

# **Cryopyrin-Associated Periodic Syndromes (CAPS): Physician Backgrounder**

## **TOPICS:**

Auto-inflammatory vs Auto-immune Disease

The Role of the Inflammasome and the CIAS1/NLRP-3 Gene Mutation

Disease Classifications and Symptoms

Diagnosis

Treatment Options

Conclusion

Cryopyrin-Associated Periodic Syndromes, or CAPS, are a group of rare inherited auto-inflammatory conditions. Signs and symptoms include recurrent rash, fever/chills, joint pain, fatigue, and eye pain/redness. In more severe forms, additional symptoms occur, such as deafness, systemic amyloidosis (protein accumulation in tissues and organs, such as the kidneys), significant central nervous system disabilities, including mental retardation and vision loss, and substantial joint and bone deformities. Three syndromes comprise CAPS: Familial Cold Auto-inflammatory Syndrome (FCAS), (previously termed Familial Cold Urticaria), Muckle-Wells Syndrome (MWS) and Neonatal-Onset Multisystem Inflammatory Disease (NOMID), which also is referred to as Chronic Infantile Neurologic Cutaneous Articular Syndrome (CINCA).

## **Auto-inflammatory vs Auto-immune Disease**

Auto-immune disease is a term commonly applied to conditions in which it appears that the adaptive (B & T cell) immune system has turned against the “self”. Such conditions are typically associated with antibody or T-cell markers of auto-immunity. Examples include anti-DNA antibodies in systemic lupus erythematosus, rheumatoid factor antibodies in rheumatoid arthritis, or auto-reactive T-cell in vasculitis. The term “auto-inflammatory disease” has recently been introduced and is used to describe idiopathic inflammatory conditions that are not associated with auto-antibodies or other features or a disordered adaptive immune system. Auto-inflammatory conditions are thought to be associated with disorders of the innate immune system. The innate immune system includes components such as monocytes, macrophages, and neutrophils, which in normal circumstances also help protect the body against pathogens and other environmental challenges. Auto-inflammatory diseases may be inherited (e.g., familial Mediterranean fever, Cryopyrin-Associated

Periodic Syndromes etc.) or acquired (e.g., systemic juvenile idiopathic arthritis, Crohn's disease, gout).

### **The Role of the Inflammasome and the CIAS1/NLRP-3 Gene Mutation**

The inflammasome, an essential component of the innate immune system, is a complex system of proteins critical in detecting and responding to microorganisms. It is believed that the inflammasome acts as an early warning system to activate the body's defense system in anticipation of invasion. When these proteins are stimulated, they cue the ultimate production of pro-inflammatory cytokines. One such protein, cryopyrin, is encoded by the CIAS1/NLRP-3 gene, (also identified as PYPAF1 or NALP3 gene). CAPS are oftentimes, but not always, distinguished from other auto-inflammatory diseases by the presence of mutations of the CIAS1/NLRP-3 gene. When CIAS1/NLRP-3 gene mutations occur, a complex cascade is activated that ultimately results in increased release of the cytokine interleukin 1 $\beta$  (IL-1 $\beta$ ), which causes the inflammation seen in CAPS.

To date, at least 50 CIAS1/NLRP-3 gene mutations have been identified in patients with CAPS. Genetic mutations, however, have not been identified in all CAPS patients.

### **Disease Classifications and Symptoms**

CAPS are comprised of three autosomal-dominant conditions: Familial Cold Auto-inflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS), and Neonatal-Onset Multisystem Inflammatory Disease (NOMID)/Chronic Infantile Neurologic Cutaneous Articular Syndrome (CINCA). Each disease shares the common symptoms of recurrent rash, fever/chills, joint pain, fatigue, and eye pain/redness. Symptoms are usually first seen in early childhood or adolescence. Some patients have features that "overlap" between syndromes.

### **Familial Cold Auto-inflammatory Syndrome**

FCAS, the most common form of CAPS, is a major cause of pain and hardship. Interestingly, patients with FCAS develop symptoms when they are exposed to even a mild degree of cold. Exposures might include a cool breeze, air conditioning, or a light mist. Following cold exposure, a systemic inflammatory response usually ensues within a few hours. Signs and symptoms include recurrent rash, fever/chills, joint pain, fatigue, and eye pain/redness. FCAS patients also can experience headache, muscle pain, excessive thirst, and nausea.

These symptoms generally last for up to 24 hours. Laboratory markers of systemic inflammation [C-reactive protein (CRP) and Serum Amyloid A (SAA) levels] are elevated. It is estimated that a few percent of FCAS patients may develop renal consequences due to secondary amyloidosis.

