Periodic Fever Syndromes

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Author Disclsure
Dr Goldsmith did not disclose any financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

Objectives

After completing this article, readers should be able to:

1. Describe the differences between the periodic fever (or autoinflammatory syndromes) and autoimmune disorders.
2. Summarize the ethnic predilection and genetic basis for the most common periodic fever syndromes.
3. Recognize the salient clinical features of the most common periodic fever syndromes
4. List the current therapeutic choices for the management of the most common periodic fever syndromes.

Introduction

Any list of the causes of fever of unknown origin in childhood is extensive and must include broad categories such as infectious diseases, neoplastic conditions, and rheumatic/inflammatory disorders. The periodic fever syndromes most often have been included in the rheumatic/inflammatory category, but their proper classification and pathogenesis remain unclear. Within the past 10 years, significant strides have been made in the understanding of the periodic fever syndromes, which now are considered to result from primary dysregulation of the innate immune system.

Many rheumatic disorders that are considered when evaluating for a cause of fever of unknown origin are defined by aberrations of the adaptive or acquired immune system. Antigen recognition by adaptive immune surveillance is accomplished through T and B lymphocytes and is characterized by the enhanced development of either autoantibodies or autoreactive T cells.

Within the innate immune system, aberrations are not based on self-targeting by autoantibodies or lymphocytes but rather occur through the activation of antigen-independent inflammatory mechanisms. Neutrophils, macrophages, and natural killer cells (rather than T and B cells) and tumor necrosis factor (TNF), interleukin-1 (IL-1), and IL-12 are the primary cellular effectors and mediators of innate immunity.

To accommodate this new information, the term *autoinflammatory disorders* has been advanced to classify these conditions more accurately. Many of these disorders are hereditary and have typical ethnic predilections. Thus, the periodic fever syndromes from the nosologic view now are considered to exist within the broader umbrella of the autoinflammatory disorders.

Many of these autoinflammatory disorders have their clinical onset during childhood and present with recurrent fevers. Although the disorders are relatively uncommon, the pediatrician must be familiar with their clinical manifestations and heritable patterns as well as methods of diagnosing them. Recent research has provided elegant insights into the function of the mutated proteins in the disorders, most of

Abbreviations

CAPS:	cryopyrin-associated periodic syndromes
CINCA:	chronic infantile neurologic cutaneous and articular syndrome
ESR:	erythrocyte sedimentation rate
FCAS:	familial cold autoinflammatory syndrome
FMF:	familial Mediterranean fever
HIDS:	hyperimmunoglobulin D syndrome
Ig:	immunoglobulin
IL:	interleukin
MVK:	mevalonate kinase
MWS:	Muckle-Wells syndrome
NOMID:	neonatal-onset multisystem inflammatory disease
NSAID:	nonsteroidal anti-inflammatory drug
PFAPA:	periodic fever, aphthous stomatitis, pharyngitis, adenitis syndrome
TNF:	tumor necrosis factor
TRAPS:	tumor necrosis factor receptor-associated periodic syndrome

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Table. Periodic Fever/Autoinflammatory Syndromes

