

Familial Periodic Fever Syndromes Erupt on Skin

BY HEIDI SPLETE
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CHICAGO — Several genetically based periodic fever syndromes have skin signs that may help clinicians 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, know-

ing 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.

“We tend to think that most often fever is due to recurrent infections,” Dr. Edwards said. Consequently, many patients with periodic fever syndromes may be told that they have recurrent infections or possibly neoplasia. But a periodic fever syndrome is actually 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.

Dr. Edwards cited one of the few stud-

ies that characterized children with periodic fever syndromes, compared with daily fevers that were associated with other illness. Overall, the 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.

“But by and large when [children with periodic fevers] are not febrile they are totally normal, and the parents say that their kids are the healthiest on the block,” Dr. Edwards said. 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.

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

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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 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 le-

sions 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. ■

New Terbinafine Formulation Knocks Out Tinea

CHICAGO — A new oral formulation of the antifungal drug terbinafine significantly improved tinea capitis in children aged 4-12 years compared with griseofulvin oral suspension, based on efficacy data from 1,286 children in the largest study of the medication to date.

These findings were presented in a poster by Dr. Sheila Friedlander at the annual meeting of the Society for Pediatric Dermatology.

Children with confirmed positive cultures for tinea capitis who were randomized to receive terbinafine had a significantly higher complete cure rate (combined mycologic and clinical cure rates) after 6 weeks of daily treatment and 10 weeks of follow-up, compared with those who received griseofulvin (45% vs. 39%), said Dr. Friedlander, a pediatric dermatologist at the University of California, San Diego Medical Center.

The new terbinafine formulation (Lamisil oral granules) consists of coated granules that can be sprinkled on food so children can swallow them easily. Both terbinafine and griseofulvin are dosed by body weight. The study was supported in part by Novartis Pharmaceuticals Corp.

Adverse event rates were similar between the two groups. About half of the patients in each group reported at least one adverse event, but almost all were mild or moderate; only 1.6% of the terbinafine patients and 1.2% of the griseofulvin patients discontinued their medications because of adverse events. The most common complaints included vomiting, diarrhea, headache, and abdominal pain.

The mycologic cure rate alone was significantly higher in the terbinafine group compared with the griseofulvin group (62% vs. 56%). The clinical cure rate alone was higher, but not significantly higher, in the terbinafine group compared with the griseofulvin group (63% vs. 59%). Terbinafine was most effective against *Trichophyton tonsurans*, which is the organism most often associated with tinea capitis, Dr. Friedlander and her associates wrote.

—Heidi Splete

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