## **Muckle-Wells Syndrome**

MWS shares many of the same inflammatory signs and symptoms of FCAS, but they are often more chronic and patients have multiple unknown triggers for symptoms onset. Cold exposure may, however, exacerbate inflammation. In addition to episodes of rash, fever/chills, joint pain, fatigue, and eye pain/redness, which can last from 2 to 3 days, MWS also is associated with synovitis and sensorineural deafness. Secondary amyloidosis may occur in as many as 25 percent of patients with MWS, often resulting in renal failure.

## **Neonatal-Onset Multisystem Inflammatory Disorder**

NOMID/CINCA is the most severe and debilitating form of CAPS with symptoms manifesting shortly after birth. Beyond those symptoms manifested in FCAS and MWS, NOMID patients also present with significant disabilities, including optic nerve abnormalities (papilledema), chronic aseptic meningitis, mental retardation, facial malformation, and arthropathy with aberrant ossification (especially in the knees and elbows.)

## **Diagnosis**

Diagnosis of CAPS is often missed due to the rarity of these conditions (low index of suspicion). Furthermore, some symptoms of CAPS may be similar to findings of more common diseases such as systemic JIA and systemic lupus erythematosus. Some features of FCAS may be mistaken for Acquired Cold Urticaria (ACU), a more prevalent condition. Both demonstrate cold-induced rash; however, in ACU, the rash is usually localized to sites of direct cold exposure, whereas in FCAS, the inflammation is more generalized, being systemic in nature.

A number of factors may be considered to help differentiate more common diseases from CAPS:

- Unlike auto-immune diseases, auto-inflammatory disorders lack high levels of autoantibodies and autoreactive T-cells.
- From a histological standpoint, the urticarial rash common in CAPS is shown to be predominantly composed of neutrophils. In addition, the rash in CAPS does not respond to antihistamine therapy, unlike ACU.
- Other differences between FCAS and ACU include the diseases' inheritance pattern (autosomal dominant vs. sporadic manifestation); age at first presentation (infancy vs. childhood/adulthood); history of occurrence of episodes (throughout life vs. spontaneously with resolution within months or years); length of time from cold exposure to symptom

onset (hours vs. minutes); duration of episodes (hours to 2 days vs. minutes to several hours); and result of diagnostic ice cube test (negative vs. positive)

- Laboratory tests of CAPS patients indicate the presence of leukocytosis with white blood cell counts of up to  $36,000/\text{mm}^3$  and elevated levels of serum IL-6, during episodes and chronically elevated erythrocyte sedimentation rates and acute-phase reactants including serum amyloid A (SAA) and C-reactive protein (CRP).

Once other conditions have been ruled out, or if there is a high index of suspicion, genetic testing to sequence the CIAS1/NLRP-3 gene should be considered to secure a definitive diagnosis. Not all CAPS patients have a detectable genetic mutation. Other rare auto-inflammatory conditions to consider include familial Mediterranean fever, Hyper-IgD Syndrome, and TNF Receptor-Associated Periodic Syndrome.

### **Treatment Options**

To date, there are no medications approved for the treatment of CAPS by the U.S. Food and Drug Administration. First-line management of FCAS includes avoiding or limiting exposure to cooling temperatures and implementing warming treatments, such as layering of clothes, taking hot baths, and drinking hot tea, to minimize disease exacerbations. In addition, nonsteroidal anti-inflammatory drugs are sometimes used to try to alleviate joint pain and fever in these patients. In the case of MWS and NOMID, which are not triggered by any discernible cause, treatment focuses on containing the inflammation. High-dose corticosteroids have been used, but side effects associated with prolonged use of these medications can negate the benefits. Other medications used but demonstrating inconsistent relief include anabolic steroids and gold. Disease-modifying anti-rheumatic drugs, such as methotrexate and tumor necrosis factor receptor antagonists, have demonstrated limited effectiveness.

### **Conclusion**

Cryopyrin-Associated Periodic Syndromes are a rare and newly discovered group of autosomal-dominant disorders that can best be diagnosed through analysis of family history, compilation of clinical history, including age of primary presentation and frequency/duration of episodes, physical examination, laboratory and histological testing, and genetic analysis. Not all CAPS patients have detectable genetic mutations. Treatment options for CAPS are limited with variable levels of effectiveness. There are no therapies approved by the U.S. Food and Drug Administration for the treatment of CAPS. Additional research into the genotype of these diseases and the use of targeted therapies to address the inflammasome cascade apparent in CAPS is warranted.