	Age at Onset	Duration/ Frequency	Key Clinical Features	Inheritance	Common Ethnicity	Mutated Gene/Encoded Protein	Therapy
Familial Mediterranean Fever (FMF)	<10 years (80%)	1 to 3 days/ 4 to 8 weeks	Fever, peritonitis, erysipelas-like rash, oligoarthritis, amyloidosis	Autosomal Recessive	Armenian Arab Turkish Italian Jewish	*MEFV*/Pyrin	• Colchicine • Thalidomide (?) • Anti-TNF agents (?) • Anti-IL-1 agents (?)
Tumor Necrosis Factor Receptor-associated Periodic Syndrome (TRAPS)	3 years (median)	Days to weeks/ irregular intervals	Fever, abdominal pain, peritonitis, severe deep muscle aches with overlying erythema, conjunctivitis and periorbital edema, large-joint arthritis	Autosomal Dominant	Initially Irish and Scottish but now worldwide	*TNFRSFIA*/ p55TNF receptor	• Corticosteroids • Anti-TNF agents (as a steroid-sparing medication) • Anti-IL-1 agents (?)
Hyperimmunoglobulin D Syndrome (HIDS)	6 months (median)	4 to 7 days/ 4 to 6 weeks	Fever, abdominal pain, diarrhea, maculopapular rash, cervical lymphadenopathy, occasional aphthous ulcers	Autosomal Recessive	French Dutch Other European	*MVK*/mevalonic kinase	• NSAIDs • Corticosteroids • Antileukotriene agents (?) • Anti-IL-1 agents (?)
Familial Cold Autoinflammatory Syndrome (FCAS) [Cryoprin-associated periodic syndrome]	<6 months	<24 hours/ related to cold exposure	Fever, chills, urticarial-like rash, severe arthralgias, conjunctivitis	Autosomal Dominant	European	*CIAS1*/cryopyrin	• Anti-IL-1 agents (recent FDA approval)
Muckle-Wells syndrome (MWS) [Cryoprin-associated periodic syndrome]	Infancy to 6 months	24 to 48 hours/ frequent, sometimes almost continuous	Bouts of malaise, severe limb pain, urticarial-like rash, hearing loss, amyloidosis	Autosomal Dominant	Northern European	*CIAS1*/cryopyrin	• Anti-IL-1 agents (recent FDA approval)
Neonatal-onset Multisystem Inflammatory Disease (NOMID)/ Chronic Infantile Neurologic Cutaneous Articular Syndrome (CINCA) [Cryoprin-associated periodic syndrome]	Infancy to 6 months	Continuous	Fever, urticarial-like rash, destructive arthropathy, chronic meningitis, hearing loss, optic neuritis	Autosomal Dominant	All ethnic groups	*CIAS1*/cryopyrin	• Anti-IL-1 agents
Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis Syndrome (PFAPA)	2 to 5 years	3 to 5 days/ every 4 to 6 weeks	Periodic fever, aphthous stomatitis, pharyngitis, adenitis	Random	All ethnic groups	None identified	• Cimetidine • Steroids • Tonsillectomy • Colchicine (?)

FDA=United States Food and Drug Administration, IL=interleukin, NSAID=nonsteroidal anti-inflammatory drug, TNF=tumor necrosis factor

which are linked to pathways of inflammation, apoptosis, and cytokine processing. This review focuses on the clinical aspects of five periodic fever/autoinflammatory disorders (Table): 1) familial Mediterranean fever (FMF); 2) TNF receptor-associated periodic syndrome (TRAPS); 3) hyperimmunoglobulin (Ig) D syndrome (HIDS); 4) cryopyrin-associated periodic syndromes (CAPS), which include familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic cutaneous and articular syndrome (CINCA); and 5) periodic fever, aphthous stomatitis, pharyngitis, adenitis syndrome (PFAPA). Gene analysis by DNA sequencing for FMF, TRAPS, HIDS, and CAPS are available in specialty commercial laboratories. There are no currently recognized mutations responsible for PFAPA.

Familial Mediterranean Fever (FMF)

FMF is the most common autoinflammatory disease and hereditary recurrent fever syndrome. FMF affects

primarily people of Arabic, Turkish, and Armenian descent; non-Ashkenazi Jews; and other Mediterranean populations such as Italians, Greeks, and Lebanese. (1) However, now that identification of the responsible gene defects is possible, FMF is recognized worldwide. FMF is a recessively inherited disorder, with 90% of patients experiencing the first attack before the age of 20 years. Approximately 80% of affected pediatric patients have their first attack before 10 years of age.

Each episode lasts from 1 to 4 days, but there is wide individual variability. Temperature usually is higher than 101.3°F (38.5°C) and is accompanied by serositis, most often peritonitis, followed in frequency by pleuritis and rarely pericarditis or scrotitis (serositis of the tunica vaginalis). The latter manifestation may be mistaken for acute testicular torsion. Approximately 50% of patients experience large-joint arthritis, most often monoarticular, that is of short duration and primarily involves the ankle, knee, or hip. An erysipelas-like rash of the dorsum of the foot and ankle occurs in about 15% to 25% of individuals. Attacks remit spontaneously, and between episodes, the child is well. Local sequelae are uncommon, but chronic arthritis of the hip or knee or encapsulating peritonitis occasionally develops. The major systemic complication of unabated episodes is generalized amyloidosis, particularly of the kidneys. Of interest, patients who have FMF have an increased incidence of polyarteritis nodosa and Henoch-Schönlein purpura. (2)

