PERIODIC fever is defined as recurrences of fever that last from a few days to a few weeks, separated by symptom-free intervals of variable duration. This pattern of fever can be caused by recurrent infections or neoplastic disorders but also by noninfectious inflammatory disorders.1 It is important to review the medical history carefully in patients with recurrent febrile attacks. Patients with periodic fever that persists for more than two years rarely have infections or malignant disorders. Attacks with a predictable course and a similar set of symptoms, along with a family history of such attacks, may suggest the presence of a noninfectious form of periodic fever. Although numerous disorders, such as juvenile rheumatoid arthritis, adult-onset Still’s disease, Crohn’s disease, and Behçet’s syndrome, can cause periodic fever, this article will focus on hereditary periodic fever syndromes. We will review the clinical, genetic, and molecular aspects of familial Mediterranean fever, the hyper-IgD syndrome, and the tumor necrosis factor (TNF) receptor–associated periodic syndrome.

FAMILIAL MEDITERRANEAN FEVER

Clinical Features

In 1908, Janeway and Mosenthal described a Jewish girl who had episodic abdominal pain and fever. Although additional cases were described subsequently,2 it took nearly half a century to establish this disorder as familial Mediterranean fever.3,4 The condition is characterized by short attacks of serositis (peritonitis, pleuritis, or arthritis) and fever.5 About 90 percent of patients have their first attack before the age of 20 years.6 Attacks of familial Mediterranean fever unfold suddenly, and the symptoms persist for only a short time (6 to 96 hours) (Fig. 1A).

Abdominal pain of one or two days’ duration occurs in 95 percent of patients,6 most of whom present with an acute abdomen, although some patients have only mild abdominal pain without overt peritonitis.7 Monoarthritis, with effusions of the knee, ankle, or wrist joints, is the sole manifestation of an attack in 75 percent of patients. Chronic destructive arthritis and migratory polyarthritis are rare. Chest pain due to unilateral pleuritis is reported in 30 percent of patients; pericarditis occurs in less than 1 percent.8 Young male patients (less than 20 years of age) may present with acute scrotal swelling and tenderness.9 Erysipel-like skin lesions on the shins or feet, considered to be a specific clinical finding for the disease, are present in 7 to 40 percent of patients.10 Severe, protracted myalgia of the legs is an uncommon symptom of familial Mediterranean fever.

Characteristically, the above-mentioned symptoms are accompanied by fever, but patients may present with fever alone. AA amyloidosis is regarded as the main complication of the disease, and amyloid deposits are found mainly in the kidneys but also in the gastrointestinal tract, liver, and spleen and eventually in the heart, testes, and thyroid. The prevalence of amyloidosis varies according to the population; it is high among Sephardic Jews and low among Ashkenazi Jews.11

Genetic and Epidemiologic Features

Familial Mediterranean fever is an autosomal recessive disease. It is the most prevalent periodic fever syndrome, affecting more than 10,000 patients worldwide. Familial Mediterranean fever predominantly affects people from the Mediterranean basin, including Sephardic Jews, Arabs, Turks, and Armenians. The disorder is unusual in other populations, but it has been described in Greeks, Italians, Cubans, and Belgians.12 The frequency of the susceptibility gene varies widely; it is very high among Armenians (ratio of persons with the gene to those without it, 1:7)13 and Sephardic Jews (1:5 to 1:16)14,15 but is much lower in Ashkenazi Jews (1:135).

Laboratory Findings

There is no specific biologic marker of familial Mediterranean fever that is clinically available. Affected patients lack a specific protease, normally present in serosal fluids, that can inactivate both interleukin-8 and the chemotactic complement factor 5a inhibitor, but the test for this protease is used only in research settings.16 Nonspecific findings include increases in inflammatory mediators, such as serum amyloid A, fibrinogen, and C-reactive protein, during febrile at-
tacks.\textsuperscript{17} Proteinuria (more than 0.5 g of protein per 24 hours) in patients with familial Mediterranean fever is highly suggestive of amyloidosis.\textsuperscript{7}

