Pædiatric Rheumatology
InterNational Trials
Organisation

Cryopyrin-Associated Periodic Syndrome (CAPS)

What is it?

Cryopyrin-associated periodic syndromes (CAPS), are a group of rare autoinflammatory diseases that include familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS) and chronic infantile neurologic cutanuous articular syndrome (CINCA), also known as neonatal onset multisystemic inflammatory disease (NOMID). These syndromes were initially described as distinct clinical entities despite some clinical similarities: patients often present with overlapping symptoms including fever, pseudo-urticarial skin rash, and joint involvement of varying severity associated with systemic inflammation.

These three syndromes exist on a continuum of severity: FCAS is the mildest condition, CINCA (NOMID) the most severe, and patients with MWS have an intermediate phenotype.

Characterization of these conditions at the molecular level demonstrated mutations of the same gene in all three disorders.

How common is it?

CAPS are very rare conditions. They are recognised worldwide.

What are the causes of the disease?

CAPS are genetic diseases. The responsible gene for the 3 clinical entities (FCAS, MWS, CINCA/NOMID) is called CIAS1 and encodes for a protein called cryopyrin or NLRP3. This protein plays a key role in inflammatory response of the body. If the gene is disrupted, it confers a gain of function to the protein and inflammatory responses are enhanced. These enhanced inflammatory responses are responsible for clinical symptoms observed in CAPS. In 30% of patients with CINCA/NOMID, no mutation of CIAS1 is found.

There is some degree of genotype/phenotype correlation; mutations found in patients with mild forms of CAPS have not been identified in severely affected patients and vice versa. Additional genetic or environmental factors might also modulate severity and symptoms of disease.

Is it inherited?

CAPS are inherited as an autosomal dominant disease. It means the disease is transmitted by one of the parents who has the disease and carries an abnormal copy of CIAS1 gene. As we have 2 copies of all our genes, the risk for an affected parent to transmit the mutated copy of the gene CIAS1 and to give the disease to each child is 50%. De novo mutation may also occurs, it means that none of the parents has the disease and none carries a mutation in CIAS1 gene but disruption of CIAS1 gene appears at the child conception. In this case, the risk for another child to develop CAPS is random.

Is it contagious?

CAPS are not contagious.

What are the main symptoms?

The rash — a key symptom in all three diseases — is usually the first notable symptom. Regardless of the syndrome, it exhibits the same characteristics: it is migratory maculo-papular rash (look like urticaria), usually non-pruritic. The intensity of skin rash can vary from patient to patient and with disease activity.
FCAS, also known as familial cold urticaria, is characterized by recurrent short episodes of fever, rash and arthralgia precipitated by exposure to cold temperatures. Other commonly reported symptoms include conjunctivitis and muscle pain. Symptoms usually begin 1–2 hours after generalized exposure to cold temperatures or to important variation of temperature, and the length of the attacks is usually short (less than 24 hours). These attacks are self-limited (meaning that they resolve without treatment). Patients frequently report a pattern of feeling well in the morning after a warm night but getting worse later in the day after a cold trigger. Early onset of the disease, at birth or within the first 6 months of life, is common. Inflammation in the blood is observed during episodes of inflammation. Quality of live of patients with FCAS may be variably affected due to frequency and intensity of symptoms. However, late complication as deafness and amyloidosis usually don't occur.

MWS is characterized by recurrent episodes of fever and rash associated with joint and eye inflammation, although fever is not always present. Chronic fatigue is very frequent.
Precipitating factors are usually not identified, and cold triggering is rarely observed. The course of the disease varies between individuals from more typical recurrent attacks of inflammation, to more permanent symptoms. As in FCAS, patients with MWS often describe a pattern of worsening symptoms in the evening. First symptoms occur early in life but late presentation in childhood has been described.
Deafness is common (occurring in approximately 70% of cases) and usually begins in childhood or early adulthood; amyloidosis is the most serious complication of MWS and develops in adulthood in approximately 25% of cases; This complication is due to deposition of amyloid, a special protein related to inflammation, in some organs (as the kidneys, gut, skin and heart). These depositions cause gradual loss of function of the organ, especially of the kidneys; it manifests as proteinuria (loss of protein in urins) followed by impaired renal function. Amiloidosis is not specific for CAPS as it may complicate other chronic, inflammatory diseases.
Inflammation in the blood is observed during episodes of inflammation or more permanently in more severe cases. Quality of live of these patients is variably affected.

