CHAPTER 24

Periodic Syndromes

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- Hereditary periodic fever syndromes are autoinflammatory diseases characterized by episodes of fever with serosal, synovial, and/or skin inflammation.
- Familial Mediterranean fever (FMF) and hyperimmunoglobulinemia D with periodic fever syndrome (HIDS) are inherited in an autosomal recessive manner and tumor necrosis factor receptor–associated periodic syndrome (TRAPS), familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID) are dominantly inherited.
- Colchicine and biologic therapies such as tumor necrosis factor alpha (TNF-alpha) and interleukin 1 beta (IL-1 beta) receptor agonists are successful in the treatment of some of these inherited diseases.

Several forms of arthritis may present with patterns of exacerbation and remission that may be considered periodic. This chapter focuses on six clinically distinct illnesses in which underlying genes have been identified, and in addition a group of disorders of unclear etiology.

HEREDITARY PERIODIC FEVER SYNDROMES

This group of diseases is characterized by episodes of fever with serosal, synovial, and/or cutaneous inflammation. Unlike the commonly recognized autoimmune diseases, there is a lack of either high titer autoantibodies or self-reactive T cells, and hence these conditions are sometimes referred to as *autoinflammatory* diseases (1). Based on clinical findings and patterns of inheritance, at least six distinct disorders have been grouped among the hereditary periodic fever syndromes (Table 24-1). Two of these illnesses, familial Mediterranean fever (FMF) and the hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), are inherited in an autosomal recessive manner. The other diseases, tumor necrosis factor (TNF) receptor–associated periodic syndrome (TRAPS), familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID, also known as chronic infantile neurologic cutaneous and articular syndrome, or CINCA), are dominantly inherited. Advances in molecular genetics have identified four genes underlying these six clinical entities.

It should be noted at the outset that there are a number of patients with unexplained recurrent fevers who do not have demonstrable mutations in these four genes, and who may not meet clinical criteria for any of the six disorders described below. In children, the syndrome of periodic fever with aphthous stomatitis, pharyngitis, and cervical adenopathy (PFAPA) is relatively common (2). In addition to the cardinal manifestations making up the acronym, abdominal pain and arthralgia are also sometimes seen. Mutations in the known periodic fever genes are an exclusion criterion, and this condition almost uniformly abates in late adolescence or early adulthood.

Familial Mediterranean Fever

Familial Mediterranean fever is a recessively inherited disease most frequently observed in Jewish, Armenian, Arab, Turkish, and Italian populations (3), with a modest male predominance (4). FMF (entry 249100 of Online Mendelian Inheritance in Man, OMIM, at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM) is caused by mutations in *MEFV* (MEditerranean FeVer), a 10-exon gene encoded on the short arm of chromosome sixteen (5,6). To date, over 70 disease-associated *MEFV* mutations have been described, many clustered in exon 10. The online database of periodic fever mutations, INFEVERS (http://fmf.igh.cnrs.fr/infevers/), provides an updated listing of *MEFV* mutations and

TABLE 24-1. THE HEREDITARY PERIODIC FEVER SYNDROMES.

CLINICAL FEATURES	FAMILIAL MEDITERRANEAN FEVER	HYPER IGD SYNDROME	TNF RECEPTOR–ASSOCIATED PERIODIC SYNDROME	FAMILIAL COLD AUTOINFLAMMATORY SYNDROME	MUCKLE–WELLS SYNDROME	NEONATAL ONSET MULTISYSTEM INFLAMMATORY DISORDER/CINCA
Mode of inheritance	Autosomal recessive	Autosomal recessive	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant
Underlying gene	*MEFV*, encoding pyrin (marenostrin)	*MVK*, encoding mevalonate kinase	*TNFRS1A*, encoding p55 TNF receptor	*CIAS1*, encoding cryopyrin (NALP3)	*CIAS1*, encoding cryopyrin	*CIAS1*, encoding cryopyrin (NALP3)
Usual ethnicity	Turkish, Armenian, Arab, Jewish, Italian	Dutch, other north European	Any ethnicity	Mostly European	Mostly European	Any ethnicity
Duration of attacks	12–72 hours	3–7 days	Days to weeks	12–24 hours	2–3 days	Continuous, with flares
Abdominal pain	Sterile peritonitis, constipation	Severe pain, vomiting, diarrhea, rarely peritonitis	Peritonitis, diarrhea, or constipation	Nausea	Abdominal pain, vomiting, diarrhea	Can occur
Pleural	Common	Rare	Common	Not seen	Rare	Rare
Arthropathy	Monoarthritis; rarely protracted arthritis in knee or hip	Arthralgia, symmetric polyarthritis	Arthritis in large joints, arthralgia	Polyarthralgia	Polyarthralgia, oligoarthritis, clubbing	Epiphyseal overgrowth, contractures, intermittent or chronic arthritis, clubbing
Cutaneous	Erysipeloid erythema on lower leg, ankle, foot	Diffuse maculopapular rash, urticaria	Migratory rash with underlying myalgia	Cold-induced urticarial rash	Urticarialike rash	Urticaria-like rash
Ocular	Rare	Uncommon	Periorbital edema, conjunctivitis	Conjunctivitis	Conjunctivitis, episcleritis	Progressive visual loss, uveitis, conjunctivitis
Neurologic	Rarely aseptic meningitis	Headache	Controversial	Headache	Sensorineural deafness	Headache, sensorineural deafness, chronic aseptic meningitis, mental retardation
Lymphatic	Splenomegaly, occasional lymphadenopathy	Painful cervical lymphadenopathy in children	Splenomegaly, occasional lymphadenopathy	Not seen	Rare	Hepatosplenomegaly, lymphadenopathy
Vasculitis	Henoch–Schöenlein purpura (HSP), polyarteritis nodosa	Cutaneous vasculitis common, rarely HSP	HSP, lymphocytic vasculitis	Not seen	Not seen	Occasional
Systemic amyloidosis	Risk depends on *MEFV* and *SAA* genotypes, more common in Middle East	Rare	Occurs in 15%, risk increased with cysteine mutations	Rare	Occurs in ~25%	May develop in some patients, usually in adulthood
Treatment	Daily colchicine prophylaxis	Anti-TNF, statins investigational	Corticosteroids, etanercept	Anakinra (anti-IL1 receptor antagonist)	Anakinra (anti-IL1 receptor antagonist)	Anakinra (anti-IL1 receptor antagonist)

