserositis, [1], is the most common entity among the group of periodic fever syndromes[9].

3.1.1. Pathogenesis

The gene responsible for FMF is mapped to a small interval on the short arm of chromosome 16p13.3. The FMF gene, designated MEFV (ME for Mediterranean and FV for fever). It is approximately 10 KB with 10 exons that express a 3.7-kb transcript encoding a 781 amino acid protein known as *pyrin*, or *marenostrin*, which is expressed in myeloid cells [9]; as MEFV is expressed predominantly in granulocytes, monocytes, dendritic cells, and in fibroblasts derived from skin, peritoneum, and synovium [11–13]. More than 50 mutations have been discovered, mostly of missense type. The five most common mutations (M694V, V726A, M694I, M680I, and E148Q) are found in more than two thirds of Mediterranean patients with FMF. The most common missense mutation is M694V (substitution of methionine with valine at codon 694), which occurs in 20–67% of cases and is associated with full penetrance. Homozygosity for M694V is associated with a greater disease severity and a higher incidence of amyloidosis. The V726A mutation occurs in 7–35% of cases and is associated with milder disease and a lower incidence of amyloidosis. The E148Q mutation is associated with low penetrance and very mild phenotype. These findings suggest that phenotypic differences may reflect different mutations. As with other recessive diseases, it is likely that some heterozygous patients may show attenuated clinical symptoms, with or without increased levels of acute phase reactants [9].

3.1.2. Epidemiology

FMF predominantly affects populations living in the Mediterranean region, especially North African Jews, Armenians, Turks, and Arabs. Among Armenians with FMF, the spectrum of mutations is similar to that in the non-Ashkenazi Jewish population [14]. The clinical picture of FMF in Arabs appears to be distinct, and the range and distribution of MEFV mutations are different from those noted in other ethnic groups [15].

Unlike the Jewish, Armenian, and Turkish populations, Ozturk et al. [16] did not find a single predominant mutation in Egyptian patients with FMF. The diversity of mutations among Egyptians was reported before [17] and could be related to the heterogeneous origin of the Egyptian population and the effect of different civilization marks (such as Romans, Byzantines, and Ottomans beside the original inhabitants, the Arabs) left on this country since ancient times because of its unique location at the crossroads between Africa, Europe, and Asia. In Egypt, there were five main founder mutations accounting for the vast majority of cases of FMF which were V726A, M694V, M680I, E148Q, and M694I [18]. Also R202Q and P706 might be disease-causing mutations [16].

The male-to-female ratio of cases is about 1.5–2:1, raising the possibility that the mutation has reduced penetrance in women. Many women report that attacks occur most commonly with menses and disappears during pregnancy and return after delivery. This pattern suggests that female sex hormones might influence the disease [19]. Furthermore, the risk of renal amyloidosis is higher in men than in women [20,21].

Approximately 90% of patients are younger than 20 years, and 60% of patients are younger than 10 years. Late-onset disease is usually more clinically benign than early-onset disease [1].

3.1.3. Clinical picture

FMF is divided into two phenotypes, type 1 and 2:

- **FMF type 1** is characterized by recurrent short episodes of inflammation and serositis including fever, peritonitis, synovitis, pleuritis, and, rarely, pericarditis and meningitis. The symptoms vary among affected individuals, sometimes even among members of the same family. Amyloidosis, which can lead to renal failure, is the most severe complication of FMF type 1.
- **FMF type 2** is characterized by amyloidosis as the first clinical manifestation of disease in an otherwise asymptomatic individual. [22–25].

Patients with FMF have recurrent acute febrile painful attacks that last 12 h to 4 days. The pain usually involves 1–2 of the following sites at a time: abdomen 90%, chest 40%, joints 70%, muscles, scrotum 5%, and skin [1].

