Periodic Fever Syndromes Are Rare, Erupt on Skin

BY HEIDI SPLETE
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CHICAGO — Many genetically based periodic fever syndromes have skin signs that may help identify the syndromes on the rare occasions when they occur, Dr. Kathryn M. Edwards said at the annual meeting of the Society for Pediatric Dermatology.

Although these syndromes, called familial periodic fever syndromes, are rare, knowing something about them will "allow you to think more about how we control fever and inflammatory processes in children," noted Dr. Edwards, professor of pediatrics at Vanderbilt University, Nashville, Tenn.

"Periodic fever is a very specific diagnosis," said Dr. Edwards, an expert vaccinologist who has conducted research for the National Institutes of Health. Periodic fevers are fevers that recur at intervals lasting from a few days to a few weeks separated by totally symptom-free intervals.

A periodic fever syndrome is a form of autoinflammatory disorder. "Generally periodic fevers that have been present for more than 2 years are never associated with infection or malignancy," she explained.

In one study, 29 children with periodic fevers tended to be younger at the onset of the fever (often less than 1 year of age), had a longer duration of symptoms before they were referred for further evaluation, and had higher maximum fever temperatures, compared with 11 children with daily fevers (J. Pediatr. 1996;129:419-23).

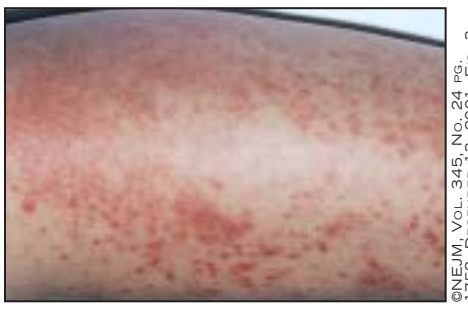
About a quarter of the periodic fever patients had a nonspecific rash, but so did the children with daily fevers. Comorbid rash and fever isn't enough to diagnose a familial periodic fever syndrome. But pharyngitis and oral ulcers or adenopathy were seen much more often in patients with periodic fever during their intervals of fever than in those with daily fevers.

The familial syndromes are characterized by identified genetic defects that inhibit the body's ability to control inflammation, and genetic testing is needed to confirm a diagnosis of these syndromes.

There are distinct patterns of ancestry for familial periodic fever syndromes and the genes have been circulating for generations, said Dr. Edwards. "The familial febrile syndromes are not easy to diagnose, and if you have a patient who you suspect has one of these syndromes, please contact the NIH for genotyping," she said.

Following are the familial periodic fever syndromes she described:

► **Familial Mediterranean Fever (FMF).** FMF is linked to a recessive gene known as MEFV. Many patients experience secondary amyloidosis, in which a protein buildup in various organs and tissues can impede their functions. FMF is common in Jewish families of Spanish, Portuguese, or Middle Eastern descent, but it is rare in Jewish families of European descent, Dr. Edwards noted.



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Petechiae and purpura associated with hyper-IgD syndrome is shown on a leg.

Clinical features include serositis and scrotal swelling, and the periodic attacks of fever often begin in childhood. The most common dermatologic manifestation is a distinctive erysipeloid rash on the lower extremities that occurs in about 15% of children with this syndrome. Studies have shown that about half of these patients also report arthritis in one ankle, knee, or hip. The fever attacks in FMF patients occur at regular intervals, and they usually respond to treatment within 12-72 hours. Colchicine treatment has been shown to be effective in preventing the fever episodes (and the subsequent rash), although not in treating the acute attacks of fever once they occur.

"If you treat people with FMF regularly with colchicine they don't get attacks of fever and they don't get amyloidosis, so it is important that FMF is diagnosed," Dr. Edwards said.

► **Hyperimmunoglobulinemia D Syndrome (HIDS).** HIDS has an early onset (the median age of onset is 6 months), and recurrent attacks of fever persist throughout the patient's life. Febrile attacks usually last for 3-7 days at irregular intervals ranging from 4 to 8 weeks. Clinical features include cervical adenitis, vomiting, and diarrhea. A patient with HIDS may present to a dermatologist with a maculopapular rash, with petechiae and purpura that appear during a febrile attack. Generalized lymphadenopathy and rash are very common in these patients.

