Rash Pattern, Duration Mark Fever Syndromes

BY BRUCE JANCIN

EXPERT ANALYSIS FROM A SYMPOSIUM SPONSORED BY THE AMERICAN COLLEGE OF RHEUMATOLOGY

SNOWMASS, COLO. – Hereditary periodic fever syndromes can be distinguished by the nature of the associated rash and the duration of attacks, according to Dr. Daniel Kastner.

These syndromes are characterized by recurrent episodes of fever with dramatic, seemingly unprovoked inflammation – both local and systemic – without evidence of autoimmunity or infection. Hereditary periodic fever syndromes result from inherited abnormalities in innate immunity. They are classified as systemic autoinflammatory diseases distinguished by inflammation in the absence of major involvement of the adaptive immune system.

These disorders include the tumor necrosis factor receptor–associated periodic syndrome (TRAPS), familial Mediterranean fever, hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), and the cryopyrin-associated periodic syndromes (CAPS), Dr. Kastner said at the meeting.

One of the world's preeminent authorities on the hereditary periodic fever syndromes, Dr. Kastner and his coworkers at the National Institutes of Health have identified the causative genes in several of these disorders. Their discoveries led directly to novel and highly effective therapies.

TRAPS was known as Hibernian fever until Dr. Kastner and his colleagues discovered the causative mutations. "We wanted a name that was short and snappy, easy to remember," recalled Dr. Kastner, scientific director of the National Human Genome Research Institute in Bethesda, Md.

Here's what Dr. Kastner thinks physicians need to know about these syndromes:

TRAPS. The rash in TRAPS is usually migratory. It often begins proximally on a limb, for example on the thigh. The next day the rash might be on the knee but no longer on the thigh. The following day it might appear on the calf, while the knee is clear. Marked periorbital edema with conjunctivitis is another distinguishing feature. Renal amyloidosis can occur in severely affected patients.

TRAPS is associated with fever and rash, often with serositis and/or arthritis. Unlike other hereditary period fever syndromes, an episode of TRAPS may last for weeks. On MRI, the inflammation is fasciitis, not myositis.

Unnecessary exploratory laparotomies are common in FMF patients because of tsevere abdominal pain.

DR. KASTNER

Onset is usually in childhood, but TRAPS often goes undiagnosed until adulthood. TRAPS is caused by autosomal dominant mutations in the tumor necrosis factor RSF1A gene, which encodes the p55 TNF receptor. The resultant protein misfolding is the mechanism underlying the disease.

Colchicine is generally not effective in TRAPS. Corticosteroids are, but the side effects are often limiting. Dr. Kastner and his colleagues showed that the anti-TNF biologic etanercept (Enbrel) can be quite effective. Surprisingly, however, the anti-TNF monoclonal antibodies infliximab and adalimumab have actually been shown to cause TRAPS flares.

Familial Mediterranean fever. The rash of FMF is usually stationary. Sometimes called erysipeloid erythema, the rash is reddish, raised, usually well demarcated, and sometimes painful. It often occurs on the dorsum of the foot, ankle, or lower leg.

The attacks typically last 1-3 days and occur on a monthly basis. These attacks are characterized by fever and rash accompanied by various kinds of inflammation, including pleural inflammation with effusion; massive joint effusions; and a nonerosive, nondeforming, monoarticular arthritis.

"Many of these patients have such severe abdominal pain during attacks that early in their disease they're mistaken for appendicitis and undergo at least one exploratory laparotomy," according to Dr. Kastner.

Histologically, huge numbers of polymorphonuclear cells are evident in the synovial fluid during a joint attack. It's comparable to what would be seen in a septic joint, except nothing can be cultured.

This disorder is seen predominantly in individuals of Arab, Armenian, Jewish, Turkish, or Italian origin. Dr. Kastner and his coworkers discovered that the disease is caused by recessive mutations in the Mediterranean fever gene, which

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encodes the pyrin protein, figuring prominently in a pathway of inflammation.

Onset of FMF is usually in childhood, but the disorder is often not diagnosed until adulthood because of a lack of awareness of the disease.

The treatment for FMF is daily colchicine, an inexpensive drug with a good track record for efficacy and a good safety profile. Systemic AA amyloidosis has become less common as a long-term complication of FMF since colchicine became the treatment of choice.