Accurate diagnosis depends on the recognition of characteristic clinical manifestations, now assisted by genetic testing. The gene (*MEFV*) for FMF is located on the short arm of human chromosome 16p. (3)(4) More than 100 mutations have been found, most encoding missense nucleotide changes in exon 2 or 10. Pyrin, the protein encoded by *MEFV*, is expressed predominantly in neutrophils and monocytes. Pyrin is a regulator of nuclear factor kappa-B activation, IL-1-beta secretion, and apoptosis. The altered pyrin protein downregulates the intensity of the inflammatory response ineffectively, leading to increased apoptosis and IL-1-beta processing. (5)

The white blood cell count, C-reactive protein, erythrocyte sedimentation rate (ESR), and serum amyloid A values rise significantly during attacks. Between episodes, concentrations of these acute-phase reactants often remain slightly elevated.

The long-term outcome of FMF depends on preventing the development of renal amyloidosis. Without medical intervention, nephrotic syndrome develops and renal failure ensues. Daily treatment with colchicine both prevents recurrent attacks and limits the progression of nephropathic amyloidosis. (6) Long-term use of colchicine in children is safe. Major adverse effects are gastrointestinal (diarrhea and nausea) and are believed to result, in part, from colchicine-induced lactose malabsorption.

With consistent colchicine prophylaxis, 67% of children experience complete cessation of attacks, and the intensity and frequency of febrile episodes decreases considerably in another 25%. Progression to amyloidosis essentially is prevented by adherance to the medical regimen. Existing amyloidosis also may improve during colchicine therapy.

Colchicine-resistant FMF is rare and believed to occur in noncompliant patients, although the M6946V mutation carries a major increased risk of amyloidosis. In verified colchicine-resistant individuals, a trial of intravenous colchicine may be helpful. There also are isolated recent reports of improvement with the anti-IL-1 agent anakinra, (7) the anti-TNF agent etanercept, (8) and thalidomide. (8)

Tumor Necrosis Factor Receptor–associated Periodic Syndrome (TRAPS)

TRAPS, originally named Hibernian fever, is an autosomal dominant disorder described initially by Williamson and associates in 1982. (9) A kindred of 13 affected individuals linking three generations of an Irish family was recognized. In 1999, the disorder was renamed TRAPS after determinant mutations were found on chromosome 12 in the gene that encodes the 55-kDa receptor for TNF (*TNFRSF1A*). (10) More than 80 mutations have been identified, with affected patients detected in many other ethnic groups.

Attacks often begin in early to mid-childhood and are characterized by recurrent fevers at irregular intervals. The time between episodes varies, with some individuals having episodes every 3 to 4 weeks and others having only two to three episodes each year.

Typical features include abdominal discomfort, pleuritic pain, and severe localized deep myalgias with overlying erythematous macules and patches. Both the myalgias and skin lesions migrate distally over the course of an episode, which should help the clinician differentiate an attack of TRAPS from typical cellulitis. Abdominal pain and associated vomiting may be sufficiently severe to mimic an acutely inflamed abdomen. Conjunctivitis, periorbital edema, and pain are seen commonly and are characteristic of TRAPS. Arthralgias occur in more than 67% of patients and usually involve the peripheral joints in an oligoarticular pattern. Frank arthritis is uncommon. (11) Clinical progression to renal amyloidosis sometimes occurs.

During episodes, concentrations of all acute-phase reactants are increased, accompanied by a prominent leukocytosis and polyclonal gammopathy, particularly IgA. Acute-phase reactant values often remain slightly elevated between attacks. Creatine kinase and aldolase values are normal. Skin and muscle biopsies of the involved areas most often show a monocytic fasciitis or lymphocytic vasculitis or, very rarely, a mild myositis. (12)

The early descriptions of TRAPS noted that many affected patients had lower serum concentrations of soluble TNFRSF1A than did normal controls. Defective shedding of the altered TNF receptors was considered to be a plausible explanation for persistent proinflammatory signaling. Additional research, however, has implicated other mechanisms, such as defective apoptosis of neutrophils and misfolded receptors that are retained in the endoplasmic reticulum and, thus, are more likely to promote autonomous ligand TNF activation. (11)

Standard therapy for TRAPS remains unsettled. Glucocorticosteroids provide significant symptomatic relief but do not diminish the frequency of episodes. If the attacks are frequent, the corticosteroid load becomes excessive, with its accompanying comorbidities. Trials of multiple other medications, such as dapsone, colchicine, azathioprine, cyclosporine, and thalidomide, have been ineffective.

