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Familial Cold Autoinflammatory Syndrome

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NORD is grateful to Dr. Hal Hoffman, Associate Professor of Pediatrics and Medicine, Division of Rheumatology, Allergy, and Immunology at the University of California at San Diego School of Medicine, for assistance in the preparation of this report.

Synonyms of Familial Cold Autoinflammatory Syndrome

- Familial cold urticaria
- FCAS

Disorder Subdivisions

General Discussion

Familial cold autoinflammatory syndrome (FCAS), also known as familial cold urticaria, is a rare, inherited inflammatory disorder characterized by intermittent episodes of rash, fever, joint pain and other signs/symptoms of systemic inflammation triggered by exposure to cold. Onset of FCAS occurs during infancy and early childhood and persists throughout the patient's life.

FCAS is one of the cryopyrin associated periodic syndromes (CAPS) caused by mutations in the CIAS1/NLRP3 gene. These syndromes are characterized by fever, rash, and joint pain.

FCAS shares symptoms, and should not be confused, with acquired cold urticaria, a more common condition mediated by different mechanisms that usually develops later in life and is rarely inherited.

Symptoms

Patients with FCAS experience mild to debilitating symptoms such as rash, fatigue, recurrent fever and chills, recurrent joint pain, and recurrent conjunctivitis (inflammation of the outer most layer of the eye causing redness, discomfort and discharge from the eye).

Other symptoms include profuse sweating, drowsiness, headache, extreme thirst, red eyes, blurred vision, eye pain, watering eyes and nausea

Symptoms occur within hours after exposure to cold. In most cases, a rash will occur within the first 1-2 hours, followed by a fever and joint pain. Episodes usually last for less than 24 hours.

Causes

FCAS is usually inherited in an autosomal-dominant fashion and is caused by a heterozygous mutation in a gene identified as the CIAS1/NLRP3 gene that codes for the protein cryopyrin (NALP3). Mutations in this gene are hypothesized to cause increased activity of a protein complex containing cryopyrin. This protein complex is known as the inflammasome and regulates inflammation in the body. Increased inflammasome activity results in increased release of a protein known as interleukin (IL) 1 β , which leads to symptoms of inflammation such as fever and joint pain.

Affected Populations

Since FCAS is a newly discovered condition, the actual incidence and prevalence of the disease is difficult to determine at this time.

Related Disorders

Symptoms of the following disorders can be similar to those of FCAS and there is significant phenotypic overlap. Comparisons may be useful for a differential diagnosis.

Neonatal-onset multisystem inflammatory disease (NOMID), also known as chronic infantile neurologic cutaneous articular (CINCA) syndrome, is a rare, congenital, systemic, inflammatory condition characterized by fever, abnormal joint findings, rash, and central nervous system (CNS) disease with onset during infancy. NOMID is the most severe form of the cryopyrin associated periodic syndromes (CAPS) and is often caused by mutations in the CIAS1/NLRP3 gene.

Muckle-Wells syndrome (MWS) is one of the cryopyrin associated periodic syndromes (CAPS). Individuals with MWS often have episodic fever, chills, and painful joints. Sometimes these symptoms are exacerbated by cold similar to the related condition FCAS, but can also be triggered by other stimuli. In most cases, MWS patients develop progressive hearing loss. In some MWS cases amyloidosis develops later in life, a disease in which an abnormal accumulation of the protein amyloid occurs in a patient's tissues and organs. Accumulation of amyloid in the kidneys results in damage and often kidney failure if untreated.

Standard Therapies

Diagnosis:

Diagnosis of FCAS is determined through an evaluation of a patient's symptoms. Confirmation of the diagnosis is achieved through DNA gene analysis and the identification of a CIAS1/NLRP3 mutation(4) although not all FCAS patients possess a mutation in this gene.

Some of the common criteria that distinguish FCAS from other hereditary periodic fevers and acquired cold urticaria include:

Recurrent, intermittent episodes of fever and rash that primarily follow exposure to cold

Family history of the disease

Age of onset of less than 6 months of age

Duration of most attacks less than 24 hours

Presence of conjunctivitis associated with attacks

Absence of swelling of the eyes, swelling of one or more lymph nodes, and serositis (the inflammation of the serous membrane which lines and encloses several body cavities including the abdomen and the heart).

