Social impact

CAPS may limit the daily activities of both children and adult patients in areas including school and work, personal relationships, and social activities. Attendance and performance are both impacted due to the unpredictability of symptoms and flares, which can add stress affecting the patient's physical and emotional well-being. Other issues include anxiety, depression, fatigue, impaired concentration/brain fog, and cognitive impacts.

Documenting symptoms

Patients are encouraged to keep a symptom calendar diary with detailed notes on all organs/body parts impacted before, during, and after flares. This type of documentation can be very helpful to track and present how the disease manifests. Recording fevers, urticaria (rashes), headaches, eye issues, GI distress, joint swelling, bone pain, fatigue status/activity, and pain levels can help the clinician have a clear overview of the symptoms occurring during a flare. Additionally, keeping a photographic diary of rashes, joint swelling, eye redness and any other visible manifestation will be helpful to share with the diagnosing medical team for symptom validation.

Post-treatment monitoring

It is recommended by EULAR (European League Against Rheumatism) for patients to have a follow up every 6 months to evaluate treatment efficacy, flare breakthroughs, and to monitor acute-phase reactants (APR). Laboratory tests are recommended to monitor liver enzymes, complete blood count, kidney function, creatinine phosphokinase (CPK) and to identify proteinuria. The preferred APR are CRP, ESR and SAA.

Emergency kit

Patients on biologics are more susceptible to infections, fungal issues, and other immunological problems due to suppression of the immune system. Despite being on treatment, patients may occasionally have breakthrough flares due to elevated levels of inflammation. Therefore, it is recommended that emergency medications be provided prior to starting any biologic to be proactively prepared.

The emergency kit should contain steroids, antibiotics, antihistamines, and pain medications. Patients should be instructed when and how to use them to control any unforeseen complications. Patients should always follow up with their treating physician, when requiring use of the emergency kit medications.

Genetics and epidemiology

CAPS is caused by a gene mutation in NLRP3 and may be inherited from one parent and in an autosomal-dominant pattern. These disorders are related to defects in cryopyrin (gene formerly known as CIAS1 or NALP3). There are more than 240 variants identified in NLRP3. CINCA/NOMID is caused by spontaneous de novo variants occurring during embryogenesis.

CAPS is an orphan disease found to be equally prevalent in both males and females. The prevalence is 2.5 to 5.5 per 1,000,000 and may be even higher due to undiagnosis.
Other genes have been identified that are also known to cause FCAS. These include NLRP12, NLRC4, PLCG2 and F12.

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The brochure has been reviewed and endorsed by PD Dr. Juergen Rech, Senior Physician and Head of the Autoinflammation Clinic, University of Erlangen.

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Cryopyrin-associated auto-inflammatory syndromes (CAPS)

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ENGLISH

Introduction

Cryopyrin-Associated Periodic Syndromes (CAPS) are a group of rare hereditary inflammatory diseases related to a defect in the cryopyrin protein gene NLRP3. It encompasses three phenotypes:

Mild: Familial Cold Autoinflammatory Syndrome (FCAS)

Moderate: Muckle–Wells syndrome (MWS)

Severe: Neonatal-Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurologic Cutaneous Articular Syndrome (CINCA)

MILD	MODERATE	SEVERE
FCAS	**MWS**	**NOMID**

Disease presentation

Patients may experience overlapping symptoms and triggers, presenting with urticarial rash (hives, itchy bumps), musculoskeletal abnormalities, ocular conjunctivitis, neurosensorial hearing loss, and neurological issues (headaches, etc.), combined with chronic systemic inflammation. CAPS is more frequent in pediatric age groups although the disease has been observed in adult patients.

FCAS typically presents within the first 6 months of life with recurrent flares of fever, arthralgia, fatigue, and urticaria (usually not pruritic) that occur after cold exposure. Symptoms such as conjunctivitis, myalgia, chills, nausea, headache, joint pain, and drowsiness, may also present.
Symptoms begin 10 minutes to 8 hours after cold exposure and generally subside within 24 hours. However, resolution may be longer in cases of prolonged cold exposure. Amyloidosis is also a risk factor over the course of the disease.

Gastrointestinal symptoms may occur and can range from mild to more severe. It is recommended to seek help from a gastroenterologist, especially if the patient is experiencing *abdominal pain, diarrhea, vomiting, nausea, and weight loss, to be evaluated via endoscopy and colonoscopy.
Raymond, K.N. and Martin, J.E.D. (2021), Cryopyrin-associated periodic syndrome with inflammatory bowel disease: A case study. JGH Open, 5: 629-631. https://doi.org/10.1002/jgh3.12523

MWS has a more moderate presentation and onset begins in the first few years of life. It is characterized by episodic fevers, chills, red eyes, joint pain, and severe headaches (aseptic meningitis) with vomiting, even in the absence of generalized cold exposure. Urticarial plaques may be painful and can last up to 24 hours. Most flares last fewer than 36 hours but may last up to 5 days.