ABBREVIATIONS: TNF, tumor necrosis factor.

polymorphisms. Carrier frequencies in high risk populations can be as high as 1 in 3.

MEditerranean FeVer is expressed in polymorphonuclear leukocytes, the major cell found in FMF inflammatory infiltrates, as well as activated monocytes and synovial and peritoneal fibroblasts. *MEFV* codes for a 781 amino acid protein called pyrin (5), also known as marenostrin (6). The N-terminal 90 amino acids of pyrin are the prototype for a motif termed *the pyrin domain*, or PYD, found in over 20 human proteins involved in the regulation of inflammation and apoptosis. Through its PYD, pyrin associates with the apoptosis-associated specklike protein with a caspase recruitment domain (ASC), and thereby may regulate interleukin 1 beta (IL-1 beta) processing and leukocyte apoptosis (7). It is likely that pyrin variants in FMF lead to accentuated innate immune responses, and may have been selected by an as-yet unknown infectious agent.

Clinical and Laboratory Features

Familial Mediterranean fever is characterized by episodes of fever, usually lasting 1 to 3 days, with or without serositis, synovitis, or skin rash. Young children may present with fever alone. The first clinical episode usually occurs in childhood or adolescence, and 80% to 90% of patients experience their first episode by age 20. The time between attacks can vary for an individual patient, and may range from days to years. The magnitude of fever and type of attack (abdominal, pleural, or arthritic) may vary over time for any patient. During attacks, laboratory abnormalities in FMF include leukocytosis and elevated acute-phase reactants, including the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fibrinogen, haptoglobin, and serum amyloid A (SAA).

Attacks comprised of fever and abdominal pain occur at some time in nearly all FMF patients. Abdominal pain may range from a dull ache to full-blown peritonitis, with rigid abdomen, absent bowel sounds, and rebound tenderness. Patients often undergo exploratory laparoscopy, which may reveal neutrophil-laden exudates. Repeated episodes of peritonitis may lead to adhesions. Constipation is common during attacks. Pleuritic episodes may occur without fever, and are usually unilateral. Other forms of serositis may occur. Pericarditis is uncommon; there have been rare reports of tamponade. Unilateral acute scrotal pain occurs in 5% of prepubertal boys, due to inflammation of the tunica vaginalis, an embryological remnant of the peritoneal membrane.

Joint involvement in FMF is particularly common in those with the M694V homozygous genotype (8). Acute monoarticular arthritis is most characteristic in FMF, particularly affecting the knee, ankle, or hip. These episodes of arthritis tend to last longer than serosal attacks, with large effusions, extreme pain, and inability to bear weight. Synovial fluid may appear septic, with as many as 100,000 polymorphonuclear leukocytes/mm^3, but is sterile. Nevertheless, erosive changes rarely develop. In the precolchicine era, up to 5% of patients developed chronic hip arthritis, with secondary osteoarthritis or osteonecrosis, requiring joint replacement. Chronic sacroiliitis may also occur in FMF, regardless of human leukocyte antigen (HLA)-B27 status or use of colchicine. Arthralgia is common in FMF, but nonspecific.