In view of the known pathophysiologic aberrations in TRAPS that augment TNF activation, it is logical to consider agents that inhibit TNF function as being potentially useful. Initial treatment with the anti-TNF agent etanercept appeared somewhat promising, but inflammatory attacks were blunted, at best, and not abolished. Partial responses also were seen with etanercept when it was used to limit the progression of established amyloidosis. Etanercept is generally agreed to be useful as a steroid-sparing agent in TRAPS, but it is not likely to alter the disease course significantly. Recent reports of persistent efficacy of the anti-IL-1 agent anakinra in controlling both clinical and laboratory manifestations of TRAPS are encouraging. (13)

Hyper-IgD Syndrome (HIDS)

HIDS is a rare autosomal recessive disorder that most often presents during the first year after birth. With ongoing case recognition, the median age of onset is now known to be 6 months. More than 60% of patients are of Dutch or French extraction. HIDS initially was reported in six patients by Van der Meer and associates in 1984. (14) These six patients experienced bouts of fever and abdominal pain with associated vomiting and diarrhea. Other common manifestations include rash, tender lymphadenopathy (usually cervical), and arthralgias as well as a large-joint, nondestructive symmetric arthritis. (15) Oral or vaginal ulcerations may occur. The rash is erythematous and generalized, most often macular or papular and rarely, nodular. Febrile episodes have a rapid onset, with temperatures often approaching 102.2°F (39°C), last from 4 to 7 days, and recur every 4 to 8 weeks without firm periodicity. Inciting factors include minor trauma, viral infections, vaccinations, and surgery. Prior to diagnosis, abdominal pain may be severe enough to mimic an acutely inflamed abdomen, which mandates an exploratory laparotomy. Between episodes, most patients appear well, but the skin lesions and arthralgias may linger for a few days. Febrile attacks persist for life, but are more frequent during childhood.

During the febrile periods, serum C-reactive protein, ESR, and white blood cell count are increased notably. Serum amyloid A values also are elevated, but amyloidosis very rarely evolves. Serum IgD concentrations are strikingly increased (>100 units/mL), as are IgA values in approximately 80% of children. IgD concentrations, however, may be normal during the first 3 years after birth.

Mutations in the mevalonate kinase (*MVK*) gene on the long arm of chromosome 12 are responsible for the clinical manifestations. (16)(17) MVK is an essential enzyme in the biosynthesis of cholesterol and isoprenoids. Although precise mechanisms are not clear, it is likely that either increased concentrations of mevalonic acid or decreased isoprenoids or a combination of both are responsible for the periodic inflammatory symptoms.

In prototypical HIDS, MVK activity is lowered to 5% to 15% of normal. When MVK activity is absent or extremely low, symptoms and signs of mevalonic aciduria such as microcephaly, failure to thrive, and dysmorphic facies also develop. More than 60 mutations in the *MVK* gene have been identified in association with HIDS. It is of interest that elevated IgD concentrations are not unique to HIDS. Up to 13% of patients who have FMF also may have increased IgD concentrations. The contribution of IgD to the pathogenesis of HIDS is unknown, but IgD has been shown to enhance release of TNF-alpha from human mononuclear cells.

No uniformly successful therapy for HIDS exists. Maximum doses of nonsteroidal anti-inflammatory drugs (NSAIDs) for 4 to 7 days may dampen the severity of each febrile episode in some patients. Similar pulse treatments with oral glucocorticoids (1 mg/kg for 4 to 7 days) often are more helpful than NSAIDs in limiting the expression of each attack, but their use is fraught with

known corticosteroid adverse effects. Nominal experience with colchicine, cyclosporine, and thalidomide has been discouraging. Although statin drugs seemed to be a logical choice for treating HIDS, results have been disappointing and have worsened episodes in some individuals. (18) During febrile episodes, urinary leukotriene values may be elevated in some patients. Montelukast, an antileukotriene drug, is under investigation for use in HIDS. (19) The anti-TNF agent etanercept has not been successful in blunting the expression of febrile episodes. (20) Experience with the IL-1 receptor antagonist anakinra is limited, but promising, and warrants further investigation. (20)

Cryopyrin-associated Periodic Syndromes (CAPS)

FCAS, MWS, and NOMID/CINCA are three dominantly inherited disorders that have been found to be linked to mutations in the *CIAS1* gene on chromosome 1p44. (21)(22)(23)(24) This gene encodes a pyrinlike protein, cryopyrin, which is expressed predominantly in peripheral blood neutrophils, monocytes, and chondrocytes. Although each of these disorders has a recognizable clinical pattern, they lie along a continuum of differing disease severity and sometimes exhibit overlapping clinical features. FCAS is the mildest clinical phenotype; NOMID/CINCA is the most severe.

