Review Article

Autoinflammatory Diseases & The Periodic Fever Syndromes

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The autoinflammatory diseases constitute a family of disorders characterized by aberrant activation of inflammatory pathways in the absence of antigen-directed autoimmunity. Since autoinflammatory diseases prominently involve mediators and cells of the innate immune system, they may broadly be considered to represent primary diseases of innate immunity, though cells more typically associated with adaptive immunity (such as lymphocytes) could potentially also contribute to autoinflammation.

The best characterized autoinflammatory diseases are relatively rare but florid conditions arising from mutations in single genes. These include the periodic fever syndromes (familial Mediterranean fever [FMF], TNF receptor-1 associated periodic syndrome [TRAPS]), the hyper-IgD syndrome; periodic fevers with aphthous stomatitis pharyngitis and adenitis (PFAPA) syndrome; and the three overlapping syndromes related to mutations in the gene for the protein cryopyrin (familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal onset multisystem inflammatory disease).

Box 1. Monogenic autoinflammatory diseases classified by leading clinical features.

Periodic fever diseases
FMF (familial Mediterranean fever);
MKD/HIDS (mevalonate kinase deficiency/hyperimmunoglobulin D syndrome);
CAPS (cryopyrin-associated periodic syndromes);
TRAPS (TNF receptor-associated periodic syndrome);
FCAS2 (familial cold autoinflammatory syndrome 2)

Diseases with pyogenic lesions
DIRA (deficiency of IL-1 receptor antagonist);
PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne) syndrome;
Majeed syndrome

Diseases with granulomatous lesions
Blau syndrome

Diseases with psoriasis
DITRA (deficiency of IL-36 receptor antagonist)

Diseases with panniculitis-induced lipodystrophy
JMP (joint contractures, muscle atrophy and panniculitis-induced lipodystrophy) syndrome;
CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature) syndrome;
NNS (Nakajo–Nishimura syndrome)

Others
APLAID (PLCγ2-associated antibody deficiency and immune dysregulation) syndrome

The Periodic Fever Syndromes

Fevers that recur over months or years in the absence of associated viral or bacterial infection.

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Familial Mediterranean Fever

FMF is the most common of the periodic fever syndromes. FMF is an autosomal recessive disorder in which there is a mutation in the MEFV gene encoding the protein pyrin, one function of which is regulation of the production of interleukin-1 beta, a mediator also implicated in several other autoinflammatory disorders.

FMF is characterized by episodic attacks of fever lasting one to three days and is accompanied, in most cases, by abdominal pain, pleurisy, and arthralgias or arthritis. Attacks are accompanied by an elevation in peripheral white blood cell count and acute phase markers, while fluid from inflamed joints exhibits a neutrophil-predominant leukocytosis. Persistent inflammation can lead to secondary (AA) amyloidosis.

The diagnosis may be strongly suggested by patient ethnicity. Sephardic Jews, Armenians, North Africans, Turks, and, to a lesser extent, Ashkenazi Jews, Greeks, and Italians are potential carriers. However, individuals outside these groups have also been affected.

Clinical Manifestations

Most patients with FMF experience their first attack in early childhood; in 65% occurs before the age of 10, and in 90% before the age of 20.[1] The typical manifestations of the disease are recurrent attacks of severe pain (due to serositis at one or more sites) and fever, lasting one to three days, and then resolving spontaneously. In between attacks, patients feel entirely well. Pain and fever are usually abrupt and reach their peak soon after onset.

Peritonitis

95% of patients with FMF have painful attacks localized to the abdomen, which is usually the dominant manifestation of the disease[1]. Pain and tenderness may initially be focal, and then progress to become more generalized. Guarding, rebound tenderness, rigidity, and an adynamic ileus are often present. These findings so closely resemble those of an acute surgical abdomen that an exploratory laparotomy is sometimes performed, during which an uninflamed appendix is usually removed.

Recurrent attacks of peritonitis may lead to adhesions, with the potential for causing small bowel obstruction. Pelvic adhesions can reduce fertility in female patients.