The most characteristic cutaneous lesion of FMF is *erysipeloid erythema*, a sharply demarcated, erythematous, tender swollen area occurring on the dorsum of the foot, ankle, or lower leg. FMF patients may rarely experience febrile myalgia, with excruciating muscle pain lasting up to several weeks; histologic features are suggestive of vasculitis. Other forms of vasculitis, including Henoch–Schönlein purpura and polyarteritis nodosum, are seen at increased frequency. Aseptic meningitis has been reported in FMF; however, a causal relationship has not been established.

The most serious complication of FMF is systemic amyloidosis (AA type), due to the deposition of a product of the acute phase reactant, SAA, in the kidneys, adrenal glands, intestine, spleen, lung, and testes. Risk factors for amyloidosis include M694V homozygous *MEFV* genotype (8), male gender, a positive family history for amyloidosis, and the SAA1 alpha/alpha genotype. Before the use of colchicine, renal failure due to amyloidosis was the most common cause of death. Amyloid deposition in the intestine may result in malabsorption. Cardiac involvement, neuropathy, and arthropathy are uncommon in the amyloidosis of FMF. Amyloidosis may rarely be the first manifestation of FMF (phenotype II). Urinalysis for protein is a rapid and inexpensive screen for amyloidosis. In patients with persistent proteinuria, amyloidosis can be evaluated directly by examination of a Congo red–stained rectal or renal biopsy specimen under polarized light.

In patients from high-risk ethnic groups with typical symptoms and a therapeutic response to colchicine, genetic testing is usually not considered necessary to confirm the diagnosis. Genetic testing may be a useful adjunct in atypical cases, or for physicians not familiar with FMF and related syndromes. Nevertheless, a significant fraction of patients with typical clinical findings of FMF have only one demonstrable *MEFV* mutation, rather than two, as would be expected in a recessive condition, and a small number of patients with clinical FMF may have no demonstrable mutations. These observations raise the possibility that there is a second FMF gene, or that *MEFV* mutations exist that are not accessible to current screening methods. Interpretation of genetic tests may be further complicated by the existence of complex alleles, where more than one mutation

is identified on a single carrier chromosome, which at times appear sufficient to cause symptoms with a second normal allele. Thus, even in the era of molecular diagnostics, clinical judgment maintains a central role in the diagnosis of FMF.

Treatment

Daily oral cochicine therapy is the mainstay of treatment; it prevents both acute attacks and the development of amyloidosis. Over 75% of adults experience near-complete improvement in symptoms. The usual daily dose is 1.2 to 1.8 mg for adults, with children over 5 years of age requiring similar doses. In younger children, lower doses may be sufficient. In patients with amyloidosis, therapy should be aimed at reducing SAA levels below 10 mg/L. Diarrhea is a common side effect of colchicine, but may be minimized by starting at a low dose and gradually titrating upwards, by dividing the daily dose, and by taking appropriate measures should lactose intolerance develop. Neuropathy and myopathy are rare complications observed mainly in the elderly and those with renal impairment. There may be a slightly increased risk of trisomy 21 in the offspring of parents taking colchicine at the time of conception. The use of intravenous colchicine to abort acute episodes may cause severe toxicity in those taking daily oral colchicine. Patients with breakthrough attacks may benefit from subcutaneous interferon alpha, the IL-1 beta receptor antagonist anakinra, or biologic therapies targeted at TNF-alpha, although all of these approaches remain investigational. FMF patients with Henoch–Schönlein purpura or protracted febrile myalgia may require corticosteroids, and those with polyarteritis nodosa may require cyclophosphamide and high-dose corticosteroids.

Hyperimmunoglobulinemia D with Periodic Fever Syndrome

Hyperimmunoglobulinemia D with periodic fever syndrome (OMIM 260920) is a recessively inherited autoinflammatory disorder described primarily in patients of Dutch or north European origin (9). In 1999, HIDS was shown to be caused by mutations in *MVK*, the gene encoding mevalonate kinase, an enzyme involved in cholesterol and nonsterol isoprene biosynthesis (10,11). As of this writing, over 50 disease-associated *MVK* mutations are listed on the INFEVERS website. HIDS mutations leave low levels of residual function of the enzyme, and lead to increased levels of the substrate, mevalonic acid, in the urine, especially during febrile attacks. Serum cholesterol levels are in the low–normal range. *MVK* mutations leading to complete loss of enzymatic activity cause mevalonic aciduria, a rare disease with mental retardation, cataracts, and failure to thrive, in addition to features seen in HIDS. Current hypotheses on the pathogenesis of HIDS are based on the possible effects of isoprenoid deficiency or excess mevalonic acid on innate immune function. Elevated serum IgD is not thought to play a primary role in pathogenesis.

