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Cryopyrin-Associated Periodic Syndromes (CAPS): Pathogenesis, Clinical Manifestations, and IL-1-Targeted Therapeutic Strategies

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Abstract
Cryopyrin-associated periodic syndromes (CAPS) are a group of rare, genetically determined autoinflammatory diseases resulting from gain-of-function mutations in the *NLRP3* gene. These mutations lead to constitutive activation of the inflammasome and overproduction of interleukin-1β and interleukin-18, driving chronic systemic inflammation. CAPS encompasses three distinct clinical phenotypes - familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and chronic infantile neurologic cutaneous and articular syndrome (CINCA/NOMID) - which vary in severity and organ involvement. FCAS presents the mildest course with cold-induced symptoms, while CINCA/NOMID is the most severe form, often associated with CNS involvement and progressive sensorineural deficits.

Recent advances in understanding CAPS pathophysiology have led to the development of targeted biological therapies aimed at IL-1 inhibition. Anakinra, canakinumab, and rilonacept have demonstrated significant clinical efficacy in reducing systemic inflammation, alleviating symptoms, and improving long-term outcomes, including prevention of organ damage. Early intervention is crucial, especially in severe forms such as CINCA/NOMID, to avoid irreversible complications. The diagnosis of CAPS is based on clinical criteria supported by elevated inflammatory markers and confirmed by genetic testing.
This review presents a comprehensive overview of CAPS, covering its molecular mechanisms, clinical manifestations, diagnostic criteria, and current therapeutic strategies, with a focus on IL-1 targeted treatments as the mainstay of care.

Keywords: Cryopyrin-Associated Periodic Syndromes, NLRP3, Anakinra, CINCA/NOMID, Muckle-Wells syndrome, Familial Cold Autoinflammatory Syndrome

Introduction

Cryopyrin-associated periodic syndromes (CAPS) are a group of rare autoinflammatory diseases caused by mutations in genes involved in the signaling pathways of the innate immune system or in their regulation [1]. The gene most commonly associated with CAPS, *NLRP3* (nucleotide-binding domain, leucine-rich repeat family, pyrin domain containing 3), formerly known as *CIAS1* (cold-induced autoinflammatory syndrome 1), was identified in 2001 through genetic linkage analysis to chromosome 1q44 in multiplex pedigrees [2,3]. These mutations lead to chronic inflammation and excessive production of interleukin-1β (IL-1β) and interleukin-18 (IL-18).
Within the CAPS spectrum, three phenotypically related clinical entities have been delineated: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and chronic infantile neurologic cutaneous and articular syndrome (CINCA), also referred to as neonatal-onset multisystem inflammatory disease (NOMID) [4]. Among these, FCAS is associated with the mildest clinical course, whereas CINCA/NOMID represents the most severe phenotype [5].
The prevalence of CAPS is estimated to range from 1 to 3 cases per million individuals [1]. The distribution of CAPS subtypes shows geographic variation: in North America, FCAS predominates, largely due to large familial clusters with a founder mutation [6]. In contrast, MWS is the most commonly reported phenotype in Europe. CINCA/NOMID is less frequently observed, as most cases result from de novo mutations [4].
In this review, the pathogenesis, clinical characteristics, and current therapeutic strategies for CAPS will be comprehensively discussed.

Pathogenesis

The primary functional consequence of the genetic background causing CAPS is the inappropriate activation of innate immune cells in response to both internal and external triggers [9].
Research on families with autosomal inheritance of MWS and FCAS led to the discovery of mutations in the NLRP3 gene, a novel gene with an initially unknown function, later named cryopyrin. [2,7]