Abdominal attacks start with the sudden onset of fever and pain affecting the entire abdomen [26]. The febrile joint attacks, manifest as recurrent episodes of nondestructive acute monoarthritis of short duration and most frequently involve the large joints of lower extremities [27]. In about 1% of patients, it is the sole disease manifestation. Myalgia is a frequent finding in patients with familial Mediterranean fever [1]. The febrile chest attacks manifest as pleuritis. Patients have unilateral chest pain that increases on inspiration [28]. The inflammation of the tunica vaginalis testis causes a picture of acute scrotum. It usually results in self-limited, unilateral, red painful swelling of the scrotum [1]. Erysipelas-like erythema is characterized by fever and hot, tender, swollen, sharply bordered red lesions that are typically 10–35 cm^2 in area and occur mainly on the legs, between the ankle and the knee, or on the dorsum of the foot, that last 1–2 days. Isolated temperature elevation lasting a few hours can occur without any pain or inflammation [29].

3.1.4. Complications

Amyloidosis type AA amyloidosis is common in untreated individuals. It presents with persistent, heavy proteinuria leading to nephrotic syndrome and progressive nephropathy leading to end-stage renal disease (ESRD). With increased longevity of individuals with renal failure through dialysis and/or renal transplantation, amyloid deposits are being found in other organs as well [24,30]. Although this condition is mainly related to the M694V homozygous genotype, it is also reported in association with other genotypes that confer a relatively mild form of the disease. Furthermore, renal amyloidosis can occur in asymptomatic individuals who do not have attacks of serositis (phenotype II) [31].

The age of onset of FMF attacks appears to be lower in persons with amyloidosis than in those without amyloidosis. FMF-related manifestations of chest pain, arthritis, and erysipelas-like erythema are more common in those with amyloidosis. Long periods between disease onset and diagnosis are associated with a high risk of developing amyloidosis [32].

3.1.5. Diagnosis

The diagnostic criteria include [33]:

- Major criteria.
  - ○ Recurrent febrile episodes of peritonitis, synovitis, or pleuritis.
  - ○ Amyloid-associated protein (AA)–type amyloidosis with no predisposing disease.
  - ○ Favorable response to continuous colchicine treatment.

- Minor criteria.
  - ○ Recurrent febrile episodes.
  - ○ Erysipelaslike erythema.
  - ○ FMF in a first-degree relatives.

A definitive diagnosis is based on two major or one major and two minor criteria. A probable diagnosis is based on one major and one minor criteria. Most cases are currently confirmed with molecular testing [33].

3.1.5.1. Laboratory studies. Targeted mutation analysis and sequence analysis of selected exons [29].

During attacks, there is increased levels of acute-phase reactants (C-reactive protein, serum amyloid A, fibrinogen, haptoglobin, C3, and C4). Urinalysis demonstrates transient albuminuria and microscopic hematuria. The synovial fluid is cloudy, filled with polymorphonuclear (PMN) cells, and sterile [1].

3.1.6. Management

3.1.6.1. Treatment of manifestations. Febrile and inflammatory episodes are usually treated with nonsteroidal anti-inflammatory drugs (NSAIDs). ESRD should be treated as for other causes of renal failure. The long-term outcome of live related-donor renal transplantation in individuals with FMF-amyloidosis is similar to that in the general transplant population [34].

3.1.6.2. Prevention of primary manifestations.

- Colchicine therapy

Homozygous or compound heterozygous for the mutation Met694Val should be treated with colchicine. Colchicine is given orally for life, 1–2 mg/day in adults. Children may need 0.5–1 mg/day according to age and weight [29]. Individuals who do not have the mutation and who are only mildly affected should either be treated with colchicine or monitored every 6 months for the presence of proteinuria. Continuous treatment with colchicine appears to be less indicated for individuals who are homozygous or compound heterozygous for the mutation Glu148Gln [29].

Complications of colchicine occasionally include myopathy, toxic epidermal necrolysis-like reaction and oligospermia. Colchicine should be continued in pregnancy. Treatment with colchicine 1 mg/day prevents renal amyloidosis even if the FMF attacks do not respond to the drug.

- Anakinra therapy

It is an IL-1-receptor inhibitor which offers a recently safe and effective treatment (100 mg daily or every other day) for persons who do not respond to colchicine [35–41]. This drug is expensive and has mild side effects, such as painful local reactions at the site of injections and possibly bronchopulmonary infection complications. Also further studies are needed if it is to be taken continuously as required in severely affected individuals with FMF.

