Autoinflammatory syndromes are defined as recurrent attacks of systemic inflammation that are often unprovoked (or triggered by a minor event) related to a lack of adequate regulation of the innate immune system. Unlike autoimmune diseases, there is a relative lack of autoantibodies or autoreactive T cells. In recent years there has been a substantial increase in the diseases classified (at least partially) as autoinflammatory because of better understanding of pathways of immune activation and regulation of the innate immune system (Box 1). Much of this understanding was obtained from knowledge gained from rare autoinflammatory diseases with a genetic etiology (Table 1). Periodic fever syndromes, the former term for this group of diseases, is not adequate because most syndromes are not truly periodic, and fever is not a necessary feature. This article includes those autoinflammatory syndromes (especially genetic) that do not fall into other diagnostic categories (eg, systemic juvenile idiopathic arthritis, vasculitis, and crystal disease).

These syndromes should be suspected in patients, mainly young children, with recurrent fever unexplained by infections and/or with episodic symptoms in various systems, especially the skin, gastrointestinal tract, chest, eyes, musculoskeletal, and central nervous system. These syndromes should also be suspected in patients with unexplained increased laboratory indices of inflammation even if the patient is asymptomatic. A family history of these syndromes is often but not always obtained, including a history of unexplained deafness, renal failure, or amyloidosis.

Most autoinflammatory syndromes have common clinical features including recurrent fevers, serositis, rashes, musculoskeletal manifestations, and increased laboratory markers of inflammation. However, a complete history and physical examination is
## Box 1
The expanding spectrum of the autoinflammatory diseases

### Autosomal-recessive
- Familial Mediterranean fever (FMF)
- Mevalonate kinase deficiency: hyperimmunoglobulinemia D syndrome (HIDS)
- Deficiency of the interleukin-1 receptor antagonist (DIRA)
- Deficiency of the interleukin-36 receptor antagonist (DITRA): generalized familial pustular psoriasis
- Majeed syndrome
- Recurrent hydatidiform mole (NLRP7)

### Autosomal-dominant
- TNF-receptor–associated periodic syndrome (TRAPS)
- Cryopyrin-associated periodic syndromes (CAPS, NLRP3)
  - Familial cold-autoinflammatory syndrome (FCAS)
  - Muckle-Wells syndrome (MWS)
  - Neonatal-onset multisystem inflammatory disease (NOMID)
- Pyogenic arthritis, pyoderma gangrenosum, acne syndrome (PAPA)
- Familial cold-autoinflammatory syndrome 2 (FCAS2-NLRP12)
- Cherubism (SH3BP2)

### Granulomatous
- Blau syndrome (autosomal-dominant)
- Early onset sarcoidosis (autosomal-dominant)
- Crohn disease (partially genetic)

### Other, nongenetic
- Periodic fever, aphthous stomatitis, pharyngitis, adenitis syndrome (PFAPA)
- Systemic juvenile idiopathic arthritis
- Behçet syndrome
- Recurrent pericarditis
- Chronic recurrent multifocal osteomyelitis (CRMO)
- Schnitzler syndrome
- Gout

### Other, nongenetic, at least partially autoinflammatory
- Spondyloarthropathies
- Type II diabetes
- Age-related macular degeneration
- Fibrosing disorders
- Hemolytic uremic syndrome
- Atherosclerosis
- Post–myocardial infarction muscle damage

**Abbreviation:** NLRP, nucleotide oligomerization domain–like receptor family, pyrin domain.
### Table 1
Genetic characteristics of selected inherited autoinflammatory syndromes

<table>
<thead>
<tr>
<th>Disease</th>
<th>Inheritance</th>
<th>Chromosome</th>
<th>Gene Defect</th>
<th>Protein Product</th>
<th>Common Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMF</td>
<td>Recessive</td>
<td>16p13</td>
<td>MEFV</td>
<td>Pyrin</td>
<td>M694V, M694I, M680I, V726A, E148Q*</td>
</tr>
<tr>
<td>HIDS</td>
<td>Recessive</td>
<td>12q24</td>
<td>MVK</td>
<td>Mevalonate Kinase</td>
<td>V377I, I268T</td>
</tr>
<tr>
<td>DIRA</td>
<td>Recessive</td>
<td>2q14</td>
<td>IL1RN</td>
<td>IL-1 receptor antagonist</td>
<td>175-kb deletion, 156_157delCA</td>
</tr>
<tr>
<td>DITRA</td>
<td>Recessive</td>
<td>2q13–14</td>
<td>IL36RN</td>
<td>IL-36 receptor antagonist</td>
<td>L27P, S113I</td>
</tr>
<tr>
<td>TRAPS</td>
<td>Dominant</td>
<td>12p13</td>
<td>TNFRSF1A</td>
<td>55-kDa TNF receptor</td>
<td>T50M, C52Y, R92Q, a P46L a</td>
</tr>
<tr>
<td>FCAS</td>
<td>Dominant</td>
<td>1q44</td>
<td>NLRP3</td>
<td>Cryopyrin</td>
<td>V198M, a R260W</td>
</tr>
<tr>
<td>MWS</td>
<td>Dominant</td>
<td>1q44</td>
<td>NLRP3</td>
<td>Cryopyrin</td>
<td>V198M, a L264 V, E311K, T348M, A439V</td>
</tr>
<tr>
<td>NOMID</td>
<td>Dominant/sporadic</td>
<td>1q44</td>
<td>NLRP3</td>
<td>Cryopyrin</td>
<td>L264F,H; D303H; V351M,L</td>
</tr>
<tr>
<td>PAPA</td>
<td>Dominant</td>
<td>15q</td>
<td>PSTPIP1</td>
<td>CD2 antigen-binding</td>
<td>A230T, E250Q,K</td>
</tr>
<tr>
<td>NLRP12</td>
<td>Dominant</td>
<td>19q13</td>
<td>NLRP12</td>
<td>NLR family, pyrin domain, containing 12</td>
<td>C850T</td>
</tr>
</tbody>
</table>

**Abbreviations:** DIRA, deficiency of the IL-1 receptor antagonist; DITRA, deficiency of the IL-36 receptor antagonist (generalized pustular psoriasis); FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulinemia D syndrome; MWS, Muckle-Wells syndrome; NLRP, nucleotide oligomerization domain–like receptor family, pyrin domain; NOMID, neonatal-onset multisystem inflammatory disorder; PAPA, pyogenic sterile arthritis, pyoderma gangrenosum, acne syndrome; TNF, tumor necrosis factor; TRAPS, TNF-receptor–associated periodic syndrome.