NLRP3 is part of the Nucleotide-binding domain and Leucine-rich repeat-containing Receptor (NLR) family, also referred to as Nucleotide-binding Oligomerization Domain (NOD)-like Receptors. These receptors function as cytosolic pattern recognition receptors (PRRs) [10]. NLRP3 acts as a sensor for danger signals and molecular patterns (DAMPs). It becomes activated in response to various stimuli, including both external pathogen-associated molecular patterns (PAMPs) and internal damage-associated molecular patterns (DAMPs) [11,12]
The mutations in NLRP3 that cause CAPS are missense changes, which lead to a gain-of-function phenotype, resulting in constitutive or enhanced NLRP3 activity [8]. Upon activation, NLRP3 undergoes oligomerization and binds to the adaptor protein ASC (Apoptosis-associated Speck-like protein containing a CARD) via pyrin domains (PYD) [13]. These protein-protein interactions lead to the formation of a protein complex called the inflammasome [5], which activates procaspase-1, converting it into active caspase-1. Caspase-1 then processes the precursors of IL-1β and IL-18, transforming them into their bioactive forms. ultimately leading to chronic systemic inflammation [13]. Figure 1 summarizes the molecular events underlying CAPS pathogenesis.

NLRP3 gain-of-function mutation
↓
Increased cryopyrin activity
↓
Autonomous inflammasome activation (no Signal 2 needed)
↓
ASC speck formation + caspase-1 activation
↓
→ Conversion of pro-IL-1β and pro-IL-18 to active forms
→ Pyroptosis (inflammatory cell death)
↓
Release of IL-1β and IL-18 → Systemic inflammation
↓
CAPS symptoms: fever, urticaria-like rash, joint pain, CNS involvement, sensorineural hearing loss, etc.

Figure 1. Schematic representation of the inflammatory cascade triggered by NLRP3 gain-of-function mutations in CAPS

Clinical Presentation of CAPS

Inflammatory flare-ups characterized by fever, urticarial-like skin eruptions, arthralgia, and increased levels of acute-phase proteins occur in all individuals with Cryopyrin-Associated Periodic Syndromes (CAPS), irrespective of the severity of their clinical presentation [15].

Familial Cold Autoinflammatory Syndrome (FCAS) represents the most clinically attenuated phenotype within the spectrum of CAPS [14]. In FCAS, flare-ups are triggered by exposure to cold and typically resolve within 12–24 hours [15]. While these episodes significantly impact the patient's quality of life, they do not cause changes in the central nervous system (CNS), bone deformities, or hearing loss. During a flare, in addition to the urticarial-like rash, conjunctivitis, arthralgia, and fever are commonly observed [5].

In **Muckle-Wells Syndrome (MWS)**, symptoms such as fever, headache, urticarial rash, arthralgia, or arthritis are present without any identifiable triggering factor. The median age of onset for febrile attacks is 0.8 years [16]. Headaches are common in MWS patients and result from intracranial hypertension, meningitis, and migraine [16,17]. Conjunctival inflammation is frequently observed, and in more severe phenotypes, ocular manifestations may include uveitis or episcleritis [17,18]. Progressive sensorineural hearing loss, typically manifesting after the age of 10, can develop in patients with MWS, likely secondary to chronic inflammation of the inner ear. This hearing loss, resulting from damage to the cochlea, is the most distinguishing clinical feature from FCAS [16,18]. Amyloidosis may also occur in affected patients, potentially resulting in proteinuria and progression to renal insufficiency [16].

CINCA/NOMID syndrome is the most severe manifestation within the clinical spectrum of CAPS [8]. The condition typically begins with a skin rash, which appears within the first 24 hours of life in most patients. This rash is usually accompanied by low-grade fever and persistent elevation of acute-phase reactants such as ESR (erythrocyte sedimentation rate) and CRP [8,20,21]. Joint involvement in CINCA/NOMID ranges from transient arthralgia to severe, progressive arthropathy. While two-thirds of patients experience only episodic pain and swelling, one-third develop deforming arthropathy, with overgrowth of the patella and epiphyses causing joint deformation. Large joints, including the knees, ankles, wrists, and elbows, are typically affected bilaterally, and radiographs show characteristic metaphyseal and epiphyseal overgrowth with irregular ossification [21] .

Short stature is another common feature of CINCA/NOMID [20], and patients often display a distinctive facial appearance, including frontal bossing, a large cephalic perimeter, and a saddle-back nose [8]. If left untreated, CINCA/NOMID leads to permanent CNS damage due to chronic inflammation. Chronic aseptic meningitis can increase intracranial pressure, resulting in hydrocephalus, brain atrophy, and papilledema. Neurological symptoms typically include irritability, intellectual disability, headaches, morning nausea, vomiting, and occasional seizures [23].