**Pathogenesis and Molecular Genetic Features**

After familial Mediterranean fever was mapped to the short arm of chromosome 16,\textsuperscript{18} two independent groups were able to clone the gene (\textit{MEFV}).\textsuperscript{19,20} The protein (pyrin, or marenostrin) encoded by \textit{MEFV} contains 781 amino acids and has a molecular weight of 86,000. \textit{MEFV} is predominantly expressed in myeloid cells, and its expression is up-regulated during myeloid differentiation. Inflammatory mediators such as interferon-\(\gamma\) and tumor necrosis factor are also effective stimuli for expression of the gene.\textsuperscript{21} The precise function of pyrin is still unclear. It is mainly expressed in the cytoplasm of mature neutrophils and monocytes and is thought to regulate neutrophil-mediated inflammation.\textsuperscript{21} At least 28 mutations in the \textit{MEFV} gene have been described, most of which are clustered in one exon (Fig. 2).\textsuperscript{22} Two common missense mutations are M694V (occurring in 20 to 67 percent of cases) and V726A (in 7 to 35 percent); their prevalence varies according to the population tested.\textsuperscript{23,24} Founder effects in familial Mediterranean fever have been established, and it is believed that the V726A and M694V mutations originated in common ancestors who lived some 2500 years ago in the

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**Figure 1.** Temporal Patterns of Fever and Associated Clinical Findings in a Patient with Familial Mediterranean Fever (Panel A), a Patient with the Hyper-IgD Syndrome (Panel B), and a Patient with the Tumor Necrosis Factor (TNF) Receptor–Associated Periodic Syndrome (Panel C).

Each panel shows the temperature during an attack of fever in a hospitalized patient and the symptoms that accompanied the febrile attack. The bar graph below each curve shows the number of attacks that the patient had in a year, when they occurred, and their approximate duration. The patient with the TNF-receptor–associated periodic syndrome had long attacks twice in one year, whereas the patient with familial Mediterranean fever and the patient with the hyper-IgD syndrome had shorter but more frequent attacks.
Middle East. The relatively high frequency of the gene might suggest that carrier status for these mutations may have conferred a heightened resistance to a pathogen that has not yet been identified. It is well established that the M694V mutation is associated with a more severe phenotype than the V726A mutation and that homozygosity for M694V carries a higher risk of amyloidosis.

Apart from MEFV mutations, it appears that polymorphisms in the gene for serum amyloid A increase the susceptibility to renal amyloidosis and that polymorphisms in a gene for the major-histocompatibility-class \( \text{I} \) \( \alpha \) chain influence the severity of the disease.

**Treatment**

Since 1972, colchicine has been the first-line treatment for patients with familial Mediterranean fever, and its efficacy has been established in two controlled clinical trials. Colchicine prevents febrile attacks in 60 percent of patients and significantly reduces the number of attacks in another 20 to 30 percent. The lack of efficacy in approximately 5 to 10 percent of patients may be due in part to non-compliance. The average dose in adults is 1 mg daily, but if there is no response, the dose may be increased to 2 mg or even 3 mg. Most patients tolerate this regimen, but diarrhea or abdominal pain may develop, necessitating a reduction in the dose. Side effects such as myopathy, neuropathy, and leukopenia are rare and occur mainly in patients with renal or liver impairment. Colchicine does not stop an established attack, and diclofenac (75 mg administered intramuscularly) may be used for pain relief. Compliance is very important, because the discontinuation of colchicine may result in an attack within a few days. Preliminary data suggested that interferon alfa might be useful in aborting febrile attacks, but a double-blind trial failed to confirm its efficacy. Other agents have limited efficacy, but anecdotal experience suggests that prazosin may be useful.

**Prognosis**

The prognosis for patients with familial Mediterranean fever is determined mainly by the presence or absence of AA amyloidosis; in its absence, life expectancy is normal. Before the introduction of colchicine, amyloidosis occurred in 60 percent of affected patients who were over 40 years of age, and it was the main cause of death in such patients. Treatment with colchicine greatly altered the prognosis by arresting amyloidosis and reversing proteinuria. Even if colchicine therapy does not prevent febrile attacks, it will prevent amyloidosis.

**Diagnostic Strategy**

It is important to take a thorough medical history and obtain all the details of a typical attack. Since examination of the patient between attacks usually reveals no abnormalities, examination during an attack is crucial. Familial Mediterranean fever is a clinical
diagnosis, and the diagnostic criteria have been validated. If a patient has a characteristic medical history and belongs to an ethnic group with a high prevalence of the disorder, the diagnosis is not difficult to make (Table 1). However, the diagnostic criteria were validated in a population with a very high prevalence of familial Mediterranean fever, and it is not known whether the reported sensitivity and specificity (99 percent in both cases) apply to other populations.