*Polymorphism, partial penetrance or mild phenotype mutation.*
crucial and often the correct diagnosis can be attained before more genetic or sophisticated tests are used. Syndromes can be differentiated by age of onset, ethnicity, attack triggers, duration of attacks, disease-free intervals between attacks, clinical manifestations, and the response to therapy (Tables 2–4). It is very useful to examine patients during an attack, or alternately to ask parents to record attacks carefully and take photos of relevant physical findings. It is also useful to obtain laboratory markers of inflammation during and between attacks, because in some syndromes attacks are only the “tip of the inflammatory iceberg” and patients consistently have increased inflammatory indices. These patients are at higher risk of developing Amyloid A (AA) amyloidosis, the major adverse outcome of the autoinflammatory syndromes.

THE INNATE IMMUNE SYSTEM AS IT RELATES TO THE PATHOGENESIS OF AUTOINFLAMMATORY SYNDROMES

The initial response to pathogens and damaged cells is mediated by the innate immune system (Fig. 1). The cells of the innate immune system, primarily epithelial, dendritic, polymorphonuclear, and macrophage cells, act not only as an immediate barrier, but also as effectors in the evolution of the inflammatory response. The innate immune system recognizes pathogen-associated molecular patterns and damage-associated molecular patterns by several complex mechanisms, involving cell-associated pattern recognition receptors and soluble recognition molecules. These receptors, such as toll-like receptors, are present on the surface of the cell. Nucleotide oligomerization domain–like receptors (NLRs) within the cell and other receptors further mediate intracellular innate immune system processes and development of the inflammatory response. NLRPs (NLRs with pyrin-domain–containing proteins) are a subfamily of the NLRs. NLRP3 assembles other proteins to form the inflammasome complex in response to cytoplasmatic pathogen-associated molecular patterns and damage-associated molecular patterns, which also triggers the expression of proinflammatory genes by transcription factors (eg, nuclear factor-κB). The inflammasome complex involving NLRP3 recruits and activates caspase 1, a protease that cleaves prointerleukin (IL)-1β and IL-18 to their active forms. The common pathogenic pathway of the autoinflammatory syndromes involves the excessive production and activity of these proinflammatory cytokines and molecules, not as a result of external stimuli but as a result of mutations in different proteins that regulate these pathways.

FAMILIAL MEDITERRANEAN FEVER

Familial Mediterranean fever (FMF), described in 1945, is the most common inherited autoinflammatory syndrome. Inherited in an autosomal-recessive manner, it results in recurrent attacks of fever, serositis, arthritis, and rash. Late complications of untreated FMF include the development of primarily renal AA amyloidosis leading to the nephrotic syndrome and renal failure.

The highest prevalence of FMF is in Sephardic Jews, Armenians, Arabs, and Turks. Because of the availability of genetic diagnosis FMF is now recognized more frequently among Ashkenazi Jews, Greeks, and Italians and even among Japanese, although the disease is usually milder in these groups. It is estimated that there are between 100,000 and 120,000 FMF patients worldwide. The carrier rate is as high as 1:3 to 1:5 among Armenians and North African Jews.

Etiology

The FMF gene (MEFV) is located on the short arm of chromosome 16. The product of this gene is a 781–amino acid protein termed “pyrin” (marenostrin in Europe). There
Table 2
Clues that may assist in the diagnosis of autoinflammatory syndromes

<table>
<thead>
<tr>
<th>Age of onset</th>
<th>NOMID, DIRA, FCAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>At birth</td>
<td></td>
</tr>
<tr>
<td>Infancy and first year of life</td>
<td>HIDS, FCAS, NLRP12</td>
</tr>
<tr>
<td>Toddler</td>
<td>PFAPA</td>
</tr>
<tr>
<td>Late childhood</td>
<td>PAPA</td>
</tr>
<tr>
<td>Most common of autoinflammatory syndromes to have onset in adulthood</td>
<td>TRAPS, DITRA</td>
</tr>
<tr>
<td>Variable (mostly in childhood)</td>
<td>All others</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethnicity and geography</th>
<th>FMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armenians, Turks, Italian, Sephardic Jews</td>
<td></td>
</tr>
<tr>
<td>Arabs</td>
<td>FMF, DITRA (Arab Tunisian)</td>
</tr>
<tr>
<td>Dutch, French, German, Western Europe</td>
<td>HIDS, MWS, NLRP12</td>
</tr>
<tr>
<td>United States</td>
<td>FCAS</td>
</tr>
<tr>
<td>Can occur in blacks (West Africa origin)</td>
<td>TRAPS</td>
</tr>
<tr>
<td>Eastern Canada, Puerto Rico</td>
<td>DITRA</td>
</tr>
<tr>
<td>Worldwide</td>
<td>All others</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Triggers</th>
<th>HIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccines</td>
<td></td>
</tr>
<tr>
<td>Cold exposure</td>
<td>FCAS, NLRP12</td>
</tr>
<tr>
<td>Stress, menses</td>
<td>FMF, TRAPS, MWS, PAPA, DITRA</td>
</tr>
<tr>
<td>Minor trauma</td>
<td>PAPA, MWS, TRAPS, HIDS</td>
</tr>
<tr>
<td>Exercise</td>
<td>FMF, TRAPS</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>DITRA</td>
</tr>
<tr>
<td>Infections</td>
<td>All, especially DITRA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Attack duration</th>
<th>FCAS, FMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;24 h</td>
<td></td>
</tr>
<tr>
<td>1–3 d</td>
<td>FMF, MWS, DITRA (fever)</td>
</tr>
<tr>
<td>3–7 d</td>
<td>HIDS, PFAPA</td>
</tr>
<tr>
<td>&gt;7 d</td>
<td>TRAPS, PAPA</td>
</tr>
<tr>
<td>Almost always “in attack“</td>
<td>NOMID, DIRA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interval between attacks</th>
<th>PFAPA, HIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>3–6 wk</td>
<td></td>
</tr>
<tr>
<td>&gt;6 wk</td>
<td>TRAPS</td>
</tr>
<tr>
<td>Mostly unpredictable</td>
<td>All others</td>
</tr>
<tr>
<td>Truly periodic</td>
<td>PFAPA, cyclic neutropenia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Useful laboratory tests</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute-phase reactants must be normal between attacks</td>
<td>PFAPA</td>
</tr>
<tr>
<td>Urine mevalonic acid in attack</td>
<td>HIDS</td>
</tr>
<tr>
<td>IgD &gt;100 mg/dL</td>
<td>HIDS</td>
</tr>
<tr>
<td>Proteinuria (amyloidosis)</td>
<td>FMF, TRAPS, MWS, NOMID</td>
</tr>
</tbody>
</table>