Pleuritis

Painful FMF attacks may also be localized to the chest. They may reflect either direct inflammation of the pleura or referred pain from subdiaphragmatic inflammation. Pleural inflammation typically manifests as unilateral pleuritic chest pain with a small, transient pleural effusion. Like episodes of peritonitis, these episodes usually resolve within three days, but may last up to one week.

Synovitis

Arthritis is another common manifestation of FMF; its incidence correlates with the patient's ethnicity. North Africans, for example, are most prone to severe, recurrent attacks of arthritis, while Armenians and Ashkenazi Jews are relatively spared[3]. The arthritis is most often monoarticular or oligoarticular, and the joints most often affected are the knee, ankle, hip, and elbow, in order of frequency. Occasionally, patients present with migratory polyarthritis resembling acute rheumatic fever.

Joint effusions are common during attacks of synovitis. Analysis of the fluid reveals 200 to 1,000,000 white blood cells/mm^3, with a predominance of neutrophils, and an elevated total protein concentration.

The arthritis often occurs independently of the other manifestations of FMF, and may last for weeks to months. The synovitis usually resolves completely without joint destruction.

Erysipelas-Like Skin Lesion

An erysipelas-like skin lesion is reported in 7-40% of FMF patients and more commonly occurs among patients in the eastern Mediterranean region. The lesion is tender, raised, and erythematous lesion (mimicking acute infectious cellulitis), occurring unilaterally on the lower leg, ankle or foot. Its overall area is about 10 to 15 cm^2. The lesion may be the presenting feature of FMF in children. Recovery is spontaneous and there is no need for antibiotics.

Other but rare acute manifestations:

Pericarditis, self-limited orchitis and recurrent aseptic meningitis, protracted bouts of febrile myalgia, polyarteritis nodosa and Henoch-Schönlein purpura (IgA vasculitis), but kidney involvement with these processes may be particularly common.

Laboratory Abnormalities

During acute attacks there are: Leukocytosis with a predominance of neutrophils is common, as is an elevation in acute phase reactants: ESR, beta-2 microglobulin, CRP, SAA (serum amyloid protein), and fibrinogen.

The presence of otherwise unexplained proteinuria in between attacks may be seen in renal amyloidosis.

Long-term complications

Secondary (AA) amyloidosis

Although the inflammatory attacks of untreated FMF are the cause of much morbidity, the major source of mortality in this disease is progressive secondary (AA) amyloidosis. Before the advent of colchicine , amyloidosis occurred in approximately 30% of Sephardic Jews and 60% of Turks with FMF, but rare in others. The incidence has decreased markedly with its use; but there is poor correlation between the severity or frequency of attacks of FMF and the extent of amyloidosis in individual patients.

In addition, analysis of the phenotypic expressions of the two most frequent mutations of the FMF gene, V726A and M694V, suggested that amyloidosis and severe arthritis are much more frequently observed with the latter defect.

Amyloid A deposition occurs in the kidney, spleen, liver, and gut. Renal involvement is the dominant feature of FMF-related amyloidosis. It begins insidiously, causing proteinuria, then progresses to symptomatic nephrotic syndrome, and eventually ends in ESRD in 2-13years.

Diagnosis

Is based upon three factors: typical clinical manifestations, a positive response to colchicine therapy, and genetic testing, although currently available tests do not detect all mutations associated with FMF.

Major criteria for the clinical diagnosis of FMF are:

- Intermittent episodes of fever with robust interim health
- Concomitant serositis with abdominal pain and tenderness or pleuritis
- Absence of an alternative cause
- Responsiveness to colchicine
- Monoarthritis

The following findings may or may not be present:

- Amyloidosis (rectal or bone marrow biopsy)
- Positive family history
- Mediterranean ancestry

Detailed criteria for the diagnosis of FMF:

Major criteria
Typical attacks
1. Peritonitis (generalized)
2. Pleuritis (unilateral) or pericarditis
3. Monoarthritis (hip, knee, ankle)
4. Fever alone
Minor criteria
1-3. **Incomplete** attacks involving one or more of the following sites:
1. Abdomen
2. Chest
3. Joint
4. Exertional leg pain
5. Favorable response to colchicine
Supportive criteria
1. Family history of FMF
2. Appropriate ethnic origin
3. Age <20 years at disease onset
4-7. Features of attacks:
4. Severe, requiring bed rest
5. Spontaneous remission
6. Symptom-free interval
7. Transient inflammatory response, with one or more abnormal test result(s) for the white blood cell count, erythrocyte sedimentation rate, serum amyloid A, and/or fibronogen
8. Episodic proteinuria/hematuria
9. Negative laparotomy or removal of normal appendix
10. Consanguinity of parents