Clinical and Laboratory Findings

The first attack usually starts in infancy, often precipitated by childhood immunizations. The duration of attacks is between 3 and 7 days. Episodes may occur once or twice a month in childhood and adolescence, and may become less frequent or severe when the patient reaches adulthood. Minor infections, trauma, surgery, and menses may act as triggers.

The attacks of HIDS often begin with chills and headache. In children diffuse tender lymphadenopathy is common, and is considered a characteristic finding of HIDS. Abdominal pain is often present, but peritoneal irritation is less common than in FMF or TRAPS. Attacks are often accompanied by vomiting and diarrhea. A number of cutaneous manifestations have been described, including diffuse painful erythematous macules, urticaria, and a morbilliform rash. Unlike FMF there is no predilection for the lower limbs and the rash does not migrate. In as many as 70% of patients, HIDS may be associated with arthralgia or arthritis, and joint symptoms sometimes coincide with abdominal attacks. In contrast with the monoarticular arthritis of FMF, HIDS arthritis tends to be polyarticular. Large joints are usually affected, synovial fluid shows a predominance of granulocytes, and x-rays do not usually show erosions. Systemic amyloidosis is uncommon in HIDS.

During inflammatory attacks, HIDS patients present with leukocytosis and elevated acute-phase reactants. Prior to the identification of the underlying gene, HIDS was defined by polyclonal elevation of serum IgD (≥100 U/mL or >10 mg/dL) on two occasions at least 1 month apart in patients with a compatible history. While most *MVK* mutation-positive patients with recurrent fevers meet these criteria, a small percentage of mutation-positive patients have normal IgD levels despite clinical symptoms (HIDS sine hyperimmunoglobulinemia D). Serum IgD levels do not correlate with severity or frequency of attacks. Over 80% of patients also have elevated serum IgA levels (9). Urinary levels of mevalonic acid are markedly increased during attacks. The diagnosis of HIDS can be confirmed in patients with a typical history, with or without an elevated serum IgD, by finding increased urinary mevalonic acid during attacks or two mutations in *MVK* on genetic analysis. Patients with typical symptoms and increased serum IgD but without mutations or increased urinary mevalonate are sometimes said to have *variant HIDS.* It is likely that this latter category represents an etiologically heterogeneous group of patients.

Treatment

There has been no proven treatment for HIDS. Nonsteriodal anti-inflammatory drugs (NSAIDs) and intra-articular steroids may be of benefit in HIDS arthritis. Corticosteroids, cyclosporine, and intravenous immunoglobulin are not generally effective in HIDS. A modest benefit from HMGCoA reductase inhibitors such as simvastatin has been described (12). A study of etanercept, a TNF-alpha inhibitor, in two patients demonstrated marked improvement. Anecdotal evidence would suggest that some patients benefit from treatment with the IL-1 beta receptor antagonist, anakinra, or the leukotriene inhibitor montelukast. HIDS does not seem to have a major effect on longevity and attacks tend to ameliorate after adolescence.

Tumor Necrosis Factor Receptor–Associated Periodic Syndrome

Tumor necrosis factor receptor–associated periodic syndrome (OMIM 142680) is a dominantly inherited autoinflammatory disease caused by mutations in *TNFRSF1A*, a gene on the short arm of chromosome 12 that encodes the p55 receptor for TNF (1). Patients with TRAPS tend to have inflammatory episodes longer than those seen in FMF or HIDS, often lasting at least 1 week and sometimes as long as 4 to 6 weeks. Prior to the identification of causative *TNFRS1A* mutations, case reports described this condition under a number of clinical names, including familial Hibernian fever (13) and benign autosomal-dominant familial periodic fever. The recognition that this disorder may be seen in a wide range of ancestries has led to the introduction of the ethnically neutral TRAPS nomenclature, which emphasizes the pathogenesis of the disorder.

The TNFRSF1A protein, also known as the p55 TNF receptor, has four highly conserved extracellular cysteine-rich domains, a transmembrane domain, and an intracellular death domain. Five of the first six mutations identified were single-nucleotide differences causing amino acid substitutions at cysteines that participate in disulfide bonds that maintain the receptor's three-dimensional conformation. Other subsequently identified mutations have been shown to interfere with hydrogen bonding or to add or delete amino acids in the extracellular domains of the receptor. To date, over 50 mutations in the *TNFRSF1A* gene have been catalogued on the INFEVERS website, about half of which involve substitutions at conserved extracellular cysteine residues. Thus far no patients have been identified with transmembrane or intracellular mutations, null mutations (in which the protein is not expressed), or mutations in the p75 TNFRSF1B receptor, encoded on chromosome 1. Two particular TNFRSF1A variants, P46L and R92Q, are found at high frequency in the African-American and Caucasian populations, respectively, and are associated with a broader spectrum of clinical findings than cysteine mutations.