(continued on next page)
may be a phenotype–genotype correlation with more severe disease and amyloidosis occurring in patients with the M694V, M694I, and M680I mutations.\(^{10}\) In most series, at least 30% of patients diagnosed with definite FMF by clinical criteria lack one or even two mutations, especially patients from Western Europe or the United States; autosomal-dominant transmission has been demonstrated in some families.\(^{11}\) Mutations or polymorphisms in genes other than \textit{MEFV} gene may impact on the development of FMF or the severity of the disease, including the development of amyloidosis.\(^{10}\)

### Pathogenesis

The pyrin protein consists of three main domains: (1) the N-terminal 92–amino acid pyrin domain, (2) the B-box, and (3) the C-terminal B30.2 domain. Most disease-causing mutations occur in exon 10 of the \textit{MEFV} gene encoding the B30.2 domain.\(^{12}\) Pyrin directly interacts and binds to caspase 1, inhibiting its ability to cleave pro–IL-1\(\beta\) to IL-1\(\beta\).\(^{13}\) Mutations in the B30.2 region of pyrin, particularly those mutations considered more severe (positions 680 and 694) interfere in this binding process, thus contributing to increased levels of IL-1\(\beta\) and inflammation with and without exogenous stimulation.

### Clinical Manifestations

Clinical signs of FMF develop by age 10 years in 80% of the patients and by age 20 years in 90%.\(^{14}\) Attacks typically last 12 to 72 hours and are characterized by fever, serositis, monoarthritis of the knee or ankle, often accompanied by an erysipelas-like rash over the involved joint (Fig. 2). Severe abdominal pain (caused by peritonitis), often mimicking appendicitis, accompanies fever in nearly 90% of patients. Pleuritis occurs in 30% to 45% of patients, and patients occasionally develop pericarditis and scrotal swelling. Acute arthritis is seen in 50% to 75% of patients and is characterized by substantial effusions with polymorphonuclear predominance and usually

| Table 2  
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response to therapy</strong></td>
</tr>
<tr>
<td>Corticosteroid dramatic</td>
</tr>
<tr>
<td>Corticosteroid partial</td>
</tr>
<tr>
<td>Colchicine</td>
</tr>
<tr>
<td>Cimetidine</td>
</tr>
<tr>
<td>Etanercept</td>
</tr>
<tr>
<td>Anti–IL-1 dramatic</td>
</tr>
<tr>
<td>Anti–IL-1 mostly</td>
</tr>
<tr>
<td>Anti–IL-1 partial</td>
</tr>
</tbody>
</table>

*Abbreviations:* DIRA, deficiency of the IL-1 receptor antagonist; DITRA, deficiency of the IL-36 receptor antagonist (generalized pustular psoriasis); FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulinemia D syndrome; IL, interleukin; MWS, Muckle-Wells syndrome; NLRP, nucleotide oligomerization domain–like receptor family, pyrin domain; NOMID, neonatal-onset multisystem inflammatory disorder; PAPA, pyogenic sterile arthritis, pyoderma gangrenosum, acne syndrome; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, adenitis; TRAPS, tumor necrosis factor receptor–associated periodic syndrome.

\(^{a}\) For intra-articular steroids.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Serositis</th>
<th>Skin</th>
<th>Musculoskeletal</th>
<th>Eyes</th>
<th>Mucous Membranes</th>
<th>Reticuloendothelial</th>
<th>Neurologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMF</td>
<td>Peritonitis, pleuritis pericarditis, scrotum</td>
<td>Erysipelas-like, vasculitis</td>
<td>Acute monoarthritis, 5%-10% chronic arthritis, exercise-related myalgia, prolonged febrile myalgia</td>
<td>No</td>
<td>Rare aphthous</td>
<td>Splenomegaly, adenopathy</td>
<td>Headaches</td>
</tr>
<tr>
<td>HIDS</td>
<td>Abdominal pain, vomiting, diarrhea</td>
<td>Maculo papular, mobiliform rash</td>
<td>Arthralgia, arthritis</td>
<td>No</td>
<td>Aphthous, vaginal sores</td>
<td>Cervical adenopathy</td>
<td>No</td>
</tr>
<tr>
<td>DIRA</td>
<td>None</td>
<td>Pustulosis</td>
<td>Bonytic lesions, osteitis</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>DITRA</td>
<td>None</td>
<td>Pustular psoriasis, nail dystrophy</td>
<td>Arthralgia, arthritis</td>
<td>No</td>
<td>Tongue lesions (geographic)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>TRAPS</td>
<td>Peritonitis, pleuritis pericarditis</td>
<td>Painful, migratory erythema, vasculitis</td>
<td>Myalgia, fasciitis, arthralgia, arthritis</td>
<td>Periorbital edema, conjunctival injection</td>
<td>Aphthous</td>
<td>Splenomegaly, adenopathy</td>
<td>Focal neuropathy</td>
</tr>
<tr>
<td>FCAS</td>
<td>No</td>
<td>Urticaria-like</td>
<td>Arthralgia</td>
<td>Conjunctivitis</td>
<td>No</td>
<td>No</td>
<td>Headaches</td>
</tr>
<tr>
<td>FCAS2/NLRP12</td>
<td>No</td>
<td>Urticaria-like</td>
<td>Arthralgia</td>
<td>Conjunctivitis, episcleritis, uveitis</td>
<td>No</td>
<td>No</td>
<td>Hearing loss, headaches</td>
</tr>
<tr>
<td>MWS</td>
<td>No</td>
<td>Urticaria-like</td>
<td>Arthralgia</td>
<td>Conjunctivitis, episcleritis, uveitis</td>
<td>No</td>
<td>No</td>
<td>Hearing loss, headaches</td>
</tr>
<tr>
<td>NOMID</td>
<td>No</td>
<td>Urticaria-like</td>
<td>Epiphyseal overgrowth with deformities, cartilage defect, arthritis</td>
<td>Conjunctivitis, uveitis, papillitis</td>
<td>No</td>
<td>Adenopathy</td>
<td>Chronic meningitis, mental retardation, headaches</td>
</tr>
<tr>
<td>PAPA</td>
<td>No</td>
<td>Pyoderma gangrenosum, acne</td>
<td>Destructive ‘pyogenic’ large joint arthritis</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>PFAPA</td>
<td>No</td>
<td>No</td>
<td>Arthralgia</td>
<td>No</td>
<td>Aphthous, pharyngitis</td>
<td>Cervical lymphadenopathy</td>
<td>No</td>
</tr>
</tbody>
</table>