3.2. Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS)

The disorder has also been described as a variant of Still's disease [42,43] or as etiocholanolone fever [44].

3.2.1. Pathogenesis

It is caused by mutations in the mevalonate kinase (MVK) gene found on chromosome 12 at 12q24. Mevalonate kinase is an enzyme that enhances the metabolism of mevalonic acid, an intermediary product of cholesterol and isoprenoid synthesis pathways. It is speculated that shortage of isoprenoid end products contributes to increased secretion of IL-1β, which subsequently leads to overt inflammation and fever. More than 40 different mutations of the MVK gene have been reported.

The most common mutation is V377I, likely of Dutch origin. Mutations are associated with decreased activity of mevalonate kinase in lymphocytes, leading to increased plasma levels of mevalonic acid, which is excreted in large amounts in the urine [9].

3.2.2. Epidemiology

This condition is reported primarily among families of European descent, especially Dutch and French [9]. The male-to-female ratio was equal in one study [45] but about 3:2 in another large series [46], which raises the possibility of reduced penetrance in women. Most patients have attacks before the end of their first year of life (median, 0.5 years). The attacks persist throughout life, although patients have a reduction in intensity and frequency of attacks after adolescence [1].

3.2.3. Clinical picture

Episodic attacks of fever occur every 4–8 weeks [1], last 3–7 days and are sometimes triggered by childhood immunizations. Minor trauma, surgery, and stress are known aggravating conditions [47]. Attacks manifest as high, spiking fever and is preceded by chills in 76% of patients [46]. Abdominal pain was reported in 72%, vomiting in 56%, diarrhea in 82%, and headache in 52%, polyarthralgia in 80% and a nondestructive arthritis in 68% of patients, skin lesions in 82%, and serositis in a minority of patients. Surprisingly, amyloidosis has not been recorded in any of the patients with this syndrome [1].

3.2.3.1. Diagnosis. Diagnostic criteria [46,47]:

- Constant: High IgD level (> 100 U/mL) measured on two occasions at least 1 month apart.
- During attacks:
  - ○ Elevated erythrocyte sedimentation rate (ESR) and leukocytosis.
  - ○ Abrupt onset of fever (temperature at least 38.5 °C).
  - ○ Recurrent attacks.
  - ○ Elevated immunoglobulin A (IgA) level.
  - ○ Cervical lymphadenopathy.
  - ○ Abdominal distress (vomiting, diarrhea, pain) ([67]).
  - ○ Skin manifestations (erythematous macules and papules).
  - ○ Arthralgias and/or arthritis.
  - ○ Splenomegaly.
  - ○ Measure urinary mevalonic acid (slight elevation).
  - ○ Genetic testing to screen for the most common V377I mutation.
  - ○ In rare cases, measure MK activity.

3.2.4. Differential diagnosis

Mevalonic aciduria (MVA) is typically a disease of infantile onset. It is characterized by psychomotor retardation, ataxia, failure to thrive, cataracts, and dysmorphic features [48–50]. Patients also have severe periodic fever attacks.

3.2.5. Treatment

Treatment is largely supportive because various standard anti-inflammatory drugs (including colchicine and steroids) fail to suppress the attacks [1]. Thalidomide resulted in a nonsignificant decrease of acute phase protein synthesis but without an effect on the attack rate [47]. A trial of simvastatin showed a beneficial clinical effect in five of six patients [9] and a decrease in the urinary mevalonic acid concentration in all patients. No adverse effects were observed [1]

3.3. Tumor necrosis factor receptor-associated periodic syndrome (TRAPs)

This syndrome was previously known by other names, including (Familial Hibernian fever, Familial periodic fever, and Autosomal dominant recurrent fever [9].

