

Periodic Fever Syndromes Are Rare, Erupt on Skin

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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, 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.

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,



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

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 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. ■

LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION

(3% and <1%); Anorgasmia (2% and <1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo \geq Lexapro: headache, upper respiratory tract infection, back pain, pharyngitis, inflicted injury, anxiety. †Primarily ejaculatory delay. ‡Denominator used was for males only (N=225 Lexapro; N=188 placebo). §Denominator used was for females only (N=490 Lexapro; N=404 placebo). Generalized Anxiety Disorder Table 3 enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia (see TABLE 3). TABLE 3. Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder¹ (Lexapro (N=429) and Placebo (N=427)).

Autonomic Nervous System Disorders: Dry Mouth (3% and 5%); Sweating Increased (4% and 1%); Central & Peripheral Nervous System Disorders: Headache (24% and 17%); Paresthesia (2% and 1%); Gastrointestinal Disorders: Nausea (18% and 8%); Diarrhea (8% and 6%); Constipation (5% and 4%); Indigestion (3% and 2%); Vomiting (3% and 1%); Abdominal Pain (2% and 1%); Flatulence (2% and 1%); Tachycardia (2% and 0%). **General:** Fatigue (8% and 2%); Influenza-like symptoms (5% and 4%); Musculoskeletal: Neck/Shoulder Pain (3% and 1%). **Psychiatric Disorders:** Somnolence (13% and 7%); Insomnia (12% and 6%); Libido Decreased (7% and 2%); Dreaming Abnormal (3% and 2%); Appetite Decreased (3% and 1%); Lethargy (3% and 1%); Yawning (2% and 1%). **Urogenital:** Ejaculation Disorder² (14% and 2%); Anorgasmia³ (6% and <1%); Menstrual Disorder (2% and 1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo \geq Lexapro: inflicted injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis. †Primarily ejaculatory delay. ‡Denominator used was for males only (N=182 Lexapro; N=195 placebo). §Denominator used was for females only (N=247 Lexapro; N=232 placebo). **Dose Dependency of Adverse Events:** The potential dose dependency of common adverse events (defined as an incidence rate of \geq 5% in either the 10 mg or 20 mg Lexapro groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Lexapro-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day Lexapro-treated patients was greater (86%). Table 4 shows common adverse events that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group. TABLE 4. Incidence of Common Adverse Events¹ in Patients with Major Depressive Disorder Receiving Placebo (N=311), 10 mg/day Lexapro (N=310), 20 mg/day Lexapro (N=125); Insomnia (4%, 7%, 14%); Diarrhea (5%, 6%, 14%); Dry Mouth (3%, 4%, 9%); Somnolence (1%, 4%, 9%); Dizziness (2%, 4%, 7%); Sweating Increased (<1%, 3%, 8%); Constipation (1%, 3%, 6%); Fatigue (2%, 2%, 6%); Indigestion (1%, 2%, 6%). †Adverse events with an incidence rate of at least 5% in either the Lexapro groups and with an incidence rate in the 20 mg/day Lexapro group that was approximately twice that of the 10 mg/day Lexapro group and the placebo group. **Male and Female Sexual Dysfunction with SSRIs:** Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain. However, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. Table 5 shows the incidence rates of sexual side effects in patients with major depressive disorder and GAD in placebo-controlled trials. TABLE 5. Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials (In Males Only: Lexapro (N=407) and Placebo (N=383); Ejaculation Disorder (primarily ejaculatory delay) (12% and 1%); Libido Decreased (6% and 2%); Impotence (2% and <1%). (In Females Only: Lexapro (N=373) and Placebo (N=636)); Libido Decreased (3% and 1%); Anorgasmia (3% and <1%). There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Prapism has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. **Vital Sign Changes:** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Lexapro treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving Lexapro indicated that Lexapro treatment is not associated with orthostatic changes. **Weight Changes:** Patients treated with Lexapro in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight. **Laboratory Changes:** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Lexapro treatment. **ECG Changes:** Electrocardiograms from Lexapro (N=625), racemic citalopram (N=351), and placebo (N=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for Lexapro and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for Lexapro and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither Lexapro nor racemic citalopram were associated with the development of clinically significant ECG abnormalities. **Other Events Observed During the Premarketing Evaluation