**Abbreviations:** DIRA, deficiency of the IL-1 receptor antagonist; DITRA, deficiency of the IL-36 receptor antagonist (generalized pustular psoriasis); FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulinemia D syndrome; MWS, Muckle-Wells syndrome; NLRP, nucleotide oligomerization domain–like receptor family, pyrin domain; NOMID, neonatal-onset multisystem inflammatory disorder; PAPA, pyogenic sterile arthritis, pyoderma gangrenosum, acne syndrome; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, adenitis; TRAPS, tumor necrosis factor receptor–associated periodic syndrome.

## Table 4
Effective treatments and strength of proof of the main autoinflammatory syndromes

<table>
<thead>
<tr>
<th>Disease</th>
<th>Colchicine</th>
<th>Corticosteroids</th>
<th>TNF Inhibitors</th>
<th>IL-1 Inhibitors</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMF</td>
<td><em>Multiple controlled studies</em></td>
<td>Effective only in prolonged febrile myalgia, vasculitis</td>
<td>Effective for arthropathy, case reports/series</td>
<td>Controlled study (two-thirds of patients), case series</td>
<td></td>
</tr>
<tr>
<td>HIDS</td>
<td>No</td>
<td>No</td>
<td>Case reports</td>
<td>About 40%, case series</td>
<td>Simvastatin shortens attacks</td>
</tr>
<tr>
<td>DIRA</td>
<td>No</td>
<td>No</td>
<td>Unknown</td>
<td>Anakinra, case series</td>
<td></td>
</tr>
<tr>
<td>DITRA</td>
<td>No</td>
<td>No</td>
<td>Case reports</td>
<td>Case reports</td>
<td>Oral retinoids cyclosporin</td>
</tr>
<tr>
<td>TRAPS</td>
<td>No</td>
<td>Yes, but loses effect over time</td>
<td>Case reports, etanercept only, not in all cases, often loss of effect over time</td>
<td>Case series</td>
<td>Anti–IL-6, case report</td>
</tr>
<tr>
<td>FCAS</td>
<td>No</td>
<td>No</td>
<td>Unknown</td>
<td>Two controlled studies</td>
<td></td>
</tr>
<tr>
<td>MWS</td>
<td>No</td>
<td>No</td>
<td>Unknown</td>
<td>Two controlled studies</td>
<td></td>
</tr>
<tr>
<td>NOMID</td>
<td>No</td>
<td>No</td>
<td>Unknown, case reports</td>
<td>Open study</td>
<td></td>
</tr>
<tr>
<td>FCAS2/NLRP12</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>No (case reports)</td>
<td></td>
</tr>
<tr>
<td>PAPA</td>
<td>No</td>
<td>Case reports (partial)</td>
<td>Case reports</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFAPA</td>
<td>30%–40%, case series</td>
<td><em>Yes, may shorten intervals between attacks</em></td>
<td>Unknown</td>
<td>Case series</td>
<td>Tonsillectomy, controlled studies; cimetidine (30%–40%), case series</td>
</tr>
</tbody>
</table>

*Abbreviations: DIRA, deficiency of the IL-1 receptor antagonist; DITRA, deficiency of the IL-36 receptor antagonist (generalized pustular psoriasis); FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulinemia D syndrome; IL, interleukin; MWS, Muckle-Wells syndrome; NOMID, neonatal-onset multisystem inflammatory disorder; PAPA, pyogenic sterile arthritis, pyoderma gangrenosum, acne syndrome; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, adenitis; TNF, tumor necrosis factor; TRAPS, TNF-receptor–associated periodic syndrome.

* Highly effective.

b Infliximab contraindicated.
lasts up to 1 week. Chronic arthritis develops in 5% to 10%, especially in the hip and sacroiliac joint. Headaches related to aseptic meningitis may occur.

Since the discovery of the genetic cause of FMF more phenotype presentations have been recognized. These include exercise-induced myalgia, recurrent abdominal pain, and recurrent arthritis without fever in appropriate ethnic groups.3

Other less common manifestations include prolonged febrile myalgia and vasculitis, especially Henoch-Schönlein purpura and polyarteritis nodosa, and glomerulonephritis. Children with frequent attacks often have growth delay and short stature. Splenomegaly is common. In children younger than 5 years recurrent fever may be the sole feature.15

Fig. 1. Schema of selected innate immune inflammatory pathways related to the autoinflammatory syndromes. The schema demonstrates the effect of external stimuli on the development of inflammation and the relationship of several regulatory proteins (pyrin, NLRP3, NLRP12, and PSTPIP1) that when mutated result in the development of autoinflammatory diseases. DAMP, damage-associated molecular patterns; IL, interleukin; NF-κB, nuclear factor-κB; NLR, nucleotide oligomerization domain–like receptors; NLRPs, NLRs with pyrin-domain-containing proteins; PAMP, pathogen-associated molecular patterns; PSTPIP, proline-serine-threonine phosphatase-interacting protein; ROS, reactive oxygen species; TLR, toll-like receptors.
Amyloidosis was the major cause of morbidity and mortality before the discovery in 1972 of colchicine as an effective therapy for FMF. Renal amyloidosis usually starts with proteinuria and progresses to the nephrotic syndrome and renal failure within 3 to 5 years. FMF can rarely present with amyloidosis (type II phenotype). Later, patients develop gastrointestinal amyloidosis resulting in abdominal pain, diarrhea, malabsorption, and weight loss. Other manifestations may include cardiomypathy, hepatosplenomegaly, macroglossia, joint stiffness, peripheral neuropathy, and bleeding disorders.