Diagnosis requires
≥1 major criterion
or ≥2 minor criteria
or 1 minor + ≥5 supportive criteria
or 1 minor criterion + ≥4 of the 1st 5 supportive

Adapted from: Livneh A, Langevitz P, Zemer D, et al. Arthritis Rheum 1997; 40:1879.

Differential Diagnosis:

- Surgical emergencies (appendicitis, intussusception, perforated peptic ulcer, etc)
- Hereditary angioedema, other rare hereditary periodic fever syndromes
- Acute intermittent porphyria
- Relapsing pancreatitis
- SLE and vasculitis
- Hypertriglyceridemia
- Abdominal epilepsy and abdominal migraine

Genetic Testing

The cloning of the FMF gene (MEFV) in 1997 makes genetic testing possible

Since FMF is inherited as an autosomal recessive trait, one would expect that two mutations in the MEFV gene would be required for clinical disease. However, some patients have only one identifiable mutation and some have no identifiable mutations up to 45%.

TNF receptor-1 associated periodic syndrome (TRAPS):

Formerly known as familial periodic fever. TRAPS is inherited in an autosomal dominant fashion with incomplete penetrance. The genetic defect in TRAPS resides in the gene that encodes the 55 kDa receptor for tumor necrosis factor (the TNFR1 gene).

Patients may present from infancy to the 40s and even beyond, though more than half develop symptoms in the first decade of life. Though many patients are of Irish (Hibernian) and Scottish descent, other ethnicities are also represented. Flares commonly last for at least five days and often continue for more than two weeks. They are typically accompanied by conjunctivitis and periorbital edema in addition to focal migratory myalgias, rash, abdominal pain, and, occasionally, monoarthritis. The rash may take a relatively characteristic form, with single or multiple erythematous patches that may spread distally down an extremity.

Hyperimmunoglobulin D syndrome (HIDS)

The HIDS is an autosomal recessive periodic fever syndrome usually associated with mutations in the MVK gene that encodes mevalonate kinase.

More than two-thirds of patients present within the first year of life with episodic attacks of fever lasting three to seven days, accompanied, in most cases, by chills, cervical lymphadenopathy, abdominal pain, and vomiting or diarrhea. Some patients experience headache, arthralgias or arthritis, aphthous ulceration, a pleomorphic rash, and, occasionally, splenomegaly. Attacks may be precipitated by vaccination, viral infection, trauma, and stress.

Most patients have characteristic abnormalities in immunoglobulins, including elevated levels of IgD (>100 international units/mL), and 80% also have elevated IgA. Acute phase reactants rise strikingly with fevers and sometimes remain elevated between episodes.

PFAPA syndrome

Periodic fever with aphthous stomatitis, pharyngitis, and adenitis (PFAPA) is a relatively common entity compared with the other periodic fever syndromes.

Briefly, the disorder is characterized by febrile episodes beginning in early childhood that recur approximately every three to four weeks and that are associated with typical clinical features in the absence of other cause.

Episodes are abrupt in onset, last three to six days, and may be accompanied by one or more of the following:

- Pharyngitis (exudative or nonexudative)
- Mild aphthous ulcerations
- Lymphadenopathy
- Chills (rigors)
- Fatigue
- Headache
- Mild abdominal pain

However, in many patients, regularly recurrent fevers are the only prominent clinical finding. Leukocytosis and elevation of inflammatory markers occur acutely during episodes and return to normal between episodes, when patients are vigorous and grow normally. Most patients with PFAPA outgrow the febrile episodes with time, and no long-term consequences have been identified.

The etiology of PFAPA has not been defined. It is discussed here because of its presentation as recurrent, unexplained fever, but whether the disease truly represents an autoinflammatory condition remains uncertain.