Ocular manifestations are also common in CINCA/NOMID, with conjunctivitis being the most frequent. In some cases, anterior and, less commonly, posterior uveitis can contribute to progressive vision loss primarily caused by optic nerve atrophy [17]. Additionally, progressive sensorineural hearing loss, leading to deafness in about 22% of patients, results from cochlear inflammation and usually becomes clinically evident in the first decade of life [15,24].
The inflammatory state in CINCA/NOMID is reflected in laboratory findings, such as increased acute-phase reactants, microcytic anemia, leukocytosis with neutrophilia, and thrombocytosis [20]. If left untreated, this chronic inflammation can lead to severe systemic complications, including irreversible damage to the CNS and sensory organs.

Diagnostic criteria for Cryopyrin-Associated Periodic Syndromes (CAPS)
The diagnostic criteria model for Cryopyrin-Associated Periodic Syndromes (CAPS) demonstrates a specificity of 94% and a sensitivity of 81%, and has been validated as effective across all CAPS subtypes [19]. Table 1 shows a model for the diagnosis of CAPS.

Criterion	**Description**
Mandatory	Elevated inflammatory markers: CRP and/or SAA
Additionally, ≥2 out of 6 symptoms:	
1	Urticaria-like rash
2	Cold- or stress-triggered attacks
3	Sensorineural hearing loss
4	Musculoskeletal symptoms (arthralgia, arthritis, myalgia)
5	Chronic aseptic meningitis
6	Skeletal abnormalities (epiphyseal overgrowth, frontal bossing)

Table 1. Diagnostic criteria for CAPS

Treatment of CAPS
The management of Cryopyrin-Associated Periodic Syndromes (CAPS) necessitates a multidisciplinary approach encompassing pharmacological intervention, physiotherapy, psychosocial support, and comprehensive supportive care. The therapeutic objectives include suppression of systemic inflammation, prevention of irreversible organ damage, preservation of physical function, and enhancement of overall quality of life [25].
Historically, conventional anti-inflammatory and immunosuppressive agents - such as glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), antihistamines, and thalidomide - have been employed with limited efficacy and poor tolerability due to adverse effects. These therapies typically offer only transient symptom control and do not alter disease progression [26].

Advancements in the understanding of CAPS pathophysiology have identified interleukin-1β (IL-1β) as a pivotal proinflammatory cytokine driving disease activity. This has led to the development of targeted biologic agents designed to inhibit IL-1 signaling. Given the central role of IL-1 in CAPS, anti-IL-1 therapy is now the recommended standard of care across the full clinical spectrum of the disorder. Currently approved IL-1 inhibitors include anakinra, canakinumab, and rilonacept [25].

Anakinra is a recombinant, nonglycosylated form of the endogenous interleukin-1 receptor antagonist (IL-1RA), which exerts its effect by competitively inhibiting the binding of IL-1β and IL-1α to the interleukin-1 receptor, thereby blocking downstream proinflammatory signaling pathways [27]. It has been approved by both the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) [25].

Due to its relatively short half-life of 4 to 6 hours, anakinra is administered via daily subcutaneous injections. The recommended dosage ranges from 1–2 mg/kg/day for patients with the milder familial cold autoinflammatory syndrome (FCAS) to up to 10 mg/kg/day for those with the more severe NOMID/CINCA phenotype [25, 27].

Anakinra has demonstrated substantial clinical efficacy in attenuating systemic inflammation, as well as musculoskeletal and cutaneous symptoms characteristic of CAPS. Its therapeutic benefit also extends to neurological manifestations, including chronic aseptic meningitis, increased intracranial pressure, and papilledema. Improvements in headache and visual symptoms have been frequently reported. Nevertheless, cognitive function often remains unaffected, likely due to irreversible CNS damage established prior to treatment initiation [27]. With regard to long-term disease outcomes, anakinra has shown the ability to stabilize sensorineural hearing loss in most patients. Amyloidosis has regressed or resolved in several reported cases. The impact on CAPS-related arthropathy is variable, with some patients experiencing stabilization, while others show continued joint deterioration [27]

Importantly, the clinical benefits of anakinra have been sustained over prolonged treatment periods, with most patients achieving long-term disease control. In addition to symptom relief, patients have reported significant improvements in quality of life, both physically and psychologically [27, 28, 29]. These clinical improvements are paralleled by rapid reductions in serological markers of inflammation—such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and serum amyloid A (SAA)—often occurring within hours after the initial administration [29, 30].