The most important risk factor for the development of amyloidosis in FMF is the geographic residence of the patient (with less amyloidosis in the United States). Other risk factors include the 694 and 680 mutations, family history of amyloidosis, male gender, the serum amyloid A genotype with an odds ratio of 7 for patients with an α/α genotype, and poor compliance with treatment.16

Amyloidosis is suspected by detecting proteinuria during routine urinalysis screening. Diagnostic methods less invasive than renal biopsy include subcutaneous abdominal fat aspiration, rectal biopsy, and nuclear 123I-labeled scan for serum amyloid P-component. The latter can be used to monitor the total body load of amyloid.17

**Diagnosis**

The diagnosis of FMF is based on clinical criteria and not genetic testing. Two major criteria have been described. The 1997 Tel-Hashomer criteria are based on clinical
manifestations, family history, and response to colchicine. Pediatric criteria proposed in 2009 require at least three attacks with the presence of two of five features, including fever lasting between 12 and 72 hours, abdominal pain, chest pain, arthritis, and positive family history. There is debate on the specificity of these criteria, across pediatric populations or varied ethnicities. Laboratory tests are nonspecific and reflect elevated acute-phase reactants, mainly during attacks but also frequently between attacks. Serum amyloid A levels may be especially helpful in monitoring treatment efficacy. Unanswered questions remain on how to manage asymptomatic patients with homozygote genetic mutations and which asymptomatic relatives of patients with genetically proved FMF should be tested for mutations (eg, if there is a family history of amyloidosis).

**Treatment**

Treatment with colchicine (1–2 mg/d [Colcrys]) is effective in preventing amyloidosis in nearly all patients and in preventing attacks in 60% to 70% of patients. However, 20% to 30% of patients respond only partially to maximal tolerated doses of colchicine and 5% of patients are nonresponders. These patients usually include those with more severe genetic mutations or those with modifying genes that may inhibit the intracellular accumulation of colchicine, such as polymorphisms in MDR-1 P-glycoprotein pump transporter genes. Many attacks occur as a result of noncompliance; in some patients missing even one dose can precipitate an attack.

Colchicine is generally well tolerated. The most common adverse effects include abdominal pain and diarrhea, especially in those receiving higher doses of colchicine and in patients with lactose intolerance. These effects are usually transient and respond to gradual dose changes, dividing the daily dose, lactose avoidance, and antidiarrheal and antibloating agents. Other rare adverse effects include myalgia and myositis, peripheral neuropathy, and bone marrow suppression. Medications that inhibit the cytochrome P-450 (CYP[3]A[4]) and P-glycoprotein pathways may increase colchicine toxicity, particularly erythromycin, clarithromycin, statins, cyclosporin, and grapefruit juice. Colchicine does not affect growth and development and seems to be safe for use in pregnancy.

IL-1 inhibitors may be effective in nonresponders or patients who do not tolerate colchicine. A recent controlled study has found that rilonacept (Arcalyst), an IL-1–soluble fusion protein receptor, significantly decreases the frequency of attacks among most patients, particularly children. Corticosteroids are effective only for prolonged febrile myalgia and FMF-related vasculitis but not the acute febrile episodes.

**HYPERIMMUNOGLOBULINEMIA D WITH PERIODIC FEVER SYNDROME**

This autosomal-recessive disease, also known as mevalonic kinase deficiency, was first described in 1984 in six Dutch patients. The mean age of onset is 6 months, with more than 70% of patients having the first episode before 12 months of age. It is seen mainly in patients from the Netherlands and Western Europe.

**Etiology and Pathogenesis**

Hyperimmunoglobulinemia D syndrome (HIDS) is a metabolic disease with mutations in the MVK gene of the long arm of chromosome 12, encoding mevalonate kinase resulting in partial absence of mevalonate kinase activity. The disease mevalonic aciduria is a result of complete absence in mevalonate kinase, and includes severe neurologic manifestations in addition to febrile episodes. In HIDS, most patients have mutations in the V377I (founder gene) and I268 T positions. Mutations result in
an unstable enzyme, which is even less active when patients are febrile, hence attacks are often precipitated by pyrogenic infection and vaccines.\(^{33}\) It seems that a deficiency of geranylgeranyl and other isoprenoid substrates resulting from the lack of mevalonate kinase is responsible for affecting inflammation, rather than excessive mevalonate.\(^{34}\) One theory is that this deficiency affects IL-1\(\beta\) processing through the effect on R-type GTPase, dependent on prenylation.

**Clinical Manifestations**

Attacks, often triggered by vaccines or infection, typically occur every 3 to 6 weeks and last 3 to 7 days.\(^{35}\) Besides fever, patients develop abdominal pain with vomiting and diarrhea; a polymorphic rash (Fig. 3); cervical lymphadenopathy; oral and genital ulceration; and arthralgia or arthritis.

**Diagnosis**

IgD levels are usually, but not always markedly elevated (>100 IU/mL). Patients younger than 3 years may have normal IgD levels. IgA is elevated in most patients. Urine level of mevalonic acid is elevated, mainly during attacks. Homozygous genetic mutations are present in 75% of patients. The term “variant HIDS” is used for patients who have clinical manifestations without genetic mutations when tested in commercial laboratories. If clinical suspicion is high, serum IgD and either MVK genetic testing or urinary mevalonic acid during an attack should be obtained.\(^3\) False-positive causes of increased IgD levels (usually not to the degree seen in HIDS) may also be found in other autoinflammatory diseases, diabetes mellitus, smoking, and pregnancy.

**Treatment and Outcome**

Nonsteroidal anti-inflammatory drugs (NSAIDs) have some symptomatic benefit. Corticosteroids, colchicine, and thalidomide are generally ineffective. Simvastatin may reduce the number of febrile days but has no effect on the frequency of attacks. Etanercept (Enbrel), a soluble tumor necrosis factor (TNF) fusion protein receptor developed for the treatment of inflammatory arthritis, and anakinra (Kineret), a recombinant IL-1 receptor antagonist, may be effective in approximately 40% of cases in decreasing the frequency of attacks\(^{35}\) or (anakinra) in shortening attacks.

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**Fig. 3.** Polymorphic rash on the hands, arms, and legs of a patient with hyperimmunoglobulinemia D syndrome (HIDS). (From Takada K, Aksentijevich I, Mahadevan V, et al. Favorable preliminary experience with etanercept in two patients with the hyperimmunoglobulinemia D and periodic fever syndrome. Arthritis Rheum 2003;48:2646; with permission.)
Attacks usually decrease in severity and frequency over time and amyloidosis is a rare complication (<3%).