Since the MEFV gene has been cloned, it is possible to establish a molecular diagnosis of familial Mediterranean fever, but there are some limitations. Genetic laboratories usually screen for the five most frequent mutations (M694V, V726A, V680I, E148Q, and V694I), and those that are more rare will be missed. Furthermore, MEFV mutations occur on both alleles in only 70 percent of typical cases. In the remaining 30 percent, only one mutation or none can be detected, even after sequencing. There is also evidence of nonpenetrance (i.e., two mutant MEFV alleles in the absence of clinical disease). Despite these limitations, molecular testing can be used as a confirmatory test in cases in which there is a high index of suspicion. Whether or not the results are positive, treatment with colchicine is warranted in symptomatic cases.

**HYPER-IgD SYNDROME**

**Clinical Features**

The hyper-IgD syndrome was recognized as a separate entity in 1984; the disorder has also been described as a variant of Still’s disease or as etiocholanolone fever. Patients with the hyper-IgD syndrome have recurrent attacks of fever that usually start before the end of the first year of life. An attack is heralded by chills, followed by a sharp rise in body temperature, and lasts for four to six days, with gradual defervescence (Fig. 1B). It can be provoked by vaccination, minor trauma, surgery, or stress. Cervical lymphadenopathy and abdominal pain with vomiting, diarrhea, or both almost always accompany the attack. Symptoms that are common include hepatosplenomegaly, headache, arthralgias, arthritis of large joints, erythematous macules and papules, and even petechia and purpura (Fig. 3). A minority of patients report painful, aphthous ulcers in the mouth or vagina. After an attack, patients are free of symptoms, although skin and joint symptoms disappear slowly. The attacks generally recur every four to six weeks, but the interval between them can vary substantially in an individual patient and from one patient to another.

**Genetic and Epidemiologic Features**

The hyper-IgD syndrome is inherited as an autosomal recessive trait, and half the patients with this syndrome have affected siblings. The frequency of the susceptibility gene is low (ratio of persons with the gene to those without it, 1:350), which is why the disorder is not observed in the parents or offspring of affected patients. The hyper-IgD syndrome registry in Nijmegen, the Netherlands, currently has

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**Table 1. Distinctive Features of Familial Mediterranean Fever, the Hyper-IgD Syndrome, and the Tumor Necrosis Factor (TNF) Receptor–Associated Periodic Syndrome.* **

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>FAMILIAL MEDITERRANEAN FEVER</th>
<th>HYPER-IgD SYNDROME</th>
<th>TNF-RECEPTOR–ASSOCIATED PERIODIC SYNDROME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ancestry</td>
<td>Jewish, Turkish, Armenian, Arab</td>
<td>Dutch, French</td>
<td>Scottish, Irish</td>
</tr>
<tr>
<td>Familial transmission†‡</td>
<td>Horizontal</td>
<td>Horizontal</td>
<td>Vertical</td>
</tr>
<tr>
<td>Age at onset (yr)</td>
<td>&lt;20</td>
<td>&lt;1</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Typical duration of attack (days)</td>
<td>2≤</td>
<td>4-6</td>
<td>&gt;14</td>
</tr>
<tr>
<td>Symptoms other than fever</td>
<td>Serositis, scrotal involve-ment, erysipelas-like erythema</td>
<td>Prominent cervical lymphadenopathy</td>
<td>Conjunctivitis, localized myalgia</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td>Low C5a inhibitor in serosal fluids</td>
<td>High serum IgD (&gt;100 IU/ml)</td>
<td>Low serum type 1 TNF receptor (&lt;1 ng/ml)</td>
</tr>
<tr>
<td>Gene</td>
<td>MEFV</td>
<td>Gene for mevalo- nate kinase</td>
<td>Gene for type 1 TNF receptor</td>
</tr>
<tr>
<td>Protein</td>
<td>Pyrin (marenostrin)</td>
<td>Mevalonate kinase</td>
<td>Type 1 TNF receptor</td>
</tr>
<tr>
<td>Therapy</td>
<td>Colchicine</td>
<td>None available</td>
<td>Corticosteroids, etanercept</td>
</tr>
</tbody>
</table>

*The features that are helpful in the diagnostic evaluation are shown. The presence or absence of a particular feature does not rule out the diagnosis.