Occasionally a patient cannot take colchicine because of either side effects or lack of response. In such cases there is a highly effective alternative which came about through studies by Dr. Kastner's group. First the investigators showed in animals that the inflammation in FMF is interleukin-1 dependent, and then they pioneered the use of high-dose anakinra (Kinaret), the IL-1 receptor antagonist, as an effective therapy.

HIDS. The rash of hyperimmunoglobulinemia D with periodic fever syndrome is diffuse and maculopapular and is most typically located on the palms and soles. Pronounced cervical lymphadenopathy is a distinctive feature in this syndrome.

The febrile episodes in HIDS typically last 3-7 days. The fever episodes are accompanied by the maculopapular rash, abdominal pain, and arthralgias. Onset is almost always within the first year of life. Episodes are often triggered by childhood immunizations. HIDS is seen mainly in people of northern European ancestry, particularly the Dutch.

HIDS is caused by recessive mutations in the mevalonate kinase gene, resulting in reduced production of geranylgeranyl pyrophosphate. HIDS is something of a misnomer in that some affected patients with mevalonate kinase mutations have normal IgD levels.

As yet there's no consensus on the treatment of HIDS, Dr. Kastner said.

CAPS. The cryopyrin-associated periodic syndromes consist of three diseases caused by dominant mutations in one gene, NLRP3, which encodes the cryopyrin protein involved in interleukin-1beta activation. The three cryopyrinopathies are neonatal-onset multisystem inflammatory disease (NOMID), Muckle-Wells syndrome, and familial cold autoinflammatory syndrome (FCAS).

What these three diseases have in common is fever, urticarial rash, and excessive production of IL-1beta. Patients with NOMID experience fever nearly every day, while in those with FCAS the fever and hives-like rash develop within a couple of hours after exposure to cold.

Cryopyrin is a central component of the inflammasome, a macromolecular scaffold promoting activation of caspase-1.

Dr. Kastner and his coworkers pioneered anti-IL-1 therapy with anakinra in CAPS patients.

Dr. Kastner declared having no relevant financial interests. ■

Raynaud's Ischemia Needs Urgent Care

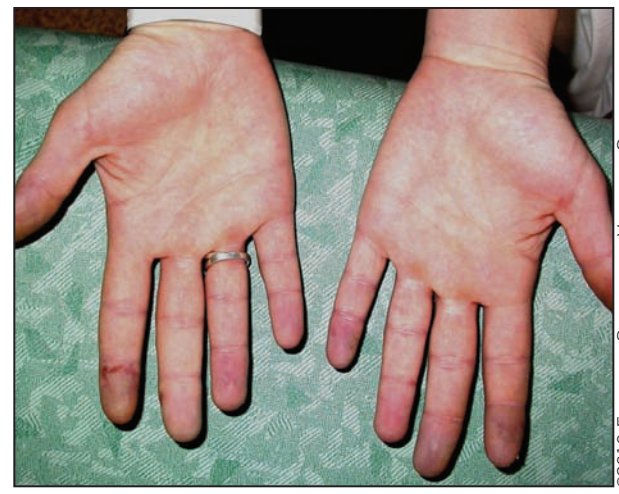
BY BRUCE JANCIN

FROM A SYMPOSIUM SPONSORED BY THE AMERICAN COLLEGE OF RHEUMATOLOGY

SNOWMASS, COLO. – Persistent pain and nonreversible digital discoloration in a patient with Raynaud's phenomenon are indicators of critical ischemia constituting a medical emergency.

"Raynaud's patients will often say, 'My fingers are uncomfortable. I feel pins and needles.' But when they say it actually hurts, you're in trouble. Particularly if they say, 'It hurts beyond my finger, it hurts in the palm of my hand and radiates up in my arm, I have to hang my hand off the edge of the bed to get relief, it's worse at nighttime,' then you've reached the point of critical ischemia and if you don't react you're going to have big trouble," Dr. Fredrick M. Wigley said at the symposium.

Although pain is the key feature marking a critical ischemic event, nonreversible discoloration is another indication. Affected digits will have well-demarcated pale-blue areas, and upon pressing down and then releasing the finger, no blood reflow is seen, explained Dr. Wigley, professor of medicine and head of the scleroderma center at Johns Hopkins University, Baltimore.



Digits have well-demarcated pale-blue areas; upon pressing down and releasing, no blood reflow is seen.

In contrast, reversibility is the hallmark of uncomplicated Raynaud's. One of the most common triggers is reaching into the frozen foods section at the supermarket. But 15 minutes after rewarming, the discoloration is reversed. Uncomplicated Raynaud's involves all the digits; the thumb is less often involved than the fingers, but it is not spared.