Musculoskeletal manifestations may include arthralgia, arthritis, and significant myalgia. Approximately 70% of patients experience progressive sensorineural deafness or partial hearing loss. If untreated, MWS patients have close to a 25% risk of renal amyloidosis that develops into renal dysfunction. Eye inflammation, such as uveitis, may be present in addition to conjunctivitis. Patients may have lymphadenopathy (swollen or enlarged lymph nodes) and/or hepatosplenomegaly (swelling or enlargement of the liver and spleen). Gastrointestinal symptoms may occur (see FCAS).

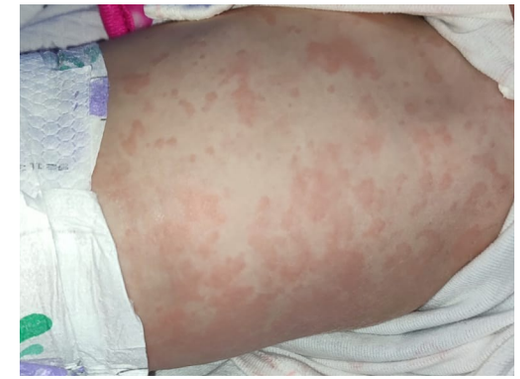
NOMID/CINCA presents in neonates with severe inflammation affecting the central nervous system (CNS), and causing urticarial migratory plaques, chronic headaches, hearing loss, intellectual disability, aseptic chronic meningitis, and possible seizures. Other manifestations include blindness secondary to optic disc changes, growth delay, distinctive osteoarthropathy impacting large joints, and overgrowth of proximal tibial epimetaphyseal cartilage. One-third of patients present with facial morphologies including a frontal prominence, saddleback nose, and facial hypoplasia.

Diagnostic criteria

Patients must have at least 2 of the 6 clinical characteristics:
- Urticarial rash
- Cold/stress-triggered flares
- Chronic aseptic meningitis
- Neurosensorial hearing loss
- Musculoskeletal symptoms (arthralgia, arthritis, myalgia)
-Skeletal abnormalities (epiphyseal overgrowth/frontal bossing)
Mandatory: elevated inflammatory markers (C-reactive protein, serum amyloid A)
References:
Welzel T, Kuemmerle-Deschner JB. Diagnosis and Management of the Cryopyrin-Associated Periodic Syndromes (CAPS): What Do We Know Today? J Clin Med. 2021 Jan 1;10 (1):128. doi: 10.3390/jcm10010128. PMID: 33401496; PMCID: PMC7794776.

Diagnosing CAPS

Diagnosis of CAPS is usually made by rheumatologists or immunologists but often patients require a multidisciplinary team to ensure clinical symptoms are validated.



Picture of urticaria on trunk in an infant with NOMID.

A physical exam should be conducted to investigate all relevant symptoms including weight, height, joint swelling, skin rashes, ocular manifestations, etc. Additional testing may be required including hearing tests, eye/retinal exam, skin biopsy, radiographs or MRIs of the brain/bones/joints/spine, and lumbar puncture.

A review of the family medical history is imperative as other members may have urticaria-like symptoms or fever patterns. This can be important for determining risk factors for NLRP3 inheritance, as the condition may be passed from parents to children.

Lab work should be done both during and in between flares to capture elevations of acute phase reactants (APR)/inflammatory markers, CRP, ESR, SAA. Additionally, proteinuria levels, renal function, CBC, liver & muscle enzymes, calprotectin, ferritin/storage percent, cytokines, and immunoglobulins should all be ordered to provide a broad picture of a patient's innate inflammatory status.

Genetic testing is recommended to confirm the clinical diagnosis.

Early diagnosis and treatment may prevent irreversible damage to bone, brain, eyes, and ears. Physical therapy and splints may help children with joint deformities. Surgery is occasionally needed. Children with hearing loss may require hearing aids. Sleep quality may be an issue for CAPS patients, and a sleep study should be ordered to evaluate for sleep apnea.

Biologic treatment

The first line of biologics recommended for CAPS patients are interleukin-1 inhibitors (IL-1). These are subcutaneous injections and include Kineret (anakinra), Ilaris (canakinumab) and Arcalyst (rilonacept – USA only).

Patients not responding to Kineret (IL-1α) should be offered Ilaris (IL-1β), and vice versa, as each medication works differently. All patients on biologics must be monitored and treated for infections, skin reactions, and lung issues.

Avoid administration of live vaccines concurrently with all IL-1 inhibitors. Patients should be updated with all recommended vaccinations prior to the initiation of therapy. It is important to know that any vaccination given while being on these medications may be less effective.

Ilaris (canakinumab)

Ilaris blocks the biologic activity of IL-1 beta. It may be used in children 2 years and older. In patients weighing less than 40kg (88lbs), the physician will calculate the medication dosage according to the patient's weight. In patients weighing over 40kg (88lbs), the starting dose is 150 mg per shot.