**DEFICIENCY OF THE IL-1 RECEPTOR ANTAGONIST (DIRA)**

This autosomal-recessive disease was described in 2009 in families from Newfoundland, Puerto Rico, Southern Netherlands, and Lebanon with onset in infancy.36,37

**Etiology and Pathogenesis**

The cause is a missense–nonsense mutation (or a 175-db deletion) in the *IL1RN* gene at the long arm of chromosome 2 that encodes the IL-1 receptor antagonist, leading to unopposed IL-1 stimulation.36,37

**Clinical Manifestations**

Affected infants present at birth or shortly after with a sterile pustular rash (localized or diffuse), multifocal osteomyelitis with lytic bone lesions, osteopenia, osteitis, arthritis, nail pits, respiratory distress with pneumonitis, oral ulcers, hepatosplenomegaly, and increased inflammatory indices. Of note, fever is absent.

**Treatment and Outcome**

Treatment with anakinra is remarkably effective in reversing clinical, laboratory, and imaging features. Before discovery of the cause and treatment of deficiency of the IL-1 receptor antagonist, infants succumbed to the disease with others suffering from skeletal deformities and failure to thrive.

**DEFICIENCY OF IL-36 RECEPTOR ANTAGONIST (DITRA): FAMILIAL GENERALIZED PUSTULAR PSORIASIS**

The discovery in 2011 of the genetic mutation that causes this rare autosomal-recessive disease is a recent discovery of a novel monogenetic autoinflammatory syndrome. The mutation has been reported in nine Tunisian families and five nonrelated European patients.38,39

**Etiology and Pathogenesis**

The cause is a missense–nonsense mutation in the *IL36RN* gene at the long arm of chromosome 2 (near the *IL1RN* gene) that encodes the IL-36 receptor antagonist, leading to unopposed IL-36 stimulation and the production of proinflammatory cytokines.38,39 The IL-36 receptor antagonist is part of the IL-1 protein family and has many homologous regions to the IL-1 receptor antagonist.

**Clinical Manifestations**

The onset of disease can occur from infancy to mid-adulthood. Patients develop flares of high-grade fever with malaise lasting 1 to 3 days, and a generalized pustular rash, lasting days to weeks. Nail dystrophy and tongue (mainly geographic) lesions are common. About 30% of patients develop arthritis and about 30% develop a chronic course of psoriasis vulgaris.

**Treatment and Outcome**

Most commonly patients are treated with oral retinoids (acitretin). Immunosuppressive medications include corticosteroids, methotrexate, dapsone, and cyclosporine. Case reports on the efficacy of TNF-α and IL-1 inhibitors have been reported.40
a high proportion of fatalities from sepsis related to the loss of the skin barrier from the widespread rash.

**THE TNF-RECEPTOR–ASSOCIATED PERIODIC SYNDROME**

First described in 1982 as familial Hibernian fever, the gene mutation for this autosomal-dominant disorder was discovered in 1999. TNF-receptor–associated periodic syndrome (TRAPS) is the most common autosomal-dominant autoinflammatory disorder. Although initially described in patients of Irish or Scottish descent, TRAPS is found in all ethnic groups. TRAPS usually presents during the first decade of life (75%, median 3 years) but can present at any age and has the highest proportion of patients with adult onset among the genetic autoinflammatory diseases.

**Etiology and Pathogenesis**

The TRAPS gene (TNFRSF1A) has been localized to the short arm of chromosome 12. The product of this gene is the 55-kDa TNF cell membrane receptor. There is a phenotype–genotype correlation with more severe disease and amyloidosis occurring in patients with protein structure altering cysteine residue mutations. Certain mutations including R92Q and P46L are frequently seen in normal controls (up to 9% of the population), do not alter the protein structure, and may represent milder mutations of low penetrance. Alternatively, these mutations may not be pathogenic by themselves but are polymorphisms that may contribute to a state of “increased” inflammation and nonspecific recurrent febrile syndromes.

The initial hypothesis to explain how the mutation results in clinical manifestations was that there is a decrease in the shedding of mutated membrane-bound TNF receptors when stimulated, leading to an increase of unopposed serum TNF. However, it is clear that the pathogenesis of TRAPS is much more complicated and includes defects in intracellular trafficking (lack of internalization of receptors, protein misfolding, and intracellular aggregation of receptors in the cytoplasm instead of the Golgi apparatus) leading to defects in TNF-induced apoptosis and stimulation of intracellular inflammatory pathways, particularly reactive oxygen species. There is also a decrease in the concentration of surface receptors.

**Clinical Manifestations**

Attacks typically last between 1 and 3 weeks (occasionally even up to 6 weeks), and occur two to six times per year. Exercise is a common trigger of attacks. Besides fever patients develop serositis (abdominal, chest, and testicular pain); conjunctivitis; arthralgia; and myalgia. Two unique features are periorbital edema and a painful, distally migrating, erythematous rash (Fig. 4). This rash represents a mononuclear perivascular infiltrate of the subcutaneous fascia with occasional panniculitis. Patients with certain mutations, particularly R92Q, may develop a shorter and milder attack, with involvement of the pharynx and oral ulcerations, often resembling the periodic fever, aphthous-stomatitis, pharyngitis, and adenitis (PFAPA) syndrome. Less common manifestations include recurrent pericarditis and central and focal neurologic abnormalities. Amyloidosis develops in 14% to 25% of patients, particularly those with cysteine mutations and a positive family history.

**Diagnosis**

The diagnosis of TRAPS is based on finding a genetic mutation in the TNFRSF1A gene, unlike other autoinflammatory diseases in which genetic mutations are only
supporting evidence. Acute-phase reactants are persistently elevated, further increasing during attacks.

**Treatment**

NSAIDs may be effective for mild attacks. Corticosteroids are often beneficial for severe attacks but frequently patients need increasing doses with a decrease in efficacy in subsequent attacks. Colchicine is not effective.