3.3.1. Pathogenesis

TRAPs is an autosomal dominant periodic fever It is caused by mutation in the soluble TNF receptor superfamily 1A gene, TNFRSF1A. It is on chromosome 12 at 12p13 and encodes for type 1A TNF receptor protein. More than 40 different mutations of the gene have been reported [9]. Most mutations in TNFRSF1A mediate their effect via decreased shedding of TNFRSF1A, thereby decreasing the amount of soluble receptor available to bind soluble TNF and subsequently initiate and maintain the inflammatory response. Defective shedding only partially explains the pathophysiologic mechanism of TRAPs because some mutations have normal shedding [51]. The dramatic response for etanercept, an anti-TNF agent, suggests that TNF plays a critical role in the inflammatory process of this disease [1].

3.3.2. Epidemiology

Most patients are of northern European descent. However mutations have been reported among patients from different ethnicities, including African American, French, Belgian, Dutch, Arab, Jewish, Irish, Scottish, and many other ethnicities [52].

A male-to-female ratio of 3:2 is reported [52]. The reason that women are more protected than men is still unknown [1].

Age ranges from 2 weeks to 53 years (median 3 years). The age of onset varies within and among families.

3.3.3. Clinical picture

On average, the attacks occur once every 6 weeks and last longer than 1 week. Few patients have daily pain without a clear resolution of symptoms. Abdominal and chest pain occur in 90% and 60% of patients, respectively. Arthralgia of the large joints is common, but arthritis is rare. Painful unilateral or bilateral conjunctivitis and periorbital edema are also common. In men, scrotal pain during attacks is reported, and the incidence of inguinal hernia is increased for unknown reasons. The myalgias are severely disabling and are a constant feature. Myalgias usually start the attacks and migrate centrifugally. About 84% of patients have tender, migratory erythematous patches, which typically overlie areas of myalgia and lasting for 4–21 days [53]. The prolonged attacks, conjunctivitis, and localized myalgias differentiate the TRAPS from the other syndromes of periodic fever [54,55]. Amyloidosis develops in up to 25% of the patients, depending on the specific gene mutation and duration of attacks [9].

3.3.4. Diagnostic criteria [52]

- Recurrent episodes of inflammatory symptoms spanning a period longer than 6 months.

- ○ Fever.
- ○ Abdominal pains.
- ○ Migratory myalgia.
- ○ Migratory erythematous patches.
- ○ Conjunctivitis, periorbital edema.
- ○ Chest pain.
- ○ Arthralgia or arthritis.

- Episodes last longer than 5 days on a average.
- Responsive to glucocorticoids but not colchicines.
- Affected family members.
- Any ethnicity.

Patients usually report an increased severity with physical or emotional stress or after physical trauma.

3.3.5. Laboratory studies

Increased levels of acute-phase reactants. The immunoglobulin D (IgD) level may be elevated (< 100 IU/mL), and levels of soluble TNFRSF1A in the serum may be reduced during and between attacks. Polyclonal gammopathy may also be present [1].

3.3.6. Medications

- Etanercept (Enbrel) binds to TNF and blocks its interaction with cell-surface TNF receptors, rendering TNF biologically inactive. It modulates biologic responses that TNF induces or regulates.
- Prednisone.

3.4. The Cryopyrinopathies

The cryopryinopathies are a spectrum of clinical disorders caused by mutations in CIAS1 [56–59] a nine-exon gene on chromosome 1q. Although a number of overlapping syndromes have been described, three relatively distinct clinical disorders are recognized: familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID, also known as chronic infantile neurologic cutaneous and arthropathy [CINCA] syndrome). An urticaria-like rash is common to all of the cryopyrinopathies and is characterized histologically by infiltrates of lymphocytes and neutrophils rather than mast cells, indicating that it is not true urticaria [4,60]. The onset of these syndromes occurs neonatally or during early childhood, usually as a generalized urticaria-like skin rash associated with an intense acute-phase reaction, and different inflammatory manifestations can be observed for each clinical entity [61].

The common genetic basis for these syndromes that has been observed by means of the identification of dominantly inherited mutations in the NLRP3 gene (formerly known as CIAS1, PYPAF1, or NALP3), which encodes for the cryopyrin protein, a key component of the inflammasome [57–59] support the hypothesis that the 3 CAPS diseases actually represent different points along a disease severity spectrum, where FCAS represents the mildest phenotype, MWS the intermediate one, and CINCA/NOMID the severest [60]. Supporting this hypothesis, some clinical cases of overlapping FCAS-MWS and MWS-CINCA/NOMID syndromes have been reported [62,63].