The medication dosage may be escalated gradually to 300 mg (2 shots) or 600 mg (4 shots) based on individual clinical judgement. The frequency of dosing is variable according to symptoms and disease control; thus, shot intervals range from 2 to 8 weeks. Higher and more frequent dosing with Ilaris may be required to control disease activity in more severe cases and to prevent complications.
https://www.ilarishcp.com/assets/pdfs/ilaris_dosing_guide.pdf

Kineret (anakinra)

Kineret blocks the biologic activity of IL-1 alpha and beta. This daily shot may be used in children 8 months or older and weighing a minimum of 10kg (22lbs). In patients weighing less than 40kg (88lbs), the physician will calculate the medication dosage according to the patient's weight. In patients weighing over 40kg (88lbs), the starting dose is 100 mg per shot. Higher and more frequent doses of Kineret may be required to control disease activity in more severe cases to prevent complications. The medication dosage may be escalated gradually up to 600 mg (6 shots daily) based on individual clinical judgement. https://www.kineretrx.com/pdf/Full-Prescribing-Information-English.pdf

ARCALYST (rilonacept)

Arcalyst blocks the biologic activity of IL-1 alpha and beta and prevents interaction with cell surface receptors. It may be used in children 12 years of age and older and is given as a weekly shot. In adolescents 12 to 17 years old, a loading dose (an initial higher dose) of 4.4mg/kg is given as 1 or 2 injections, up to a maximum of 320 mg. A weekly maintenance dose of 2.2 mg/kg is given as a once-weekly injection, up to a maximum of 160 mg. In adults 18 years and older, the loading dose (an initial higher dose) of 320 mg is given as two injections of 160 mg each. A weekly maintenance dose of 160 mg is given as a once-weekly injection. https://www.arcalyst.com/sites/default/files/2023-11/PI_IFU.pdf

Triggers

Triggers for CAPS flares may be variable and include exposure to cold and sudden fluctuations in environmental temperatures, emotional and physical stress, illness/infection, lack of sleep, physical activity, and accidents/trauma.

Laboratory Tests & Findings

CAPS patients present with elevated levels of acute-phase reactants such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and serum amyloid A (SAA) (even between flares), as well as leukocytosis (elevated WBC).

Elevated levels of serum amyloid A (SAA) are seen frequently in Muckle-Wells syndrome (MWS) and CSF leukocytosis in NOMID due to aseptic meningitis. Moreover, complete blood count (CBC) may show slightly decreased hematocrit levels and mild neutrophilia. Anaemia of chronic disease and elevated white blood cells count, especially neutrophils, may be detected.

Photo by National Cancer Institute on Unsplash.

Flares

CAPS patients may note their symptoms worsen towards evening or nighttime hours. Flare duration can be intermittent or continuous and last several days.

Rare adverse reactions of IL-1 inhibitors

Apart from the side effects listed below, patients using these medications may also experience weight gain (despite no dietary changes), swollen lymph nodes, fluid retention, post-nasal drip, synovitis, lung problems, etc.

The most common side effects of KINERET include: Injection site skin reactions, including redness, swelling, bruising, itching, and stinging. Most injection site reactions are mild, happen early during treatment, and last about 14 to 28 days. Kineret may also cause: headaches, nausea, vomiting, diarrhea, joint pain, fever, flu-like symptoms, sore throat or runny nose, sinus infection, abdominal pain.
Source: https://www.kineretrx.com/

The most common adverse reactions of ILARIS when used for the treatment of CAPS are: nasopharyngitis, diarrhea, influenza, rhinitis, nausea, headache, bronchitis, gastroenteritis, pharyngitis, weight increased, musculoskeletal pain, and vertigo.
Source: https://www.novartis.com/us-en/sites/novartis_us/files/ilaris.pdf

Pregnancy

CAPS patients have successfully taken *IL-1 biologics, as directed, before, during, and after their pregnancy. These medications have been deemed beneficial per clinical data with no major obstetrical complications reported. It is important for patients not to discontinue any treatment during pregnancy.

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*Chang Z, Spong CY, Jesus AA, Davis MA, Plass N, Stone DL, Chapelle D, Hoffmann P, Kastner DL, Barron K, Goldbach-Mansky RT, Stratton P. Anakinra use during pregnancy in patients with cryopyrin-associated periodic syndromes (CAPS). Arthritis Rheumatol. 2014 Nov;66(11):3227-32. doi: 10.1002/art.38811. PMID: 25223501; PMCID: PMC4323990.

*Brien ME, Gaudreault V, Hughes K, Hayes DJL, Heazell AEP, Girard S. A Systematic Review of the Safety of Blocking the IL-1 System in Human Pregnancy. J Clin Med. 2021 Dec 31;11(1):225. doi: 10.3390/jcm11010225. PMID: 35011965; PMCID: PMC8745599.