Initial case reports showed that etanercept is beneficial. However, recent literature has indicated that etanercept is not effective in all patients and in others may become less effective over time. Infliximab (Remicade), a TNF antibody, may worsen symptoms and should be avoided. IL-1 inhibitors may be effective in most etanercept-resistant patients. A case of the efficacy of tocilizumab (Actemra), an antibody to the IL-6 receptor, was recently reported in a patient who failed etanercept and anakinra. In general, aggressive therapy should be reserved for patients with severe disease, cysteine mutations, or a family history of amyloidosis.

**THE CRYOPYRIN-ASSOCIATED PERIODIC SYNDROMES**

**Etiology and Pathogenesis**

Three autosomal-dominant syndromes constitute cryopyrin-associated periodic syndromes (CAPS): (1) familial cold autoinflammatory syndrome (FCAS), (2) Muckle-Wells syndrome (MWS), and (3) neonatal-onset multisystem inflammatory disease (NOMID). They are considered variants of the same process that vary by severity of symptoms, systems involved, and outcome and all respond dramatically to IL-1 inhibitors. They are caused by single base mutations on the \( \text{NLRP3} \) gene located on the long arm of chromosome 1 encoding the protein cryopyrin. Mutations may be specific or overlap among the three syndromes. No \( \text{NLRP3} \) mutations are found in about 50% of patients with NOMID and 25% to 33% of patients with MWS; these patients have a similar phenotype and response to treatment as mutation-positive patients. Recently, it was found that nearly 70% of NOMID patients with a “negative” mutation have somatic mosaicism mutations in 4.2% to 35.8% of the cells.

The cryopyrin protein has an important role in regulation of the assembly of the inflammasome (see **Fig. 1**). The mutated cryopyrin protein probably increases the
rate of the inflammasome assembly independently of the usual stimuli needed in wild-type protein.\textsuperscript{53}

**Familial Cold Autoinflammatory Syndrome**

FCAS (previously called familial cold urticaria) is the mildest form of CAPS. The first description was in 1940 and the genetic mutation was discovered in 2001. Almost all patients have a genetic mutation in the NLRP3 gene and live in the United States. FCAS often presents at birth and is apparent in 95\% of the patients by 6 months.

**Clinical manifestations**

Attacks usually start 2 to 3 hours after generalized (not by direct contact) cold exposure. Patients develop an urticaria-like rash, low-grade fever, arthralgia, conjunctivitis, nausea, extreme thirst, sweating, and headaches that peaks at 6 to 8 hours and lasts up to 24 hours. The attack frequency is variable but is often debilitating. The pathology of the rash is a perivascular polymorphonuclear cellular infiltrate in the dermis rather than mast cells as in true urticaria. Amyloidosis is rare, occurring in 2\% to 4\% of patients.

**Treatment**

IL-1 inhibitors are very effective in alleviating symptoms. Rilonacept and canakinumab (specific humanized antibody to IL-1\(\beta\) [Ilaris]) have been shown to be highly effective in controlled trials.\textsuperscript{54,55} NSAIDs and antihistamines are not effective. High doses of corticosteroids can alleviate symptoms but are associated with many adverse effects.

**Muckle-Wells Syndrome**

MWS, the intermediate severity CAPS, was described in 1962 and the genetic mutation was also discovered in 2001. MWS can appear at any age and usually starts later in life than FCAS with most described cases coming from Europe.

**Clinical manifestations and treatment**

A typical attack lasts up to 3 days and includes fever, a more persistent urticaria-like rash than FCAS (Fig. 5), arthralgia, arthritis, myalgia, headaches, conjunctivitis, episcleritis, and uveitis. There are usually no triggers for attacks. Often starting in adolescence, 50\% to 70\% of patients develop sensorineural hearing loss, usually starting in high-frequency sounds. Amyloidosis develops in 25\% of the patients. MWS also responds dramatically to IL-1 inhibitors.\textsuperscript{54,55} However, existing hearing loss is

![Fig. 5. Urticaria-like rash in a patient with Muckle-Wells syndrome.](image-url)
reversible in only about one-third of cases.\textsuperscript{56,57} In a 2-year follow-up of canakinumab use for MWS, nearly 25\% of children needed dose increases or increased frequency of administration to sustain the effect.\textsuperscript{57} Overall more than 70\% retained complete, relapse-free remission throughout the study.

**Neonatal-Onset Multisystem Inflammatory Disease**

NOMID, the most severe of the CAPS, was first described in 1981 and the association with the \textit{NLRP3} gene was found in 2002. In Europe NOMID is called “chronic infantile neurologic, cutaneous, articular syndrome.”

**Clinical manifestations**

Patients present at birth or shortly after with urticaria-like rash and fever, often occurring daily with chronic aseptic meningitis.\textsuperscript{58} Up to 50\% of the infants are born prematurely. Symptoms associated with meningitis include headaches, irritability, and vomiting. Late complications include hydrocephalus, developmental delay, mental retardation, and hearing loss. Ocular findings include conjunctivitis, uveitis, and papillitis of the optic nerve resulting in visual loss. About 50\% of NOMID patients develop a severe arthropathy (nonsynovial) by age 2 years, with cartilage growth abnormalities leading to substantial pain, bony overgrowth, ossification irregularities, deformities, and disabilities. Patients have characteristic morphologic abnormalities of short stature; frontal bossing; macrocephaly; saddle nose; short, thick extremities with clubbing of fingers; and wrinkled skin. Before modern therapy about 20\% succumbed by age 20 years and others developed amyloidosis.

**Treatment**

Anakinra has dramatic effect on the rash, fever, and meningitis of NOMID with normalization of acute-phase reactants.\textsuperscript{59} Existing hearing loss, neurologic, and joint manifestations are reversible only in a minority of patients.\textsuperscript{56,57} Early recognition and treatment is crucial in preventing long-term damage and disability. Anti-inflammatory medications other than IL-1 inhibitors are of marginal effect.