†Horizontal transmission denotes disease in one or more siblings of an affected patient, and vertical transmission disease in one or both parents or in one or more uncles or aunts.
clinical data on more than 170 published and unpublished cases worldwide (information is available at http://www.hids.net). Most patients with the hyper-IgD syndrome are white and are from western European countries; some 60 percent are either Dutch or French.

**Laboratory Findings**

The hyper-IgD syndrome is diagnosed on the basis of characteristic clinical findings and continuously high IgD values (more than 100 IU per milliliter). However, IgD values may be normal in very young patients (those less than three years old), and persistently low levels were reported in a patient with typical clinical findings and the genotype for the syndrome. In siblings with the disease, there may be marked differences in IgD levels, with very high values in one sibling but low values in another. More than 80 percent of patients have high IgA levels in conjunction with high IgD levels. During an attack, there is a brisk acute-phase response, with leukocytosis, high levels of serum C-reactive protein and serum amyloid A, and activation of the cytokine network. Elevated urinary excretion of neopterin, a marker of an activated cellular immune response, reflects disease activity.

**Pathogenesis and Molecular Genetic Features**

A recent genome-wide search established the linkage of the susceptibility gene for the hyper-IgD syndrome to the long arm of chromosome 12. This information, along with the fortuitous detection of mevalonic acid in a urine sample obtained during a febrile attack in a patient with the hyper-IgD syndrome, led to the identification of mutations in the gene for mevalonate kinase as the cause of the syndrome. Mevalonate kinase is a key enzyme in the cholesterol metabolic pathway and follows 3-hydroxy-3-methylglutaryl–coenzyme A reductase (Fig. 4). In patients with the hyper-IgD syndrome, the activity of mevalonate kinase is reduced to 5 to 15 percent of normal; as a result, serum cholesterol levels are slightly reduced, and during attacks, urinary excretion of mevalonic acid is slightly elevated.

Most patients are compound heterozygotes for missense mutations in the gene for mevalonate kinase. One mutation, V377I, is present in more than 80 percent of patients; the other mutations are less frequent. The V377I mutation results in a slight reduction of the stability of recombinant human mevalonate kinase protein and in the catalytic activity of the enzyme. Less than 1 percent of patients have a complete deficiency of mevalonate kinase, which is associated with mevalonic aciduria, a rare inherited disorder characterized by developmental delay, failure to thrive, hypotonia, ataxia, myopathy, and cataracts. In mevalonic aciduria, the disease-associated mutations are mainly clustered within a specific region of the protein. How a deficiency of mevalonate kinase is linked to an inflammatory periodic fever syndrome is not yet known.

**Treatment**

No uniformly successful treatment of the hyper-IgD syndrome is available. There are anecdotal reports of a benefit of treatment with corticosteroids, intravenous immune globulin, colchicine, or cyclosporine in some cases, but these approaches have failed in others. In a recent double-blind, randomized, crossover trial involving six patients, treatment with thalidomide failed to reduce the disease activity. A trial of simvastatin is under way.

**Prognosis**

Patients with the hyper-IgD syndrome have febrile attacks throughout their lives, although the frequency of attacks is highest in childhood and adolescence. Patients may be free of attacks for months or even years. Amyloidosis has not been reported in association with the hyper-IgD syndrome. As a rule, attacks of arthritis do not lead to joint destruction, but there are exceptions.

**Diagnostic Strategy**

A clinical assessment should be the first step in diagnosing the hyper-IgD syndrome (Table 1). Hyper-IgD syndrome almost always develops in infancy. If a patient presents with symptoms suggestive of the syndrome, IgD and IgA should be measured. If both are elevated, the diagnosis can be made. For confirmation, we recommend screening for the V377I mu-
tation. If the result is negative and the clinical suspicion is high, sequencing of the gene to detect other mutations is possible. Mevalonate kinase activity can be measured, although the procedure is time-consuming. Measurement of urinary mevalonic acid is not useful, since there is only a slight elevation in the amount excreted during an attack.

**Figure 4.** Metabolism of Mevalonate and Biosynthesis of Cholesterol in Mammalian Cells. Mevalonate is the first committed intermediate of the cholesterol metabolic pathway. 3-Hydroxy-3-methylglutaryl (HMG)–coenzyme A (CoA) reductase, which is the rate-limiting enzyme, can be inhibited by the administration of statins. Mevalonate kinase is the defective enzyme in the hyper-IgD syndrome, and the defect results in an accumulation of trace amounts of mevalonate in the urine of affected patients. The structural formulas corresponding to the intermediates in the branched pathway of cholesterol are shown at the left.