3.4.1. Muckle–Wells Syndrome

It characterized by periodic episodes of non itchy skin rash, fever, joint pain, conjunctivitis, progressive hearing loss, and kidney damage [64]. Patients have recurrent "flare-ups" that arise spontaneously or be triggered by cold, heat, fatigue, or other stresses.

Hearing loss is caused by progressive nerve damage (sensorineural deafness) typically becomes apparent during the teenage years. Amyloidosis cause progressive kidney damage in about one-third of people and these deposits may also damage other organs. In addition, pigmented skin lesions may occur [65].

3.4.1.1. Diagnosis. History of acute febrile inflammatory attacks that last 24–72 h that result in abdominal pain, polyarthralgias, or arthritis (of large joints), myalgia, urticaria (mostly on the trunk and extremities), and conjunctivitis. Late in the course of the disease, sensorineural deafness occurs. This feature distinguishes Muckle–Wells syndrome from other inflammatory disorders. After several years, amyloidosis of the AA type develops.

3.4.1.2. Differential Diagnosis. It includes other HPFSs, Alport syndrome (which has the common features of renal, ear, and ocular involvement), amyloidosis, conjunctivitis, and arthritis [1].

Laboratory tasting: mutation detection. To date, more than 90% of mutations in CAPS have been identified in exon 3 of the NLRP3 (CIAS1) gene [1].

3.4.1.3. Medication.

- The drug of choice for is a selective recombinant IL-1 receptor antagonist, Rilonacept. Common adverse effects include injection site reaction and upper respiratory tract infections. It may interfere with immune response to infections, and serious, life-threatening infections have been reported [1].
- Anakinra, an interleukin 1 receptor antagonist, can lead to an improvement in hearing loss [1,66].

Live vaccines should not be given concurrently [1].

3.4.2. Familial Cold Autoinflammatory Syndrome (FCAS) (familial cold urticaria)

3.4.2.1. Diagnosis. Recurrent urticarial rash is the most consistent trait occurring in all affected subjects. Additional recurrent fever and chills (93%), polyarthralgia (96%), and conjunctivitis (84%). Other commonly reported symptoms after exposure to cold include profuse sweating (78%), drowsiness (67%), headache (58%), extreme thirst (53%), nausea (51%), and myalgia [57]. Arthritis was not reported as a feature of this disease.

3.4.2.2. Differential Diagnosis.

- Acquired cold urticaria (ACU) is one of the most common forms of physical urticaria. The pathophysiology of ACU involves mast-cell degranulation and histamine effects. ACU typically occurs in adulthood and spontaneously resolves. It develops within minutes of direct contact with cold, resolves within hours, and can be accompanied by angioedema, wheezing, and hypotension [1].
- Other HPFS, especially MWS should be considered.

3.4.2.3. Laboratory studies.
- Serum IL-6 concentrations may be high.
- Numbers of mast cells and tissue histamine levels are normal [1].

3.4.2.4. Other tests.
- The ice cube test is performed by placing an ice cube directly on the skin for 5 min. Patients with the disease have no urticaria in response.
- Mutations detection in exon 3 of the NLRP3 (CIAS1) gene.
- **Treatment**

Recombinant IL-1 receptor antagonists (e.g., rilonacept, anakinra, and canakinumab).

3.4.3. Chronic infantile neurologic, cutaneous, articular syndrome (CINCA)
It is also known as neonatal-onset multisystem inflammatory disease (NOMID) [68].

3.4.3.1. History. It is characterized by the triad of skin rash, chronic aseptic meningitis, and arthropathy [69,70]. The typical features include a persistent and migratory urticarial rash (which is often present from birth), fever, adenopathy, hepatosplenomegaly, and a severe and deforming arthropathy (which predominantly affects the large joints). Short episodes of recurrent fevers frequently occur. The arthropathy starts early in life and has distinctive radiographic findings of premature patellar and epiphyseal long-bone ossification and resultant osseous overgrowth that leads to severe joint contractures and disability [71,72].

