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UCSD Researchers Find Effective Treatment For Unusual Fever Syndrome Caused By Cold Exposure

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Remember when Grandma used to say 'don't go out in the cold; you'll get sick"? It turns out that she was right for a small number of people who have a condition called familial cold autoinflammatory syndrome (FCAS), in which individuals are afflicted by rash, fever, joint pain and flu-like symptoms after exposure to cold conditions as mild as an air-conditioned room or fall breeze.

The disorder became a hot protocol for research labs in 2001 after investigators at the University of California, San Diego (UCSD) School of Medicine discovered the mutated gene that caused FCAS *****. Now, the same UCSD team reports in the November 13, 2004 issue of the journal Lancet, that they've found an effective treatment - one that inhibits an abnormal immune response that leads to symptoms in FCAS-affected patients.

"We witnessed a truly remarkable response and a life-changing therapy for these patients," said Hal M. Hoffman, M.D., a UCSD assistant professor of medicine and pediatrics, and the lead author of the study in Lancet. "On a scientific level, the investigation of uncommon disorders such as FCAS can provide important insights into the mechanisms of more common diseases. For example, inflammation has been shown in recent years to be important in many disorders from arteriosclerosis to Alzheimer's disease."

Because cold triggers fever in FCAS patients, in 2001 the UCSD team named the disease-causing protein they discovered "cryopyrin," which means icy fire. In their new studies with seven individuals, four afflicted with FCAS and three normal subjects, the investigators determined that cryopyrin regulates the release of interleukin-1 (IL-1), an important mediator of fever and systemic inflammation during the body's initial immune response. After finding increased levels of IL-1 in the skin of the FCAS patients following an experimental cold challenge, the researchers administered a recombinant IL-1 receptor antagonist, a drug called anakinra, which inhibits the action of IL-1 and thus prevents acute inflammation, fever and flu-like symptoms. The treatment prior to cold exposure prevented the clinical and laboratory manifestations of the disease in the FCAS patients. Anakinra is currently approved by the Food and Drug Administration for treatment of rheumatoid arthritis.

FCAS is a hereditary disorder thought to affect nearly 300 Americans, with 90 percent of them tracing their ancestry to a man from Northern Europe who migrated to the U.S. in the 1600s. FCAS is one of a family of seven distinct, single-gene defects that are considered to be hereditary periodic fever disorders ******, characterized by recurrent bouts of systemic inflammation involving several tissues, including joints and skin.

Over the past seven years, Hoffman has studied FCAS by drawing blood samples at different family reunions held throughout the United States, from Georgia, Ohio, Illinois and Missouri, to Utah and California. Frequently, the individuals with FCAS didn't know they had distant relatives in other states with the same condition. Interviewing hundreds of patients in divergent regions of the country, Hoffman said he found a similar story that had been passed along through the years.

"One older family member told me that the disease started with his great-great-great-great grandfather who was working on a farm during a hot day, and he fell into cold water," Hoffman said. "Then, at another reunion,

someone else would tell me that the problem started with a man who got shipwrecked and was in cold water for a long period of time. The common thread was always cold water."

In actuality, the common thread was exposure to cold. When individuals with FCAS get cold, within an hour or so they develop fever, chills, joint pain, red eyes, achy muscles and rash. In severe cases, patients develop kidney failure related to the disorder.

A typical FCAS patient is 77-year-old Arlene Fowler of Menifee in Southern California California. "I've had this all my life," she said. "My Mom, who had it, told me that some long-distant cousin caused the problem by daring our relative to jump in ice water."

"I couldn't live back east; it's far too cold," Fowler noted. "Even a slight change of temperature causes a rash, swollen joints, chills, a headache and painful red eyes. It's hard for me to breathe when I get out in the cold air. I feel miserable, but I've learned to live with it. Having a hot tub to warm up helps!"

Fowler and her two daughters with FCAS were among the individuals who participated in Hoffman's study at UCSD. With the other study participants, they spent 45 minutes in a cold-storage room. Hoffman accompanied them, telling jokes and keeping the conversation going, to keep their minds off the 36 degree temperature.

One of Hoffman's FCAS patients who has greatly benefited from his new findings is 63-year-old Peggy Furst of Vacaville, in northern California. She suffered from the severe form of FCAS that had caused kidney failure in several generations of her family. Since she began injections of anakinra every other day, her symptoms have disappeared, her kidneys are working normally, and Furst says she's never felt better.

"My quality of life has had such dramatic improvement that I feel like shouting from the rooftops," she said. "I've gone snowmobiling, walked on the beach in the cold and fog, enjoyed the San Francisco chilly dampness, and, best of all, no longer make my husband suffer by keeping the house constantly at 80 degrees."

While anakinra eliminates symptoms of FCAS, it has a couple of disadvantages, according to Hoffman. "Frequent injections are required, and they sting a bit. In addition, it's very expensive...about $30 a shot," he said.

The cost is what keeps many of Hoffman's FCAS patients from benefiting from the new therapy.

"When my daughters and I got the injections during the clinical trial, our symptoms went away," Fowler said. "But, I can't afford the high cost and my insurance company won't pay for it. I really wish my daughters and my granddaughter in college could use the drug, but right now, none of us can afford it."

The Hoffman team plans further clinical trials with anakinra to determine optimal dosing and they hope to get FDA approval for anakinra treatment of FCAS. "This would help with insurance coverage," he said.

The senior author of the Lancet article was Gary Firestein, M.D., chief of the UCSD Division of Rheumatology, Allergy and Immunology and director of the UCSD Clinical Investigation Institute. Additional UCSD authors from the Division of Rheumatology, Allergy and Immunology were Sanna Rosengren, Ph.D.; David L. Boyle, B.S; Jae Y. Cho, M.D.; and Jyothi Nayar, B.S. Participating from the UCSD Department of Pediatrics were James L. Mueller, B.S. and Justin P. Anderson, B.S. Hoffman and ueller are also members of the Ludwig Institute of Cancer Research.

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***** Fire and ice: An altered protein brings fever, chills http://health.ucsd.edu/news/2001/10_23_Hoffman.html

****** In addition to FCAS, additional hereditary periodic fever disorders are: Familial Mediterranean fever (FMF) TNF receptor-associataed periodic syndrome (TRAPS) Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS) Blau syndrome Muckle-Wells syndrome (MWS) Neonatal-onset multisystem inflammatory disease (NOMID)