When *TNFRSF1A* mutations were first described, mechanistic studies suggested that TRAPS might be caused by a failure to shed mutant TNF receptors from the cell surface (1). Ordinarily, p55 receptors are cleaved by metalloproteases from leukocyte cell membranes upon cellular activation, thereby preventing repeated TNF signaling and creating a pool of soluble receptors that might compete for ligand with membrane-bound receptors. TRAPS patients have lower than normal levels of soluble p55 in the serum, and studies of leukocytes from three patients with the C52F mutation demonstrated impaired ectodomain cleavage upon activation. While this "shedding defect" was subsequently corroborated in patients with at least some other *TNFRSF1A* mutations, a number of other functional abnormalities in TRAPS-mutant receptors have been identified. These include reduced binding to TNF, decreased signaling for apoptosis, and impaired trafficking in the cell. This latter abnormality may lead to ligand-independent cellular activation through multiple pathways, and may account for the dominant inheritance of the TRAPS phenotype. It is interesting to note that, to date, it has been difficult to identify any effect of the R92Q TNFRSF1A variant on leukocyte function.

Clinical and Laboratory Features

In common with the other hereditary recurrent fever syndromes, TRAPS is characterized by episodes of fever and localized inflammation (14). Although there is a great degree of variability, attacks may last more than 1 month at a time. The cutaneous manifestations can be quite distinctive, the most characteristic of which is a migratory macular area of erythema that can occur on the torso (Figure 24-1), or on the limbs and migrate distally, with myalgia in the underlying muscle groups. Magnetic resonance imaging has demonstrated inflammatory changes extending into the muscle compartments (Figure 24-1). Ocular involvement is quite common in TRAPS, presenting with periorbital edema or conjunctivitis but rarely uveitis. The combination of prolonged attacks, characteristic rash, and ocular involvement, with more pronounced response to corticosteroids than to colchicines, are all suggestive of TRAPS.

Attacks of TRAPS are associated with a marked acute-phase response. Systemic AA amyloidosis may develop in approximately 15% of patients with TRAPS (Figure 24-1) and can result in renal failure. The risk of amyloidosis may be somewhat higher among those with a positive family history of amyloidosis and those with mutations causing substitutions at cysteine residues. The diagnosis of TRAPS should be considered in all patients with unexplained inflammatory episodes even when no