Progressive neurologic impairment results from chronic aseptic meningitis caused by polymorphonuclear neutrophil (PMN) infiltration. Neurologic manifestations include progressive visual defect and high-frequency hearing loss (which frequently occurs with age), cerebral ventricular dilatation, cerebral atrophy, and mental retardation.

3.4.3.2. Physical examination. Include fever, urticaria like skin rash, splenomegaly and lymphadenopathy, dysmorphic features (saddle-back nose, frontal bossing, and protruding eyes), short stature with short and thick extremities, macrocephaly, finger clubbing, and joint contractures (especially in the knees) without evidence of synovial thickening on palpation. Funduscopic examination may reveal papilledema and uveitis.

3.4.3.3. Laboratory studies.
- Serum IL-6 concentrations may be high.
- Numbers of mast cells and tissue histamine levels are normal [1]
- The ice cube test: no urticaria in response.

3.4.3.4. Medication.
- Treatment with colchicine, NSAIDs, and glucocorticoids may provide some relief.
- Remarkable responses to anakinra in 3 family members with MWS and 18 patients with CINCA have been reported [9].

3.5. Pyogenic arthritis, Pyoderma gangrenosum, and Acne (PAPA) and Blau syndromes

PAPA is an autosomal dominant disorder with mutations in the gene encoding the adaptor protein proline serine threonine phosphatase-interacting protein (PSTPIP1) located on chromosome 15 at 15q24.

Blau syndrome autosomal dominant disorder that manifests with early-onset granulomatous arthritis, uveitis, rash, and flexion contractures at the fingers associated with mutations in the gene encoding CARD15 (caspase recruitment domain 15 protein), known also as NOD2 (nucleotide-binding oligomerization domain 2 protein) located on chromosome 16 at 16q12. These two syndromes are additional rare members of the hereditary periodic fever syndromes family [9].

3.6. Marshall's syndrome or PFAPA (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis) syndrome

It is a pediatric periodic disease characterized by recurrent febrile episodes associated with head and neck symptoms. The origin of this syndrome, which can last for several years, is unknown. During healthy periods, patients grow normally [9].

3.6.1. Clinical picture
PFAPA occurs sporadically with no ethnic predilection. Symptoms begin around 2–6 years of age and include fever, malaise, exudative appearing tonsillitis with negative throat cultures, cervical lymphadenopathy, and aphthae, and, less commonly, headache, abdominal pain, and arthralgia. The episodes last 4–6 days, regardless of antipyretic or antibiotic treatment, and occur at a frequency of 8–12 episodes/year. Findings during the episodes may include mild hepatosplenomegaly, mild leukocytosis, and elevated acute phase reactants. Both the frequency and intensity of the episodes diminish over time [9,73].

3.6.2. Diagnostic criteria [74]
Regularly recurring fevers with an early age of onset (< 5 years of age).

Symptoms in the absence of upper respiratory tract infection with at least one of the following clinical signs:

(a) aphthous stomatitis;
(b) cervical lymphadenitis and
(c) pharyngitis.
Exclusion of cyclic neutropenia.
Completely asymptomatic interval between episodes.
Normal growth and development.

3.6.3. Diagnosis

- Cultures from the oropharynx for bacterial, fungal, and viral pathogens;
- Chest radiography and
- Laboratory studies: leukocytosis and an elevated erythrocyte sedimentation rate during febrile attacks [73].

3.6.4. Treatment
Resolution of symptoms within 24 h after a single dose of prednisone (1–2 mg/kg) or bethamethasone (0.3 mg/kg). Complete resolution has also been reported after tonsillectomy. Affected children grow normally and have spontaneous resolution within 4–8 years with no long-term sequelae [9].

4. Conclusion

Some of these fevers are not rare and should be put in mind in deferential diagnosis of recurrent fever.

They should be differentiated from other causes of acute abdomen, arthralgia, pleuritic pain, other autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis in that they lack high-titer autoantibodies or antigen-specific T-cells.

Conflict of interest

The authors declare that there is no conflict of interest.

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