

# Cryopyrin Associated Periodic Syndromes (CAPS): Overview

TOPICS:

Etiology of CAPS

Autoinflammatory vs. Autoimmune Diseases

Role of the Inflammasome and *NLRP3* Gene Mutations

Disease Symptoms and Subtypes

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Cryopyrin-Associated Periodic Syndromes (CAPS) are a group of rare, inherited, autoinflammatory diseases with the same genetic basis and overlapping symptomatology.<sup>1</sup>

There are 3 subtypes of CAPS<sup>1,2</sup>:

- Familial Cold Autoinflammatory Syndrome (FCAS)
- Muckle-Wells Syndrome (MWS)
- Neonatal-Onset Multisystem Inflammatory Disease (NOMID) (also called Chronic Infantile Neurologic Cutaneous Articular, or CINCA, Syndrome)

## Etiology of CAPS

CAPS are generally caused by autosomal-dominant mutations of the *NLRP3* (nucleotide-binding domain, leucine-rich family [NLR], pyrin domain containing 3) gene (formerly the *CIAS1* [cold-induced autoinflammatory syndrome 1] gene) and resultant alterations in the protein cryopyrin, which *NLRP3* encodes.<sup>1,2</sup>

Cryopyrin is critical to the production of the inflammatory cytokine interleukin-1 $\beta$  (IL-1 $\beta$ ). IL-1 $\beta$  can trigger an inflammatory response when it binds to inflammatory cells. Alterations in cryopyrin lead to IL-1 $\beta$  overproduction, resulting in an inflammatory response and the symptoms of CAPS.<sup>2</sup>

*NLRP3* mutations have been detected in only half of patients diagnosed with CAPS, suggesting that additional mutations may exist.<sup>1</sup>

## **Autoinflammatory vs. Autoimmune Diseases**

Autoinflammatory diseases have symptoms that may resemble those of autoimmune disorders, but they also have distinct clinical pathophysiological features. The underlying diseases are characterized by an inflammatory reaction that is seemingly unprovoked. Recurrent episodes occur with clinical manifestations that vary by disease. Unlike autoimmune diseases, autoinflammatory diseases are not associated with high-titer autoantibodies or antigen-specific T cells.<sup>2</sup>

Autoimmune diseases are characterized by misdirected immune responses in which the immune system mistakenly attacks and destroys healthy tissue.<sup>3</sup> Autoimmunity is demonstrated by the presence of high-titer autoantibodies or antigen-specific T cells reactive with host antigens.<sup>2</sup> Over 80 different types of autoimmune diseases have been described. Autoimmune diseases include systemic lupus erythematosus, rheumatoid arthritis, type 1 diabetes, Graves disease, and multiple sclerosis.<sup>3</sup>

## **Role of the Inflammasome and *NLRP3* Gene Mutations**

The inflammasome, an essential component of the immune system, is a complex system of proteins critical in detecting and responding to microorganisms. 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 proinflammatory cytokines.<sup>2,4-7</sup> One such protein, cryopyrin, is encoded by the *NLRP3* gene.<sup>2</sup> CAPS are often distinguished from other autoinflammatory diseases by the presence of *NLRP3* gene mutations.<sup>1,2</sup> When *NLRP3* gene mutations occur, a complex cascade is activated that results in increased release of IL-1 $\beta$ , causing the inflammation seen in CAPS.<sup>2</sup>

## **Disease Symptoms and Subtypes**

Symptoms common to most patients with CAPS include<sup>2</sup>

- Rash
- Fever/chills
- Joint pain
- Eye redness/pain
- Fatigue

## FCAS

Symptoms may develop when patients are exposed to even a mild degree of cold (e.g., a cool breeze, air-conditioning, or a light mist). Following cold exposure, a systemic inflammatory response usually ensues within a few hours. Symptoms include recurrent rash, fever/chills, arthralgia, conjunctivitis, and fatigue. Duration of most flares is <24 hours.<sup>8</sup>

## MWS

MWS has inflammatory symptoms similar to those of FCAS, but they may be more chronic and have random, unknown triggers.<sup>2,9</sup> Stress, exercise, or cool temperatures may also be triggers.<sup>2,9</sup> Episodes of rash, fever/chills, arthralgia, conjunctivitis, and fatigue can last 24 to 48 hours.<sup>2</sup> Patients may develop progressive, sensorineural hearing loss.<sup>4,10</sup> MWS poses a risk for reactive amyloidosis (deposition of amyloid fibrils in the kidneys, heart, and other organs),<sup>9-11</sup> with renal dysfunction as a potential consequence.<sup>4</sup>

## NOMID

NOMID is the most severe form of CAPS. Diagnosis usually occurs shortly after birth. In addition to having rash, fever/chills, and other symptoms of CAPS, patients with NOMID present with significant disabilities, including optic nerve abnormalities (papilledema), chronic aseptic meningitis, mental impairment, facial malformation, and arthropathy with aberrant ossification (especially in the knees and elbows).<sup>1,9</sup>

## Diagnosis and Treatment

Diagnosing CAPS is often challenging because of the rarity of the syndromes and the overlap of symptoms with certain autoimmune and other diseases.<sup>12-14</sup> For example, FCAS may be confused with acquired cold urticaria (ACU), a more common condition. Both demonstrate cold-induced rash; however, in ACU, the rash responds to antihistamines. ACU seldom appears in infancy and often resolves spontaneously within months or years. It also does not present with fever and arthralgia, and episodes usually last less than several hours (unlike several hours to days with FCAS).<sup>8,9</sup>

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

- Unlike autoimmune diseases, autoinflammatory diseases (including CAPS) are not associated with high-titer autoantibodies or antigen-specific T cells<sup>2</sup>
- The rash in CAPS is composed predominantly of neutrophils and does not respond to antihistamines<sup>8,9</sup>
- In CAPS, laboratory tests show polymorphonuclear leukocytosis (white blood cell counts of up to 36,000/mm<sup>3</sup> and elevated levels of serum IL-6) during episodes, as well as chronically elevated erythrocyte sedimentation rates and acute-phase reactants (e.g., Serum Amyloid A and C-Reactive Protein)<sup>8,13</sup>

After ruling out other conditions, including familial Mediterranean fever, hyper-IgD syndrome, and tumor necrosis factor receptor-associated periodic syndrome, clinicians should consider genetic testing to sequence the *NLRP3* gene.<sup>15</sup> Not all patients with CAPS have a detectable genetic mutation.<sup>1</sup>

There are FDA-approved therapies to treat the symptoms of FCAS and MWS.<sup>9</sup> There is no drug indicated specifically for the treatment of NOMID.

## **Conclusion**

CAPS are a group of rare, inherited, autoinflammatory diseases<sup>1</sup> that can best be diagnosed through analysis of family and medical history (including age of primary presentation and frequency/duration of episodes), physical examination, and laboratory and genetic testing.<sup>13</sup> Not all patients with CAPS, however, have detectable genetic mutations.<sup>1</sup>