An acute ischemic crisis requires urgent care. Dr. Wigley's management approach begins with rest and warming of the affected hand, followed quickly by a local digital block. He injects 2% lidocaine into the web at the base of the affected finger, placing the needle tip close to the digital nerve. This brings immediate pain relief, and it lets him see whether acute vasodilation occurs in response to the injection, an encouraging finding.

If the patient isn't already on oral vasodilator therapy with a long-acting oral calcium channel blocker, he starts amlodipine immediately. In an acute ischemic crisis, Dr. Wigley resorts to low-dose epoprostenol infused into a peripheral vein at 0.5-2.0 ng/kg per minute continuously for 3 or more days. To avoid hospitalization, he allows patients to undergo the prostacyclin infusions on an outpatient basis and go home at the end of each treatment day.

Although it's not a well-studied intervention, 48 hours of anticoagulation with unfractionated heparin or low-molecular-weight heparin makes sense in a patient with acute, rapidly advancing digital ischemia who is at risk of losing a digit, he said.

Dr. Wigley disclosed that he has received consulting fees and/or research grants from Actelion, Amira, KineMed, MedImmune, Novartis, Orion, Pfizer, and United Therapeutics. ■

Predictors of Raynaud's Progression ID'ed

BY BRUCE JANCIN

EXPERT ANALYSIS FROM A SYMPOSIUM SPONSORED BY THE AMERICAN COLLEGE OF RHEUMATOLOGY

SNOWMASS, COLO. – Abnormal findings on nailfold capillary microscopy and the presence of scleroderma-specific autoantibodies in patients presenting with new-onset Raynaud's phenomenon without overt connective tissue disease are powerful independent predictors of progression to definite scleroderma.

A landmark Canadian prospective study in 586 consecutive patients presenting with isolated Raynaud's phenomenon showed that 13% of them developed scleroderma during 3,197 person-years of follow-up. Another 1% developed other connective tissue diseases. Fewer than 2% of those with normal nailfold capillaries and no scleroderma-specific antibodies went on to develop definite scleroderma during 15-20 years, and the majority who did progress to scleroderma did so within the first year or two, noted Dr. Fredrick M. Wigley.

In contrast, 80% of patients with baseline evidence of microvascular damage on nailfold microscopy together with one or more scleroderma-specific autoantibodies developed scleroderma. Two-thirds of patients with these baseline findings in the University of Montreal study (Arthritis Rheum. 2008;58:3902-12) progressed to definite scleroderma within the first 5 years of follow-up, added Dr. Wigley, professor of medicine and director of the scleroderma center at Johns Hopkins University, Baltimore.

Scleroderma developed in 80% of those with both nailfold changes and specific autoantibodies.

DR. WIGLEY

Raynaud's patients with one or more scleroderma-specific autoantibodies but no nailfold capillary abnormalities had a 35% rate of progression to scleroderma, with 60% of cases being diagnosed within the first 5 years. Patients with nailfold capillary abnormalities but no scleroderma-specific autoantibodies had a 26% long-term rate of progression to scleroderma, with roughly 90% of cases occurring within 5 years.

Nailfold microscopy is a simple matter. It can be carried out using a drop of immersion oil and an ophthalmoscope set at diopter 40. The microvascular damage that portends subsequent definite scleroderma follows a characteristic chronologic sequence consisting of enlarged capillary loops, followed by capillary loss, and capillary telangiectasias, the rheumatologist explained.

The autoantibodies that proved predictive were anticentromere (anti-CENP-B) anti-TH/To, anti-topoisomerase I, and anti-RNA polymerase III.

The findings in the Canadian study, which was the first large prospective study of predictors of scleroderma in patients with Raynaud's phenomenon, were remarkably consistent with those obtained earlier through a literature search by investigators at Dartmouth-Hitchcock Medical Center, Lebanon, N.H. They analyzed 10 published articles including 639 patients with primary Raynaud's phenomenon and determined that 13% of them developed a connective tissue disease during 2,531 person-years of follow-up, compared with 14% of patients in the Montreal study.

Scleroderma accounted for the great majority of the cases of connective tissue disease in the Dartmouth-Hitchcock analysis, he said.

Dr. Wigley declared that he receives consulting fees and/or research grants from Actelion, Amira, KineMed, MedImmune, Novartis, Orion, Pfizer, and United Therapeutics. ■