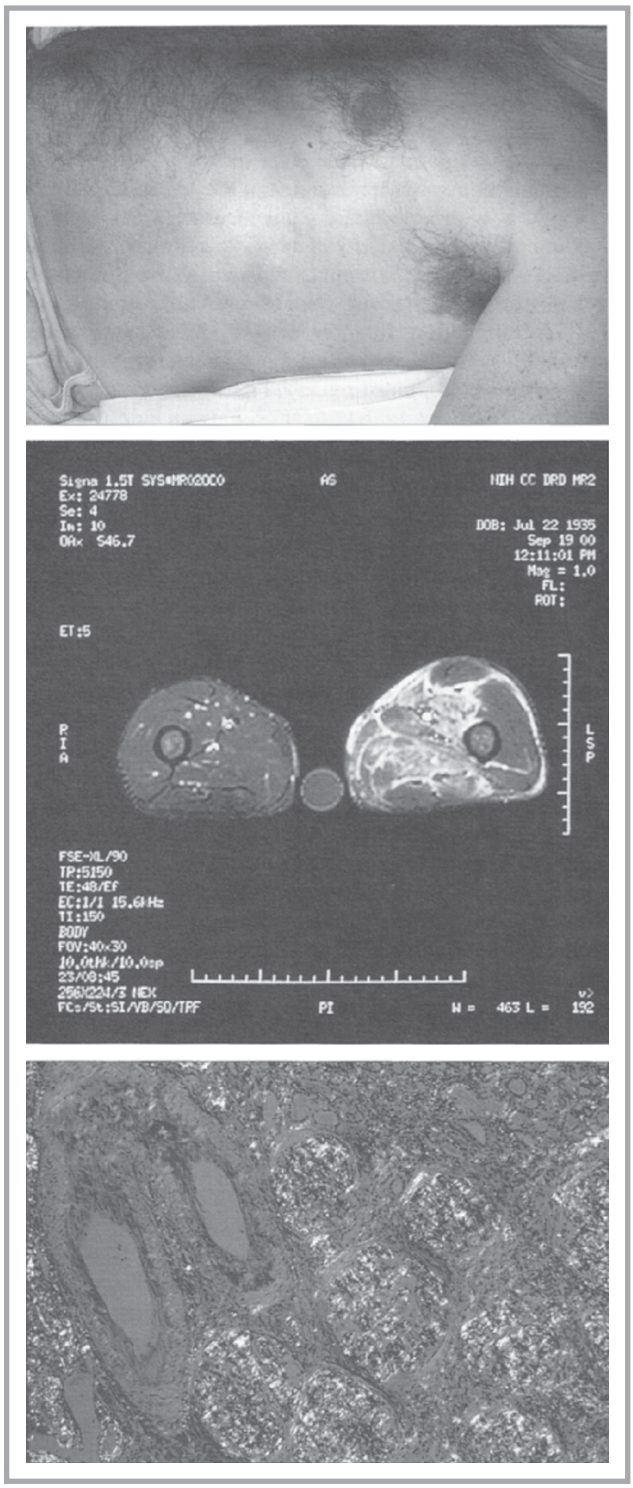

FIGURE 24-1

Clinical features of the tumor necrosis factor (TNF) receptor–associated periodic syndrome (TRAPS). (Top) Typical migratory erythematous rash on the trunk of a patient with the T50M mutation. (Center) Magnetic resonance image of a person with TRAPS (T50M) with skin rash and myalgia of the left thigh. The biopsy demonstrated fasciitis and panniculitis, but no myositis. (Bottom) Photomicrograph demonstrating amyloidosis in the kidney of a TRAPS patient with the C52F mutation. The kidney section was stained with Congo red and viewed under polarizing light.

family history has been elicited, as de novo *TNFRS1A* mutations have been reported. To make a diagnosis of TRAPS, the patient should have a documented *TNFRS1A* mutation and history suggestive of the disease. Patients with TRAPS-like illnesses who do not have mutations in *TNFRSF1A* have been described, but the molecular basis of their illness(es) remains unknown. Although TRAPS attacks are debilitating, they are self-limited. The prognosis of TRAPS is largely dependent on whether the patient develops amyloidosis.

Treatment

Daily colchicine neither prevents acute attacks nor prevents the development of amyloidosis. NSAIDs may be used in mild attacks, with corticosteroids reserved for more severe cases. Patients on corticosteroids frequently require increasing doses over the course of their illness with attendant increased adverse effects. Studies using etanercept, the p75 TNF receptor fusion protein, suggest a favorable response in clinical and laboratory parameters. It has been suggested that modifying the etanercept dose in response to normalized SAA levels may be important to prevent the development or progression of amyloidosis in patients at increased risk. Apropos of recent data suggesting a ligand-independent pathophysiology of TRAPS, there are anecdotal data indicating that TRAPS patients who cannot tolerate etanercept may respond to the IL-1 beta receptor antagonist, anakinra.

Cryopyrinopathies

The cryopyrinopathies include FCAS (OMIM 120100) (15), MWS (OMIM 191900) (16), and NOMID/CINCA (OMIM 607115) (17). These three disorders comprise a clinical spectrum, with FCAS the mildest and NOMID/CINCA the most severe, caused by dominantly inherited mutations in *CIAS1* (cold-induced autoinflammatory syndrome 1) (18,19). The protein encoded by *CIAS1,* denoted cryopyrin or NALP3, has an N-terminal PYD, thus establishing a relationship with the FMF protein pyrin, a central NACHT domain thought to be involved in nucleotide-binding and oligomerization, and a C-terminal leucine-rich repeat domain that may interact with microbial products. Nearly all of the over 50 disease-associated mutations in cryopyrin listed in the INFEVERS database reside in the NACHT domain, encoded by exon 3 of *CIAS1*.

The cryopyrin protein forms a macromolecular complex called the *inflammasome*, which activates caspase-1 and thereby cleaves IL-1 beta from its 31 kDa precursor to the biologically active 17 kDa fragment. Cryopyrin-deficient mice exhibit a number of immunologic abnormalities, most notably the inability to produce active IL-1 beta in response to certain bacteria

or bacterial products. Leukocytes from patients with the cryopyrinopathies exhibit accentuated IL-1 beta production at baseline or in response to various stimuli.

Clinical and Laboratory Features

Patients with the cryopyrinopathies usually present very early in life with fever, an urticarialike skin rash, and an intense acute-phase response. The rash is not true urticaria, in that there are infiltrates of granulocytes and lymphocytes rather than mast cells. The severity of joint and neurological involvement, along with the risk of amyloidosis, helps to distinguish among the three clinical disorders, although there is considerable overlap.

Familial cold autoinflammatory syndrome has a clear episodic quality, with attacks of rash, fever, polyarthralgia, and constitutional symptoms occurring 1 to 2 hours after generalized cold exposure. Amyloidosis is rare, and patients usually have normal life expectancy. In MWS, attacks occur with no clear relationship to cold exposure, and are manifested by fever, urticarial skin rash, limb pain, arthralgia, or arthritis, and sometimes abdominal pain, conjunctivitis, or episcleritis. Sensorineural hearing loss occurs in most patients, and AA renal amyloidosis may develop in about one quarter.