Canakinumab is a selective monoclonal antibody against interleukin-1β (IL-1β), with a long half-life (26–28 days), allowing for its administration every 8 weeks via subcutaneous injection. It has been approved by the FDA for the treatment of CAPS in patients over the age of 4.

The recommended dose of canakinumab is 150 mg every 8 weeks for patients weighing over 40 kg. For children weighing between 15 kg and 40 kg, the dose is 2 mg/kg, while for patients weighing between 7.5 kg and 15 kg, the dose is 4 mg/kg. Infants aged 2 to 4 years are also recommended to receive 4 mg/kg every 8 weeks.

Clinical efficacy of canakinumab was demonstrated within 24 hours of the first dose – both clinical symptoms and inflammatory markers (CRP, SAA) showed rapid and sustained normalization. Full remission was achieved in 89% of patients within one week, and in 97% after 48 weeks.

In patients with more severe forms of CAPS, including CINCA/NOMID, improvement in neurological symptoms was observed (including reduction in intracranial hypertension, meningitis, improvement in hearing and visual acuity), although cognitive impairments typically persisted. In severe cases, higher doses (4–8 mg/kg every 4 weeks) or shorter intervals between doses were necessary.
Adverse events were rare and mainly consisted of mild injection site reactions (up to 9%) and dizziness (up to 14%) [26, 27, 31].
Rilonacept is an IL-1 trap cytokine inhibitor approved by the FDA in 2008 for patients over 11 with FCAS and MWS. It works by binding cytokines with high affinity and is administered weekly via subcutaneous injection due to its 6,8-day half-life, offering a more convenient alternative to daily anakinra injections.
In clinical trials, 160 mg of rilonacept per week resulted in an 84% reduction in disease activity, compared to 13% with placebo. Symptoms of CAPS (fever, rash, eye redness, fatigue, and arthralgia) improved within 24 hours. Some patients required a dose escalation to 320 mg per week to achieve remission. Long-term, 50% to 70% of patients showed symptom improvement after 18 months.
Common side effects included injection-site reactions (48%) and upper respiratory infections (3x higher than placebo). Rarely, weight gain and headaches occurred, but these generally diminished over time. While rilonacept doesn't directly cross the blood-brain barrier, it may help reduce neurological symptoms by controlling systemic inflammation, particularly during meningitis flares [26, 27, 31].

Conclusion

Cryopyrin-Associated Periodic Syndromes (CAPS) are rare hereditary autoinflammatory disorders caused by gain-of-function mutations in the NLRP3 gene, leading to excessive activation of the NLRP3 inflammasome and overproduction of proinflammatory cytokines—especially interleukin-1β (IL-1β) and interleukin-18 (IL-18). CAPS includes three main clinical phenotypes: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and chronic infantile neurologic cutaneous and articular syndrome (CINCA/NOMID). Common symptoms include fever, urticarial rash, arthralgia, and in severe forms, sensorineural hearing loss, aseptic meningitis, and progressive organ damage.
Diagnosis is based on clinical presentation, elevated inflammatory markers (e.g., CRP, SAA), and fulfillment of specific diagnostic criteria.
A major advancement in CAPS management is the use of IL-1 inhibitors, which include:

- Anakinra – a short-acting IL-1 receptor antagonist requiring daily injections.
- Canakinumab – a long-acting monoclonal antibody given every 8 weeks.
- Rilonacept – a weekly IL-1 trap offering a more convenient option.

These biologics have significantly improved disease control, reduced systemic inflammation, and prevented long-term complications. Early diagnosis and treatment are essential to minimize irreversible organ damage and improve quality of life in affected patients.

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