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55 Kenosia Avenue
PO Box 1968
Danbury, CT 06813-1968
Phone: 203.744.0100
Toll Free: 1-800-999-6673
Fax: 203.798.2291

Muckle-Wells Syndrome

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Synonyms of Muckle-Wells Syndrome

- MWS

Disorder Subdivisions

General Discussion

Muckle-Wells syndrome (MWS) 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.

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, Muckle-Wells syndrome (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.

Symptoms
Common symptoms of MWS include recurrent rashes beginning in infancy or early childhood, intermittent fevers, joint pain (usually with no apparent changes in tissue and cartilage), recurrent conjunctivitis (the inflammation of the outer most layer of the eye causing redness, discomfort and discharge from the eye), progressive hearing loss and amyloidosis. Symptoms can be unprecipitated, but can also be triggered by cold exposure as well as stress or exercise. Episodes generally last between 24 to 48 hours.

Causes
MWS 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) 1ß, which leads to symptoms of inflammation such as fever and joint pain.

Affected Populations
Since MWS is a newly discovered condition, the actual incidence and prevalence of the disease is difficult to determine.

Related Disorders
Symptoms of the following disorders can be similar to those of Muckle-Wells syndrome and there is significant phenotypic overlap. Comparisons may be useful for a differential diagnosis.

Familial cold autoinflammatory syndrome (FCAS), also known as familial cold urticaria, is 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 considered to be one of the cryopyrin associated periodic syndromes (CAPS) and also is caused by mutations in the CIAS1/NLRP3 gene.

Neonatal-onset multisystem inflammatory disease (NOMID), also known as chronic infantile neurologic cutaneous articular (CINCA) syndrome, is a rare, congenital, systemic, inflammatory condition distinguished by fever, joint disease, rash and central nervous system (CNS) disease presenting 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.

Standard Therapies

Diagnosis

Diagnosis of MWS is determined through an evaluation of a patient's symptoms. Confirmation of the diagnosis is achieved through genetic testing and the identification of a CIAS1/NLRP3 mutation although not all MWS patients possess a mutation in this gene.

Treatment

To correct the hearing loss that often occurs, hearing aids may be used. 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. There are no medications currently indicated for the treatment of MWS.

On February 27th of 2008, the U.S. Food and Drug Administration also 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/.

In June 2009, the FDA approved Canakinumab, an IL-1 receptor antagonist, Ilaris as the first approved treatment for patients as young as four years old suffering from two forms of CAPS, familial cold auto-inflammatory syndrome and Muckle-Wells syndrome.

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 Food and Drug Administration for the treatment of MWS.

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.

In Februrary of 2008, FDA approved Arcalyst (rilonacept, an Interleukin-1 blocker) for the long term treatment of Muckle-Wells Syndrome. Arcalyst blocks interleukin-1 which is a signaling protein secreted by certain immune-related cells in the body. Interleukin-1 acts as a messenger to regulate inflammatory responses, but in excess it can be harmful and has been shown to be key in the inflammation seen in MWS.

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

Organizations related to Muckle-Wells Syndrome

- Genetic and Rare Diseases (GARD) Information Center

  PO Box 8126
  Gaithersburg MD 20898-8126
  Phone #: 3015193194
  800 #: 8882052311
  e-mail: gardinfo@nih.gov
  Home page: http://www.genome.gov/10000409

- MUMS (Mothers United for Moral Support, Inc) National Parent-to-Parent Network

  150 Custer Court
  Green Bay WI 54301-1243
  Phone #: 9203365333
  800 #: 8773365333

e-mail: mums@netnet.net
Home page: http://www.netnet.net/mums/

- Madisons Foundation

  PO Box 241956
  Los Angeles CA 90024
  Phone #: 3102640826
  800 #: N/A
  e-mail: getinfo@madisonsfoundation.org
  Home page: http://www.madisonsfoundation.org

- NIH/Office of Rare Diseases

  Steve Groft, Pharm.D.
  Bethesda MD 20892-
  Phone #: 3014024336
  800 #:
  e-mail: hh70f@nih.gov
  Home page: http://www.rarediseases.info.nih.gov/ord/

- NOMID Alliance, Inc.

  P.O. Box 590354
  San Francisco CA 94159
  Phone #: 4158318782
  800 #: N/A
  e-mail: site_manager@nomidalliance.net
  Home page: http://www.nomidalliance.net

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