**Familial Cold Autoinflammatory Syndrome II Related to Mutations in the NALP12 Gene**

This autosomal-dominant disease with a clinical phenotype between FCAS and MWS was reported in several families, particularly from Guadeloupe, as a result of mutations in the \textit{NALP12} gene that is an important regulator of nuclear factor-\kappaB.\textsuperscript{60} Usually triggered by generalized cold exposure patients develop from the first year of life frequent attacks of fever, urticaria-like rashes, arthralgia, myalgia, and headache lasting 2 to 15 days.\textsuperscript{61} Many patients develop sensorineural hearing loss. Unlike CAPS-related FCAS, IL-1 inhibition was only transiently effective.\textsuperscript{62}

**Pyogenic Sterile Arthritis, Pyoderma Gangrenosum, Acne Syndrome**

PAPA, a very rare syndrome, was first described in 1997\textsuperscript{63} and is the result of mutations in the \textit{PSTPIP1} gene on the long-arm of chromosome 15 encoding the CD2 antigen-binding protein.\textsuperscript{64} This cytoskeleton protein binds to pyrin, thus similar to FMF, which may affect IL-1 activity.\textsuperscript{65}

**Clinical Manifestations and Treatment**

Attacks are often triggered by minor trauma and result in fever and sterile joint effusion in large joints with massive polymorphonuclear infiltrates.\textsuperscript{63} Patients develop pyoderma gangrenosum, severe scarring acne mainly in adolescence, and often
develop diabetes mellitus and depression. Intra-articular corticosteroid injections can alleviate the acute inflammatory arthritis. Anti-TNF and anakinra therapy have been reported to be effective for the pyoderma gangrenosum.

PERIODIC FEVER, APHTHOUS STOMATITIS, PHARYNGITIS, ADENITIS SYNDROME

PFAPA is the most common autoinflammatory syndrome in childhood and was initially described in 1987. The etiology is unknown but increased gene expression related to IL-1β, interferon, complement, and Th1 chemokines are found during attacks. Although no specific genetic mutations have been found, familial cases of PFAPA are known and many Middle Eastern patients have heterozygous FMF mutations. The latter patients may have a milder disease course.

Clinical Manifestations

The onset of PFAPA is almost always before 5 years (mode 2–3 years); however, rare adult-onset cases have been reported. This syndrome is truly periodic (parents can often predict the day of the attack) with attacks occurring usually every 21 to 28 days and fever lasting 4 to 7 days. Patients usually report an aura of “glazed” eyes or feeling unwell several hours before the start of an attack. Pharyngitis and cervical adenopathy are present in 80% to 100% of patients and aphthous stomatitis in 60% to 70%. Patients frequently complain of abdominal pain, nausea or vomiting, arthralgia, and headaches.

Diagnosis

Diagnostic criteria have been defined for children with typical clinical features with the exclusion of cyclic neutropenia. For correct diagnosis, it is crucial that patients are completely asymptomatic (with normal acute-phase reactants) between attacks and exhibit normal growth and development. Other autoinflammatory syndromes, particularly TRAPS or HIDS, need to be considered in patients with nontypical features or who are not completely well between attacks. Application of the Gaslini diagnostic score (http://www.printo.it/periodicfever/index.asp) can help differentiate patients with PFAPA from other hereditary autoinflammatory syndromes.

Treatment

A single dose of prednisone (0.6–2 mg/kg) at the onset of symptoms usually aborts that attack. However, the intervals between attacks may shorten. In about one-third of the patients cimetidine (Tagamet) may be effective as a prophylactic agent (40 mg/kg/d, in two divided doses). Colchicine is effective in preventing attacks in few patients, particularly those with MEFV mutations. Anakinra administration at the start of attacks may shorten or abort attacks without the effect of shortening intervals between attacks. Recent controlled studies have shown that tonsillectomy (with or without adenoidectomy) is curative in most patients with a meta-analysis showing complete resolution in 83% (95% confidence interval, 77%–89%) and may be an option for those with frequent need for corticosteroids or with marked effect on quality of life.

Outcome

Patients do not develop amyloidosis. The frequency and severity of attacks decrease with time and tend to resolve during the second decade of life. However, a recent study has indicated than approximately 15% of patients continued to have attacks for at least 18 years.
CHRONIC RECURRENT MULTIFOCAL OSTEOMYELITIS

Chronic recurrent multifocal osteomyelitis (CRMO), first described by Giedion and colleagues in 1972, is usually sporadic with an unknown cause. However, up to 25% of patients have a positive family history for either psoriasis or inflammatory bowel disease. There are several rare genetic autoinflammatory bone disorders resembling CRMO including deficiency in IL-1 receptor antagonist; Majeed syndrome (CRMO with congenital dyserythropoietic anemia); cherubism (bone degradation of the jaws); and a mouse model of CRMO with mutations in the *pstpip2* gene.

**Clinical Manifestations**

Patients with CRMO develop recurrent episodes of bone pain with or without fever with sterile osteolytic lesions surrounded by sclerotic bone, especially in the metaphysis of long bones. Other bones can be involved, particularly the clavicle, vertebral bodies, and ribs. Often asymptomatic lesions are found by technetium nuclear bone scans or whole-body MRI scans. Associated clinical findings may include synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO syndrome); isolated palmoplantar pustulosis; psoriasis; sacroiliitis; inflammatory bowel disease; and pyoderma gangrenosum. Patients have spontaneous remissions with healing of lesions and relapses. Chronic disease may develop in approximately 50% of patients with long-term bone sequela, leg length inequality, and disability.

**Treatment**

Most patients respond to NSAIDs with occasional need for corticosteroids. Bisphosphonates have been reported to be effective in several case series. Other treatments described in case reports include methotrexate, sulfasalazine, azithromycin, interferon, anakinra, and the anti-TNF agents infliximab and etanercept.

THE OUTCOME OF PATIENTS WITH UNDIAGNOSED NONINFECTIOUS RECURRENT FEVER

Despite the major advances in the autoinflammatory syndromes in the last decade more than 60% of children with recurrent fever still go undiagnosed at tertiary centers (personal observation). Most of these children do well, with resolution of their febrile episodes or decrease in the frequency and severity. Only a small minority later develop a recognizable autoinflammatory or rheumatic disease.

SUMMARY

Several authors have offered stepwise pathways to the clinical and genetic diagnosis of the expanding spectrum of the autoinflammatory diseases. A thorough history and physical examination often leads to a diagnosis. It is crucial to see the child during an attack or ask the family to take photographs of findings. Genetic testing should be performed in a logical manner and be reserved to confirm the diagnosis and gather prognostic information while recognizing limitations. A simple interactive tool available on the Internet (http://www.printo.it/periodicfever/index.asp) based on an Italian cohort of 228 patients with recurrent fever can help differentiate patients with a high risk of a genetic autoinflammatory disease, realizing the limitation that this score may not fully apply to cohorts of differing ethnicitites. Families of those patients who remain undiagnosed after a thorough investigation should be reassured of a general good prognosis.
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