New Hope For 'Man on Fire Syndrome'

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By Anthony Accurso, M.D.

Pamela Costa has never known a day without agonizing pain in her legs and feet.

At age 11, the Seattle native was diagnosed with inherited erythromelalgia, a genetic condition that causes such severe pain and redness some call it "Man on Fire Syndrome."

"Think of the feeling that you get when you come in from the cold and your hands and feet are rewarming too fast," said Costa, 47. "I have that feeling all of the time."

Inherited erythromelalgia is a disease of small nerves and blood vessels that causes severe pain in response to heat, pressure, exertion or stress.

"These people feel excruciating, scalding pain while putting on shoes or putting on a sweater," said Dr. Stephen Waxman, a neuroscientist at Yale University and the West Haven Veterans Affairs Hospital. "They will keep their feet on ice to the point of getting gangrene, just to relieve the sensation."

When Costa was growing up, playing outside would trigger the unbearable burning sensation.

"I used to come in from recess and just hold my hands on the cool metal of my school desk," said Costa, who has more than two dozen relatives with the same affliction. "I have had cousins suffer devastating injuries from over-cooling themselves."

Although the disease is rare, researchers are searching for clues to its cause with hopes of uncovering treatments for chronic pain of all kinds. The story starts at the molecular level within tiny nerves that conduct pain signals.

An Overactive Channel Protein

Pain comes in different forms, depending on the type of nerve that senses it. And for chronic pain patients, the pain is not quick and specific, but instead slow and sharp.

This slow pain is transmitted from the limbs and body to the brain along small nerves in the spinal cord called C-fibers. Messages move along these nerve fibers due to the action of special proteins in their membranes called channels. One specific type of channel is the Nav1.7 sodium channel, which is present in great numbers in the C-fibers of the spinal cord.
Work by Waxman and others has shown that patients with inherited erythromelalgia have a defect in their Nav1.7 channels that allows too many sodium ions to enter the C-fibers, causing an increase in the sensitivity of the nerves.

The specific atomic structure of the Nav1.7 channel has been modeled by Waxman's lab, and the results are detailed in the current issue of Nature Communications. Armed with this new model of the Nav1.7 channel, the lab has been able to show why some patients with inherited erythromelalgia respond well to an anti-epileptic drug called Carbamazepine.

Furthermore, in studying the channel structure in many different people, Waxman and colleagues have found variations in the channel from person to person. These variations may cause some people to be more likely to experience chronic pain than others.

**A New Drug Target**

Patients with a completely defective Nav1.7 suffer from the opposite condition, known as congenital indifference to pain. These people do not experience pain at all, with case reports of being able to walk on hot coals without pain.

As the role of Nav1.7 in the mechanism for pain sensation becomes clearer, biotechnology and pharmaceutical companies will likely take notice, according to Waxman.

"I anticipate a race to develop Nav1.7 specific blockers," he said.

Current drug therapies for pain include medicines like morphine, as well as aspirin and ibuprofen. While all of these decrease the sensation of pain, they also interact with other tissues such as the brain, heart and stomach, causing side effects.

Nav1.7 does not appear to be present in large quantities outside of the C-fibers of the spinal cord. As such, new drugs targeting this protein could herald a new class of pain treatments with many fewer side effects than our current drugs for pain.

Costa said she hopes to see a day where such a medicine would be available to her, providing her with full relief for the first time in her life.

*For more information about Erythromelalgia, visit www.erythromelalgia.org. The Erythromelalgia Association (TEA) is a non-profit organization working to identify, educate, and support those suffering EM. Pamela Costa is a member of TEA.*