**TNF-RECEPTOR–ASSOCIATED PERIODIC SYNDROME**

**Clinical Features**

The TNF-receptor–associated periodic syndrome was first described in 1982 in a large Irish family and was called familial Hibernian fever.57 The affected family members had recurrent fever with localized
myalgia and painful erythema. The autosomal dominant inheritance of this disorder and its response to corticosteroids differentiated it from familial Mediterranean fever. Although there were descriptions of other families with autosomal dominant periodic fever, the genetic defect had to be discovered before it could be established that these families had the TNF-receptor–associated periodic syndrome.

Patients with this syndrome can have attacks that last for at least one or two days, but prolonged attacks (longer than one week) are common, and they can last for weeks (Fig. 1C). Localized pain and tightness of one muscle group and a migratory pattern of the symptoms are prominent features, occurring in more than 80 percent of patients. Abdominal pain, sometimes colicky, is common and may be associated with diarrhea or constipation, nausea, and vomiting. Painful conjunctivitis, periorbital edema, or both are also common, and chest pain due to sterile pleuritis or local myalgia has been reported in half of patients. During febrile attacks, painless cutaneous lesions may develop on the trunk or extremities and may migrate distally. More than 60 percent of patients have erythematous macules or edematous plaques due to a perivascular and interstitial mononuclear-cell infiltrate. Arthralgia of large joints is common, but arthritis is rare. Other symptoms include testicular pain and headache. The prolonged attacks, conjunctivitis, and localized myalgias differentiate the TNF-receptor–associated periodic syndrome from the other syndromes of periodic fever (Table 1). Still, the clinical manifestations of the TNF-receptor–associated periodic syndrome in an individual patient can be surprisingly vague. Some patients notice only periodic muscular pain or periodic conjunctivitis, and others present with fever alone.

Genetic and Epidemiologic Features

Although the most thoroughly characterized pedigree is a large Irish and Scottish family, the autosomal dominant inheritance of the TNF-receptor–associated periodic syndrome has been reported in many ethnic groups. So far, more than 20 families have been described in Australia, France, Puerto Rico, the United States, Finland, and the Netherlands.

Laboratory Findings

During a typical attack, there is neutrophilia, an increased level of C-reactive protein, and mild complement activation. Polyclonal immunoglobulin levels, particularly IgA levels, may be elevated. The IgD level may also be elevated, but the value is almost always less than 100 IU per milliliter. The most discriminatory laboratory finding is a low serum level of the soluble type 1 TNF receptor.

Pathogenetic and Molecular Genetic Features

Linkage analysis mapped the susceptibility gene for two separate families to the short arm of chromosome 12. Positional cloning identified several missense mutations in the gene for the type 1 TNF receptor, which is a 55-kD cell-membrane–coupled receptor with four cysteine-rich extracellular domains and an intracellular motif involved in signal transduction through protein–protein interaction. The receptor is expressed on a large variety of cells and allows signaling of TNF-α. A pleiotropic molecule, TNF-α induces cytokine secretion, activation of leukocytes, fever, and cachexia. Activation of the receptor causes cleavage and shedding of its extracellular part into the circulation, where it acts as an inhibitor of TNF-α. At least 16 mutations in the type 1 TNF receptor have been detected, all in the first two cysteine-rich subdomains of the protein spanning exons 2, 3, and 4 of the genomic sequence. It has been suggested that the subsequent structural changes in the protein interfere with receptor shedding (Fig. 5), leading to continuous TNF-α signaling and, hence, uncontrolled inflammation. However, this hypothesis is inconsistent with the fact that at least two mutations are not associated with any apparent shedding defect.

Treatment

Patients with the TNF-receptor–associated syndrome have responses to high doses of oral prednisone (more than 20 mg). There is a dramatic initial response that wanes with time, necessitating an acceleration of the dose. Colchicine is ineffective in the treatment of this syndrome. Etanercept is a dimeric recombinant fusion protein consisting of two copies of the soluble, extracellular ligand-binding domain of the type 2 TNF-α receptor, linked by the constant (Fc) portion of human IgG1. The drug binds very effectively to both soluble and cell-bound TNF-α and attenuates its biologic effects. The presence of the Fc portion of IgG1 results in a relatively long elimination half-life. Treatment with 25 mg of etanercept, given twice weekly, led to marked improvement in six of eight patients. A similar regimen reversed the nephrotic syndrome in a patient with amyloidosis. We found that a single course of etanercept (25 mg given on three consecutive days) in a patient with a severe case of the TNF-receptor–associated periodic syndrome resulted in a remission that lasted for six months (unpublished data).