Patients with NOMID/CINCA usually present in infancy with nearly continuous clinical findings. These include fever, urticarial skin rash, and constitutional symptoms. Chronic aseptic meningitis also occurs, which can lead to headache, increased intracranial pressure, and intellectual impairment. Sensory organ involvement includes sensorineural hearing loss, conjunctivitis, and uveitis, sometimes leading to deafness and/or blindness. NOMID/CINCA patients may also develop a distinctive arthropathy with overgrowth of the epiphyses of the long bones. Untreated, about 20% die before reaching adulthood, and amyloidosis may occur later in life. Although all three disorders are dominantly inherited, NOMID/CINCA was not initially recognized as a genetic disease because of decreased reproductive fitness in patients carrying the diagnosis.

Genetic testing usually focuses on sequencing exon 3 of *CIAS1*. As is the case for FMF, TRAPS, and HIDS, there are patients who meet clinical criteria for the cryopyrinopathies who do not have identifiable mutations. This is particularly the case for NOMID/CINCA, where only about half of the patients carrying the clinical diagnosis have demonstrable *CIAS1* mutations. Nevertheless, the availability of genetic testing has markedly increased the awareness of these disorders.

Treatment

Promising results have been obtained with the IL-1 beta receptor antagonist, anakinra, in all three cryopyrinopathies. Patients with FCAS and MWS exhibit almost complete remission of all disease symptoms. In a trial involving 18 patients with NOMID/CINCA who had failed to respond to either corticosteroids or TNF blockers (20), treatment with daily subcutaneous injections of anakinra resulted in disappearance of rash and conjunctivitis within 3 days. In the 12 patients for whom cerebrospinal fluid (CSF) could be obtained, intracranial pressure, protein, and white cell counts decreased significantly. Vision remained stable in all patients, and hearing actually improved in one third. Complete remission of inflammation occurred in 10 of the 18 symptoms after 6 months of treatment. Magnetic resonance imaging demonstrated marked reduction in cochlear and leptomeningeal enhancement. These findings suggest that CNS as well as peripheral manifestations of NOMID/CINCA are mediated by an excess of IL-1 beta, and that these symptoms can be ameliorated by the administration of anakinra. The discontinuation of anakinra led to a relapse of symptoms within days, and re-treatment led to rapid improvement, thus supporting the need for continuous use of anakinra in NOMID/CINCA. Longer term follow-up will be required to determine whether IL-1 inhibition will prevent the intellectual sequelae of NOMID/CINCA, or the development of amyloidosis.

IDIOPATHIC INTERMITTENT ARTHROPATHIES

In contrast to the hereditary periodic fever syndromes, which are systemic diseases, these disorders primarily affect joints and adjacent structures (Table 24-2), and genetics appears to play a less important role.

Palindromic Rheumatism

Initially described in 1944, palindromic rheumatism (PR) describes intermittent, relatively brief episodes of typically monoarticular arthritis or periarthritis (inflammation of the soft tissues adjacent to the joint). The prevalence is roughly 20-fold less than that of rheumatoid arthritis (RA). The mean age of onset is approximately 45 years, with a relatively even gender balance. Occasional families have been reported with multiple cases of PR, or in which PR and RA have occurred together. Recent series suggest increased prevalence of the shared epitope DRB-0401 and DRB-0404 alleles in PR relative to controls (21). In the absence of laboratory and radiographic clues to the diagnosis, it is likely that PR represents a heterogeneous group of disorders.

Clinical and Laboratory Features

In PR, attacks occur suddenly, initially affect one joint, and last from hours to days. Recurrences can occur over

TABLE 24-2. IDIOPATHIC PERIODIC SYNDROMES.

FEATURE	PALINDROMIC RHEUMATISM	INTERMITTENT HYDRARTHROSIS	EOSINOPHILIC SYNOVITIS
Attacks	~2 days; monoarticular arthritis or periarticular soft tissue inflammation	3–5 days, monoarticular arthritis, large effusions	1–2 weeks, monoarthritis triggered by trauma
Joints involved	MCPs, PIPs, wrists, shoulders, MTPs, ankles	Knee to hip, ankle, elbow	Knee, MTP
Associated conditions	Familial aggregation with RA	Episodes may coincide with menses; heterozygous *MEFV* mutations?	Personal or family history of atopy, dermatographism
Prognosis	~50% persistent palindromic rheumatism, ~33% develop RA	Attacks often occur at predictable intervals; sometimes spontaneous remissions	Self-limited episodes, benign prognosis
Treatment	Injectable gold, antimalarials, sulfasalazine	NSAIDs, colchicine, intra-articular steroids, synovectomy	Symptomatic

ABBREVIATIONS: MCP, metacarpophalangeal joint; MTP, metatarsophalangeal joint; NSAID, nonsteriodal anti-inflammatory drug; PIP, proximal interphalangeal joint; RA, rheumatoid arthritis.

irregularly spaced intervals. The joints affected include the interphalangeal joints of the hands and feet, the wrists, shoulders, and ankles (22). Tender periarticular swelling, 2 to 4 cm in diameter, may accompany an attack, or occur independently. Small, sometimes painful subcutaneous nodules may develop near the elbows, wrists, or knees, with a particular predilection for the fingers. Periarticular swelling and nodule formation are usually transient.