of Lexapro:** Following is a list of events that reflect treatment-emergent adverse events, as defined in the introduction to the ADVERSE REACTIONS section, reported by the 1428 patients treated with Lexapro for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. All reported events are included except those already listed in Tables 2 & 3, those occurring in only one patient, event terms that are so general as to be uninformative, and those that are unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with Lexapro, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients. **Cardiovascular - Frequent:** palpitation, hypertension. **Infrequent:** bradycardia, tachycardia, ECG abnormal, flushing, varicose vein. **Central and Peripheral Nervous System Disorders - Frequent:** light-headed feeling, migraine. **Infrequent:** tremor, vertigo, restless legs, shaking, twitching, dysequilibrium, tics, carpal tunnel syndrome, muscle contractions involuntary, sluggishness, coordination abnormal, faintness, hyperreflexia, muscular tone increased. **Gastrointestinal Disorders - Frequent:** heartburn, abdominal cramp, gastroenteritis. **Infrequent:** gastroesophageal reflux, bloating, abdominal discomfort, dyspepsia, increased stool frequency, belching, gastritis, hemorrhoids, gagging, polyposis gastric, swallowing difficult. **General - Frequent:** allergy, pain in limb, fever, hot flushes, chest pain. **Infrequent:** edema of extremities, chills, tightness of chest, leg pain, asthenia, syncope, malaise, anaphylaxis, fall. **Hemic and Lymphatic Disorders - Infrequent:** bruise, anemia, nosebleed, hematoma, lymphadenopathy cervical. **Metabolic and Nutritional Disorders - Frequent:** increased weight. **Infrequent:** decreased weight, hyperglycemia, thirst, bilirubin increased, hepatic enzymes increased, gout, hypercholesterolemia. **Musculoskeletal System Disorders - Frequent:** arthralgia, myalgia. **Infrequent:** jaw stiffness, muscle cramp, muscle weakness, arthritis, muscle weakness, back discomfort, arthropathy, jaw pain, joint stiffness. **Psychiatric Disorders - Frequent:** appetite increased, lethargy, irritability, concentration impaired. **Infrequent:** jitteriness, panic reaction, agitation, apathy, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, amnesia, anxiety attack, bruxism, carbohydrate craving, confusion, depersonalization, disorientation, emotional lability, feeling unreal, tremulousness nervous, crying abnormal, depression, excitability, auditory hallucination, suicidal tendency. **Reproductive Disorders/Female⁴ - Frequent:** menstrual cramps, menstrual disorder. **Infrequent:** menorrhagia, breast neoplasm, pelvic inflammation, premenstrual syndrome, spotting between menses. *% based on female subjects only. **H-305 Respiratory System Disorders - Frequent:** bronchitis, sinus congestion, coughing, nasal congestion, sinus headache. **Infrequent:** asthma, breath shortness, laryngitis, pneumonia, tracheitis. **Skin and Appendages Disorders - Frequent:** rash. **Infrequent:** pruritus, acne, alopecia, eczema, dermatitis, dry skin, folliculitis, lipoma, furunculosis, dry lips, skin nodules. **Special Senses - Frequent:** vision blurred, linitis. **Infrequent:** taste alteration, sarcoma, conjunctivitis, vision abnormal, dry eyes, eye irritation, visual disturbance, eye infection, pupils dilated, metallic taste. **Urinary System Disorders - Frequent:** urinary frequency, urinary tract infection. **Infrequent:** urinary urgency, kidney stone, dysuria, blood in urine. **Events Reported Subsequent to the Marketing of Escitalopram:** Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with escitalopram treatment during post marketing experience and were not observed during the premarketing evaluation of escitalopram: abnormal gait, acute renal failure, aggression, akathisia, allergic reaction, anger, angioedema, atrial fibrillation, choreoathetosis, delirium, delusion, diplopia, dysarthria, dyskinesia, dystonia, ecchymosis, erythema multiforme, extrapyramidal disorders, fulminant hepatitis, hepatic failure, hyposaesthesia, hypoglycemia, hypokalemia, INR increased, gastrointestinal hemorrhage, glaucoma, grand mal seizures (or convulsions), hemolytic anemia, hepatic necrosis, hepatitis, hypotension, leucopenia, myocardial infarction, myoclonus, neuroleptic malignant syndrome, nightmares, nystagmus, orthostatic hypotension, pancreatitis, paranoia, photosensitivity reaction, priapism, prolactinemia, prothrombin decreased, pulmonary embolism, QT prolongation, rhabdomyolysis, seizures, serotonin syndrome, SIADH, spontaneous abortion, Stevens Johnson Syndrome, tardive dyskinesia, thrombocytopenia, thrombosis, torsade de pointes, toxic epidermal necrolysis, ventricular arrhythmia, ventricular tachycardia and visual hallucinations.

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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 de-

signed 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