Prognosis

The prognosis for patients with the TNF-receptor–associated periodic syndrome is determined mainly by the presence or absence of amyloidosis. AA amyloidosis occurs in about 25 percent of affected families. Amyloid deposits generally lead to renal impairment, but hepatic failure has also been noted. Amyloidosis in a patient with the TNF-receptor–associated
periodic syndrome places other affected family members at high risk for this complication. Since proteinuria is the initial manifestation of renal amyloidosis, it is advisable to screen urine samples from affected family members regularly by dipstick examination.

**Diagnostic Strategy**

The level of type 1 TNF receptor is less than 1 ng per milliliter in most patients with the TNF-receptor–associated periodic syndrome. However, the value may be normal during an attack. Furthermore, in patients with renal amyloidosis, the value increases because the type 1 TNF receptor is cleared by the kidneys. Thus, molecular analysis provides the most straightforward diagnosis. DNA sequencing of the gene will detect any of the known mutations, but also novel ones; this service is available in commercial laboratories. Since the TNF-receptor–associated periodic syndrome is characterized by incomplete penetrance, not all patients with mutations will have symptoms.

**FURTHER CONSIDERATIONS**

Despite the discovery of the genetic defects that cause the three types of hereditary periodic fever, the temporal features of the clinical attacks remain unexplained. One might speculate that the mutated protein functions adequately much of the time but that it decompensates under stressful conditions. This ex-
planation is compatible with the clinical observations, since most patients with periodic fever have had attacks after localized trauma or minor surgical interventions. Other precipitating factors might be of environmental origin, since both viral infections and active immunizations can provoke febrile attacks in patients with the hyper-IgD syndrome.

Apart from the three disorders we have described, there are other periodic fever syndromes, although they have been less well characterized. Familial cold urticaria is a rare autosomal dominant disorder that develops in the first year of life. Exposure to cold air in affected patients may cause a delayed, nonpruritic, nonurticarial maculopapular rash. The rash is sometimes associated with chills, fever, arthralgias, conjunctivitis, myalgias, headache, and fatigue. Amyloidosis develops in some patients. The Muckle–Wells syndrome is similar to familial cold urticaria with two exceptions: the symptoms are not triggered by exposure to cold, and progressive sensorineural deafness is frequently present. The attacks are associated with abdominal pain and arthritis. Both familial cold urticaria and the Muckle–Wells syndrome have been mapped to chromosome 1 (1q44). The two disorders are caused by different missense mutations in the CIASI gene. This novel gene encodes a protein with a pyrin domain, a nucleotide-binding site domain, and a leucine-rich repeat motif region—features that suggest that the protein has an inflammatory role.

Children may have a syndrome of periodic fever, aphthous stomatitis, pharyngitis, and tender cervical adenitis. The disorder usually develops before the age of five years. The episodes, which are not due to infections, last for about four days and recur every two to eight weeks. The prognosis for patients with this syndrome is more favorable than that for patients who have other periodic fever syndromes, with spontaneous resolution in four to eight years and no sequelae. Most patients have a response to a course of prednisone (1 to 2 mg per kilogram of body weight) given for one or two days. The serum IgD level may be elevated, but the value is lower than that in patients with the hyper-IgD syndrome. A family history of the disorder is usually absent, and it is unclear whether there is a genetic defect.

Great progress has been made in our understanding of the three well-established periodic fever syndromes, and it has become easier to diagnose these disorders (Table 1). Still, in a substantial number of patients with periodic fever, the specific syndrome cannot be identified. Among patients with periodic fever of unknown origin, the chance of establishing a diagnosis is less than 50 percent if the three main syndromes have been ruled out.1

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REFERENCES


44. Drenth JP, Mariman EC, Van der Velde-Visser SD, Repers HH, Van der Meer JW. Location of the gene causing hyperimmunoglobulinemia D and periodic fever syndrome differs from that for familial Mediterranean fever. Hum Genet 1994;94:616-20.