During attacks, there is a mild-to-moderate acceleration of the ESR (22). Antibodies to cyclic citrullinated peptide (anti-CCP) and rheumatoid factor (RF) are positive in about half of patients with PR. Antinuclear antibodies are negative with normal complement levels. Synovial biopsies and fluid taken during an attack demonstrate polymorphonuclear leukocytes. Biopsies of subcutaneous nodules demonstrate inflammatory cells, and notably lack the areas of fibrinoid necrosis and palisading mononuclear cells seen in rheumatoid nodules.

Longitudinal data on patients with PR demonstrated that 33% eventually develop RA, the conversion heralded by conversion to seropositivity for RF, and development of more aggressive disease (22). A retrospective study identified RF positivity, female gender, and involvement of the wrist in proximal phalangeal joints as the greatest risk factors for the development of RA (23), and more recent data suggest that antibodies to CCP may be a better predictor than RF.

Treatment

Anecdotal evidence suggests a role for NSAIDs, injectable gold, antimalarials, or sulfasalazine. There have been no large randomized, controlled trials in the treatment of PR.

Intermittent Hydrarthrosis

Intermittent hydrarthrosis is characterized by periodic episodes of monoarticular or pauciarticular arthritis. Constitutional symptoms are rare. Attacks are notable for the periodicity of their nature, such that patients can accurately predict their next attack. Spontaneous remission occurs in some cases (24). Prevalence data are not available; however, it is a relatively rare condition. The usual age of onset is between 20 and 50, with a relatively even gender balance. There are cases in which attacks began at menarche, coincided with menses, and remitted during pregnancy and following menopause. Generally, familial clustering of this condition does not occur. Recently, three cases of intermittent hydrarthrosis with heterozygous *MEFV* mutations were reported from Spain, raising the intriguing possibility that this disorder might be a forme fruste of the more well-recognized autoinflammatory diseases.

Clinical and Laboratory Features

Attacks involve episodes of pain, swelling, and limitation of movement, usually affecting a single joint, although occasionally more than one joint may be affected. In most cases, attacks last 3 to 5 days, with massive joint effusions but no erythema or warmth. In an individual patient, a limited number of joints may be affected, the most commonly affected being the knee, with the hip, ankle, and elbow less frequently involved.

Laboratory findings during attacks demonstrate a normal ESR and leukocyte count. Synovial fluid is mildly inflammatory with less than 5000 white blood cells/mm^3. An inflammatory infiltrate with edema is present on synovial biopsy (24). Radiographs demonstrate soft tissue swelling but no erosions, even in patients with repeated attacks.

Treatment

A number of therapeutic interventions have been tried, including NSAIDs, colchicine, intra-articular corticosteroids, surgical synovectomy, and intra-articular radioactive gold.

Eosinophilic Synovitis

This rare condition is described in individuals with a history of atopy. Both genders are affected equally, and the typical age of onset is between 20 and 50 years (25). Minor trauma may trigger episodes of acute, painless monoarthritis. Synovial fluid demonstrates up to 50% eosinophils. Eosinophilic synovitis has been proposed to be the synovial equivalent of dermatographism. It has been speculated that trauma may trigger activation of mast cells, attracting eosinophils and thus producing an effusion (25). The knee is most commonly affected. Episodes are self-limiting, lasting up to 2 weeks, but require only symptomatic treatment.

Clinical and Laboratory Features

Swelling develops rapidly, usually over 12 to 24 hours, and lasts for 1 to 2 weeks. Although the effusions are large, there is little associated pain, warmth, or erythema. The ESR is not elevated. The peripheral white cell count, and in particular the eosinophil count, is normal, although some patients have elevated IgE levels. Synovial fluid shows mildly elevated leukocyte counts, with 16% to 52% eosinophils in the initial series (25). Charcot–Leyden crystals (bipyramidal, hexagonal-shaped protein crystals) are formed by products of intracellular lipases in eosinophils, and may be demonstrated following overnight incubation at 4°C. Synovial eosinophilia resolves following an attack. There are no long-term radiographic changes.

Numerous conditions are associated with synovial eosinophilia, including RA, psoriatic arthritis, rheumatic fever, infectious arthritidies including parasitic, tuberculous, and Lyme arthritis, and the hypereosinophilic syndrome. Synovial eosinophilia is also seen in patients with metastatic adenocarcinoma and following arthrography. Features suggestive of eosinophilic arthritis, in contrast to the wide differential mentioned, include a personal or family history of allergy and dermatographism (25).

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