Cryopyrin-Associated Periodic Syndromes (CAPS)

Three clinically overlapping autoinflammatory disorders are known collectively as CAPS or cryopyrinopathies: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal onset multisystem inflammatory disorder (NOMID, also known as chronic infantile neurological cutaneous and articular [CINCA] syndrome).

The CAPS all arise from point mutations in a single gene, NLRP3, which encodes the cryopyrin protein. Cryopyrin is important in innate immunity as part of the multiprotein inflammasome complex. Inheritance of these disorders is autosomal dominant with variable penetrance. NLRP3 mutations are thought to promote aberrant formation of the inflammasome and inappropriate production of active IL-1 beta.

Familial cold autoinflammatory syndrome (FCAS), formerly called familial cold urticaria, is the mildest of the cryopyrin-associated disorders. It is an unusual condition in which exposure to generalized cold, such as an air-conditioned room, results in a stereotyped systemic inflammatory response including fever, an urticarial rash, conjunctival injection, and substantial arthralgias. Symptoms usually develop in the first year of life. Attacks usually resolve within 24 hours, though considerable variability is observed. The presence of conjunctivitis helps to discriminate FCAS from other periodic fever disorders.

Muckle-Wells syndrome (MWS) is a rare condition characterized by the triad of intermittent episodes of fever, headache, urticarial rash, and joint pain (arthralgias or arthritis); progressive sensorineural hearing loss; and secondary (AA) amyloidosis with nephropathy. Febrile episodes occur at irregular intervals every few weeks, lasting 12 to 36 hours before resolving spontaneously. Age of onset is variable. Precipitating factors vary and cannot always be identified, but they may include both heat and cold.

Abnormalities in cryopyrin are responsible for some, but not all, cases of neonatal-onset multisystem inflammatory disease (NOMID), which is also known as chronic infantile neurological cutaneous and articular (CINCA) syndrome. Clinical features, including a migratory, erythematous rash resembling urticaria, fever, impaired growth, abnormal facies with frontal bossing, protruding eyes, and saddle-shaped nose, are characteristic and generally develop at or near the time of birth. Other manifestations affecting the brain, eyes, joints, liver, and spleen may also be present, and AA amyloidosis can occur. NOMID may cause premature death.

A central role for IL-1 beta in these disorders is confirmed by the effectiveness of therapies directed against IL-1 in preventing and alleviating symptoms and in substantially reducing levels of inflammatory indices, including serum amyloid A. These therapies include anakinra , rilonacept , and canakinumab .

An autoinflammatory syndrome distinct from the cryopyrinopathies is characterized by the neonatal onset of sterile multifocal osteomyelitis, periostitis, a neutrophilic dermatosis, and elevated acute phase reactants without fever. Untreated patients may die from multiorgan failure. The patients have a deficiency of the interleukin (IL)-1-receptor antagonist (IL-1RN) due to homozygous germ-line mutations, which may result in hyperresponsiveness to IL-1 beta stimulation and the clinical syndrome. The most effective treatment has been with the interleukin-1 receptor antagonist, anakinra.

The *provisional* Eurofever diagnostic/classification criteria

FMF		MKD		CAPS		TRAPS	
Presence	**Score**	**Presence**	**Score**	**Presence**	**Score**	**Presence**	**Score**
Duration of episodes < 2 days	9	Age at onset <2 years	10	Urticarial rash	25	Periorbital oedema	21
Chest pain	13	Aphthous stomatitis	11	Neurosensorial hearing loss	25	Duration of episodes > 6 days	19
Abdominal pain	9	Generalized enlargement of lymph nodes OR splenomegaly	8	Conjunctivitis	10	Migratory rash^	18
Eastern Mediterranean° ethnicity	22	Painful lymph nodes	13			Myalgia	6
North Mediterranean° ethnicity	7	Diarrhea (sometimes/often)	20			Relatives affected	7
		Diarrhea (always)	37				
Absence		**Absence**		**Absence**		**Absence**	
Aphthous stomatitis	9	Chest pain	11	Exudative pharyngitis	25	Vomiting	14
Urticarial rash	15			Abdominal pain	15	Aphthous stomatitis	15
Enlarged cervical lymph nodes	10						
Duration of episodes > 6 days	13						
Cut-off	**≥60**	**Cut-off**	**≥42**	**Cut-off**	**≥52**	**Cut-off**	**≥43**

Papa Syndrome

The syndrome of pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) is a rare autosomal dominant condition that presents in the first decade of life with pauciarticular, destructive arthritis typically involving the elbow, knee, and/or ankle. Severe cystic acne develops in most patients in early adolescence, while pyoderma gangrenosum and pathergy-like sterile abscesses at injection sites occur in a subset of patients. Bone marrow suppression in the event of exposure to sulfonamide medications may also be observed.