Treatment

While there are no medications currently indicated for the treatment of FCAS, non-steroidal anti-inflammatory drugs are often used to alleviate joint pain. High doses of corticosteroids have shown to be somewhat effective, but may cause short- and long-term side effects.

On February 27th of 2008, the U.S. Food and Drug Administration today approved a drug to help ease the suffering faced by those with certain chronic inflammatory diseases. Arcalyst (rilonacept, an Interleukin-1 blocker) is now approved for the long term treatment of two Cryopyrin-Associated Periodic Syndromes (CAPS) disorders: Familial Cold Auto-Inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS).

The most commonly reported side effects associated with use of Arcalyst were injection-site reactions and upper respiratory infections.

The FDA granted the drug a priority review, which speeds the review process for patients who have unmet medical needs.

Arcalyst is manufactured by Regeneron Pharmaceuticals Inc., Tarrytown, N.Y.

For more information on the Orphan Drug Act, visit: www.fda.gov/orphan/.

Investigational Therapies

In recent clinical studies, investigational interleukin-1 inhibitors had encouraging preliminary results in addressing the inflammatory features of the conditions in study patients, but these product candidates have not been approved by the US Food and Drug Administration for the treatment of FCAS.

Regeneron Pharmaceuticals submitted to the US Food and Drug Administration a biologics license application (BLA) for its IL-1 Trap (rilonacept) for consideration as a long-term treatment for CAPS. The IL-1 Trap is a long-acting inhibitor of interleukin (IL) 1 and if approved, would be the first medication indicated for the treatment of CAPS.

Information on current clinical trials is posted on the Internet at www.clinicaltrials.gov. All studies receiving U.S. government funding, and some supported by private industry, are posted on this government web site.

For information about clinical trials being conducted at the NIH Clinical Center in Bethesda, MD, contact the NIH Patient Recruitment Office:

Tollfree: (800) 411-1222

TTY: (866) 411-1010

Email: prpl@cc.nih.gov

For information about clinical trials sponsored by private sources, contact:
www.centerwatch.com

Anakinra, an IL-1 receptor antagonist, has shown promise in improving symptoms in several small series and reports of patients with MWS; however, it is not approved by the FDA for the treatment of MWS or any of the CAPS diseases at this time.

Novartis Pharmaceuticals is currently developing an IL-1 antibody, which has been reported to be effective in CAPS.

Organizations related to Familial Cold Autoinflammatory Syndrome

- Genetic and Rare Diseases (GARD) Information Center

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Home page: <http://www.madisonsfoundation.org>

- NIH/Office of Rare Diseases

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- NOMID Alliance, Inc.

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Home page: <http://www.nomidalliance.net>

References

1. Hoffman, H.M., Mueller, J.L., et al. Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle-Wells syndrome. *Nature*. 2001;29,301-305.
2. Hoffman, H.M., Wanderer, A.A., & Broide, D.H. Familial cold autoinflammatory syndrome: Phenotype and genotype of an autosomal dominant periodic fever. *J Allergy Clin Immunol*. 2001;108(4),615-620.
3. Stojanov, S. & Kastner D.L. Familial autoinflammatory diseases: genetics, pathogenesis and treatment. *Current Opinion in Rheumatology*. 2005;17,586-599.
4. Drenth, J.P.H. & van der Meer, J.W.M. The Inflammasome - A Linebacker of Innate Defense. *New England Journal of Medicine*. 2006;355(7),730-732.
5. Familial Cold Autoinflammatory Syndrome (FCAS). Available at:

<http://www.nomidalliance.net/subpage1.html>. Accessed on November 21, 2006.

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INTERNET:

Hoffman, HM. Cold Autoinflammatory Syndrome, Familial. Orphanet Encyclopedia. November 2003: <http://www.orpha.net/data/patho/GB/uk-FCAS.pdf>

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