FCAS, formerly called familial cold urticaria, was described initially in 1940. (25) Fever, chills, and urticarial skin lesions develop 30 minutes to 4 to 6 hours after exposure to cold temperatures. Symptoms persist for up to 24 hours. Attacks also are associated with conjunctivitis, severe arthralgias, and joint swelling. Although onset is within the first 6 months after birth, episodes most often are problematic during early adulthood. Leukocytosis frequently is present during each episode. Amyloidosis also may develop, particularly with continuous repetitive episodes.

MWS was described initially in 1962 as a dominantly inherited disorder characterized by generalized nonpruritic urticaria, progressive neurosensory hearing loss, and the evolution of amyloidosis. (26) Episodic attacks of severe lancinating limb pains, synovitis, fever, and severe malaise occur and initially were referred to as "augey bouts." Conjunctivitis also may occur. Symptoms most often start in infancy, and hearing deficits gradually emerge in adolescence. Severe amyloidosis develops in 25% of patients.

NOMID/CINCA was first reported in the early 1980s by several authors. (27)(28) Since then, the disorder has been referred to most often as NOMID in North America and as CINCA in Europe. Overlapping clinical features of NOMID/CINCA, FCAS, and MWS include an urticarial eruption, recurrent fever, and arthralgias/arthritis.

The clinical phenotype of NOMID/CINCA is usually more severe and its symptoms more constant than those of FCAS, MWS, and other inherited periodic fever syndromes such as FMF. NOMID/CINCA is characterized by nearly constant cutaneous eruption, fever, and malaise as well as the development of destructive arthropathy, often with severe cartilaginous overgrowth and early ossification (particularly patellar). Central nervous system involvement frequently is aggressive and includes chronic aseptic meningitis, neurosensory hearing loss, papilledema and optic nerve atrophy, uveitis, and intellectual disability. Often there is a facial dysmorphic appearance, with frontal bossing and enlarged cranial volume. With ongoing inflammation, systemic amyloidosis may develop. The long-term prognosis for normal function frequently is poor.

More than 40 disease-linked mutations of the *CIAS1* gene have been identified in CAPS, almost all being nucleotide missense alterations in exon 3. Cryopyrin, the *CIAS1* gene product, shares a similar PYRIN domain with pyrin (mutated protein in FMF) and, therefore, participates in downstream signaling, which enhances the processing of IL-1, IL-18, and nuclear factor kappa-B. (29) The altered cryopyrin appears to overcome the usual pyrin inhibition of this latter pathway. Such regulatory processes occur in a multimolecular protein complex called the inflammasome.

Other genes or environmental influences also presumably play roles in the pathogenesis of CAPS because *CIAS1* mutations are found only in 50% of patients who have NOMID/CINCA. (22) Reduced penetrance also is likely because nonaffected family members may have the same mutation as affected family members. Although some mutations are associated with unvarying phenotypes, a single missense mutation also may produce a variant phenotype that has considerable overlapping clinical features.

Prior to the recognition of specific mutations associated with CAPS and the recent evidence of the seemingly pivotal role of upregulated IL-1, treatment of CAPS with many aggressive therapeutic agents was uniformly disappointing. More recently, however, therapy with anti-IL-1 agents has been encouraging. All 18 patients who had NOMID/CINCA responded favorably in a multicenter National Institutes of Health-based study when treated with anakinra over 6 months. (30) In February

2008, the IL-1 blocker rilonacept was approved by the United States Food and Drug Administration for use in FCAS and MWS.

Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis Syndrome (PFAPA)

After a report in 1987 of 12 patients who had clinical symptoms of periodic fever, pharyngitis, and aphthous stomatitis, the term "PFAPA" emerged. (31) In 1999, two larger series of patients were reported. (32)(33)

PFAPA presents most often between the ages of 2 and 5 years. Thus far, no adult-onset cases have been identified. There is a slight male predominance, and no particular ethnic group is overrepresented. Unlike most other periodic fever syndromes, PFAPA occurs sporadically, with no recognizable heritable pattern. *MEFV* gene analysis in a group of affected children did not show characteristic mutations. (34) A recent study of 40 children who had abdominal PFAPA found no increase in the frequency of CARD15/NOD 2 polymorphisms. (35)

Clinical onset is characterized by an abrupt fever, often associated with chills. Temperature rises rapidly, often to 104.0° to 105.8°F (40.0°C to 41.0°C). Each episode lasts for 3 to 5 days and recurs at exquisitely regular intervals of 3 to 5 weeks. Between febrile episodes, all children are well, continuing to grow and develop normally.

Relatively small aphthous ulcers develop from 12 to 24 hours after the onset of fever, usually on the lips or buccal mucosa. These mucosal lesions are moderately painful and heal completely without scarring. Both cervical adenopathy and nonexudative pharyngitis occur in most episodes. Other nonspecific complaints include abdominal pain, arthralgias, and headache.

Most children exhibit a modest elevation of the ESR and C-reactive protein values as well as a transient leukocytosis, all of which normalize between episodes. Throat cultures are consistently negative for group A *Streptococcus.* Elevated IgD concentrations have been reported primarily in the Israeli cohort. (33) Increased IgD concentrations do not approach those values seen in HIDS.

A diagnosis of PFAPA depends on clinical criteria proposed by Thomas and associates. (32) All three of the following must be present: 1) three or more documented episodes of fever that last no more than 5 days and occur in regular intervals of 3 to 6 weeks; 2) tender cervical lymphadenopathy, pharyngitis, or aphthous ulcers; and 3) unimpaired growth parameters and normal health between episodes. Exclusion criteria include: 1) neutropenia during an attack or immediately preceding an attack (cyclic neutropenia always must be considered in the differential diagnosis), 2) atypical symptomatology, 3) elevated acute-phase reactants between attacks, and 4) a family history of periodic fever.

PFAPA is a self-limited disease. Within 5 to 7 years, most children no longer are symptomatic. Infrequent and irregular episodes continue to occur for several years in a small number of children, however, after the classic clinical syndrome has disappeared.

No consensus exists concerning the management of PFAPA. In view of its benign natural history, treatment remains optional, and management must be weighed against possible medication-induced adverse effects. Both the usual NSAIDs and acetaminophen appear to be relatively ineffective.

Three major forms of therapy are available. Cimetidine at a dose of 20 to 40 mg/kg per day offers relief to approximately 30% to 40% of children. (32)(36) Short courses of corticosteroids also are effective in blunting each episode. (37) An ongoing concern, however, is that repeated courses of corticosteroids seem to decrease the time intervals between episodes. This observation has been more prevalent among patients reported from North America than in the Israeli cohort.

Tonsillectomy also has been considered a reasonable therapeutic choice for children unresponsive to medical management. Two recent studies, one of which was a randomized, controlled trial, indicated that this procedure is considerably effective. (38)(39) Therapy for each child who has PFAPA must be individualized, depending on the frequency and severity of attacks, physician judgment, and parental preferences.

Practical Clinical Advice

PFAPA is a common disorder and recognized worldwide. FMF also is seen frequently in multiple but specific ethnic groups. The other autoinflammatory disorders are admittedly rare, but with recently increased familiarity by the medical community, they are being diagnosed more frequently.

For any child who has suggestive symptoms and signs, the clinical findings that are more likely to indicate the presence of one of these disorders that, in turn, implies the need for genetic testing, need to be identified.

Gattorno and associates (40) recently examined a population of 228 children who had clinical histories of periodic fever and found that the following features were correlated independently with positive gene analyses: young age of onset, positive family history of periodic fever, thoracic pain, abdominal pain, diarrhea, and oral aphthosis. Their investigation was limited to patients who had FMF, TRAPS, and HIDS.

Therefore, if a child experiences two or three documented episodes of characteristic fever coupled with a clustering of the previously noted clinical findings, the clinician should consider a diagnosis of one these disorders and seek the advice of a pediatric specialist in rheumatology or infectious diseases to guide decisions about what, if any, gene tests should be obtained. Several commercial and research laboratories perform gene analysis for all of these disorders.

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