Distinctive laboratory features include an elevated IgD (greater than 14.3 mg/dL), but this elevation is not present in all HIDS patients. The gene for HIDS has been mapped to chromosome 12 and at least 8 different mutations or deletions have been seen, but the syndrome is most likely to occur in people with Dutch or French ancestry, Dr. Edwards said.

► **Tumor Necrosis Factor–Receptor Associated Periodic Syndrome (TRAPS).** Children with TRAPS may have a lifelong history of febrile episodes that last 2-3 weeks at a time, but the febrile episodes only occur 2-3 times per year.

Conjunctivitis and raised red lesions distinguish TRAPS from other familial periodic fever syndromes. One study of 25 TRAPS patients showed that 21 (84%) had erythematous patches, including both wavy and circular lesions (N. Engl. J. Med. 2001;345:1748-57). Other clinical features of TRAPS include myalgia, arthralgia, and abdominal pain.

Skin manifestations are much more common with TRAPS than with the other familial periodic fever syndromes. "Almost all of these children will have skin lesions that may persist even when the fever is gone," Dr. Edwards noted.

When a febrile episode occurs, TNF receptors are suppressed, which creates an uncontrolled inflammatory response. Consequently, TNF inhibitors can be used to treat these patients, Dr. Edwards said.

► **Muckle-Wells Syndrome/Familial Cold Urticaria.** These two syndromes are both associated with mutations of the CIAS1 gene family. Mutations in these genes lead to autoinflammatory syndromes in which large numbers of cytokines are generated, which means that amyloidosis is very frequent in these individuals.

Patients with Muckle-Wells syndrome (MWS) generally present with urticaria and progressive sensorineural loss and deafness. Because MWS is a disease of dominant genes, the parent may show signs of hearing problems, which should prompt clinicians to include MWS in the differential diagnosis of recurrent urticaria and fever.

By contrast, patients with familial cold urticaria will present not only with urticaria and wheals, but with complaints of painful joints, chills, and fever. Febrile episodes in patients with familial cold urticaria generally occur several hours after exposure to cold. Both syndromes are associated with German, English, French, and North American ancestry. ■

Tacrolimus Prevents Flares in Atopic Dermatitis

CHICAGO — Intermittent treatment with tacrolimus ointment kept atopic dermatitis under control with no need for corticosteroids in patients aged 2-15 years whose conditions had stabilized, according to a presentation at the annual meeting of the Society for Pediatric Dermatology.

Concerns persist about the long-term effects of corticosteroid use by children and teens, so safe and effective alternatives are needed for the long-term management of atopic dermatitis (AD). The black box warning attached to tacrolimus (Protopic) says that continuous use should be avoided, so Dr. Amy S. Paller of Northwestern University, Chicago, and her colleagues designed a plan that involved applying tacrolimus ointment to the affected skin three times weekly for 40 weeks.

The goal was to prevent flares in patients whose AD had stabilized. The randomized trial of the protocol's safety and effectiveness was sponsored by Astellas Pharma US Inc.

A total of 206 patients were randomized, but 54 discontinued the study. The most common reason for discontinuation was loss to follow-up (15 patients). Ten children dropped out because of uncontrolled rebound exacerbation of their AD, and five dropped out because of an adverse event.

Overall, those who received tacrolimus ointment had significantly fewer relapse days (47) than those who received a control ointment containing alclometasone (76 days). The tacrolimus patients remained stable for significantly more days before their first relapses (116 days vs. 31 days).

Only 6% of the children in the tacrolimus group relapsed for up to 3 days during the study period. In the control group, 19% of the children relapsed for up to 6 days. The most common adverse events reported by tacrolimus patients were burning and itching at the application site, which reflects results from previous safety studies.

—Heidi Splete