Linkage analysis identified mutations in the gene PSTPIP1, encoding a protein that interacts with pyrin (the protein mutated in familial Mediterranean fever). These mutations strikingly increase the binding of the PSTPIP1 protein to pyrin, presumably interfering with the inhibitory effect of pyrin on the production of

active IL-1. Treatment has been with glucocorticoids, although anti-TNF therapy with etanercept , as well as IL-1 antagonism with anakinra , appears promising.

Blau Syndrome

Blau syndrome is an autosomal dominant condition characterized by granulomatous inflammation of the skin, eye, and joints (MIM 186580). Patients exhibit a papular erythematous rash, sometimes only transiently. Arthritis develops in the first decade of life, often as minimally symptomatic swelling in wrists, ankles, knees, and/or elbows with progressive flexion contractures of the fingers (camptodactyly). Biopsy usually reveals synovial granulomas. Granulomatous uveitis may also occur and can lead to glaucoma and blindness.

Blau syndrome appears to be due to mutations in NOD2 that are located in a different region from mutations of the same gene seen in some cases of Crohn's disease, another disease of granulomatous inflammation. Mutations in NOD2 (also called CARD15 and IBD1) are also found in children with early-onset sarcoidosis (MIM 609464), a sporadically occurring condition usually appearing before age four that shares an identical phenotype with Blau syndrome. Blau syndrome and early sarcoid are believed to belong to the same disease spectrum.

Treatment of Autoinflammatory Diseases: Results from the Eurofever (EF) Registry:

- FMF: Colchicine beneficial in 95%
- CAPS: Anakinra- or canakinumab 70% complete response
- TRAPS: Etanercept effective in 87% (complete response in only 34%), and anakinra or canakinumab in 82%
- MKD: Etanercept effective in 51% (complete response in only 13%), and anakinra or canakinumab in 80%
- PFAPA: Steroids aborted attacks in 78%

The Periodic Fever Syndromes

Disease	Gene Locus	Age of onset	Inher-itance	Ethnicity	Length of fevers	Clinical features	Amyloid	Diagnosis	Therapy
FMF	MEFV	<20 y	AR	Sephardic Jews Armenians Turks Arabs Ashkenazi Jews	1-3d	Abdominal pain Pleurisy Arthralgia/arthritis Scrotal swelling Erysipeloid rash	>20* percent	Mutational testing	Colchicine
TRAPS	TNFR1	<20 y	AD	Irish Scottish other	>5d	Conjunctivitis Abdominal pain Regional myalgia Arthralgia/arthritis Rash	25 percent	Mutational testing	Glucocorticoids Etanercept
HIDS	MEVK	<1 y	AR	Dutch French other	3-7d	Cervical lymph-adenopathy Abdominal pain Arthralgia/arthritis Rash Splenomegaly	rare	Serum IgD >100 IU/ml IgA elevated >80 percent Mutational testing for V377I (>80 percent)	NSAIDs Glucocorticoids
PFAPA	unknown	<5 y	?	any	3-4d	Cervical lymph-adenopathy Aphthous stomatitis	No	none	Glucocorticoids Tonsillectomy

FMF: familial Mediterranean fever; TRAPS: tumor necrosis factor alpha receptor 1 associated syndrome; HIDS: hyperimmunoglobulin D syndrome; PFAPA: periodic fever with aphthous stomatitis, pharyngitis, and cervical adenitis; MEFV: pyrin/marenostrin gene located on chromosome 16p; TNFR1: tumor necrosis factor alpha receptor-1 gene located on chromosome 12 p; MEVK: mevalonate kinase gene located on chromosome 12q; AR: autosomal recessive AD: autosomal dominant.

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