CINCA (NOMID) is associated with the most severe symptoms in this spectrum of diseases. The rash is usually the first sign and occurs at birth or in early infancy. A third of patients may be premature or small for gestational age. Fever can be intermittent, very mild, or in some cases absent. Patients frequently complain of fatigue.
Bone and joint inflammation vary in severity: in approximately two-thirds of patients, joint manifestations are limited to joint pain or transient swelling during flare-ups. In a third of cases however, severe and disabling joint involvement occurs resulting from growth cartilage overgrowth. These overgrowth arthropathies can cause gross deformity of the joints, with pain and limited range of motion. Knees, ankles, wrists, and elbows are the joints most commonly affected in a symmetric pattern. Radiological manifestations are distinctive. Overgrowth arthropathies, when present, usually occur early in live before the age of 3 years old.
Abnormalities of the central nervous system (CNS) are present in almost all patients and are caused by chronic aseptic meningitis (non infectious inflammation of the membrane surrounding the brain and spinal cord). This chronic inflammation will be responsible for chronic increased intra-cranial pressure. Symptoms related to this condition will vary in

intensity and are chronic headaches sometimes vomiting, irritability in young children, papilledema in fundoscopy (specialised ophthalmologic exam). Epilepsy (seizures) and cognitive impairment occurs occasionally in severely affected patients.
Eyes can also be affected by the disease: inflammation can occur at the anterior and/or posterior part of the eye, regardless the presence of papilledema. Ocular manifestations can progress to ocular disability in adulthood (loss of vision). Perceptive deafness is frequent and develops in late childhood or later in life. Amyloid A amyloidosis develops with increasing age in 25% of patients. Growth retardation and delay in pubertal traits development may be observed as a consequence of chronic inflammation. Blood inflammation is permanent in most cases.
Careful examination of patients with CAPS usually reveals extensive overlapping of clinical symptoms. Patients with MWS might report symptoms consistent with FCAS, such as cold susceptibility (i.e. more frequent attacks in winter), or symptoms consistent with mild CNS involvement, such as frequent headaches or asymptomatic papilledema, as seen in patients with CINCA (NOMID). Similarly, symptoms related to neurological involvement can become obvious in patients with increasing age. CAPS affected members of a same family can present mild variability of severity; however, severe manifestations of CINCA (NOMID) as overgrowth arthropathy or severe neurological involvement have never been reported in members of families affected by mild forms of CAPS (FCAS or mild MWS).

Is the disease the same in every child?
A huge variability of severity is observed among CAPS. Patients with FCAS have a mild disease with good long term prognosis. MWS patients are more severely affected, due to possible deafness and amyloidosis. CINCA/NOMID patients have the most severe disease. Among this group, variability also exists depending on severity of neurological and joint involvement.

How is it diagnosed?
Diagnosis of CAPS is based on clinical symptoms before being genetically confirmed. Distinction between FCAS and MWS or MWS and CINCA/NOMID might be difficult because of overlapping symptoms. It is based on clinical symptoms and medical history of the patient. Ophtalmologic evaluation (in particular fundoscopy), CSF examination (lumbar puncture) and radiological evaluation will be helpful to distinguish contiguous diseases.

Can it be treated or cured?
CAPS cannot be cured since it’s a genetic disease. However, thanks to substantial advances in the understanding of these disorders, new promising drugs are now under investigation.

What are the treatments?

Recent works on genetic and physiopathology of CAPS showed that IL-1, a powerful cytokine (protein) of inflammation, is overproduced in these conditions and plays a major role in onset of the disease. Currently, a number of drugs that inhibit the IL-1 are in various stages of development. The first drug used in these conditions was the anakinra (Kineret ®). It was shown to be rapidly efficient to control inflammation, rash, fever, pain and fatigue in all CAPS. This treatment is also efficient to improve neurological involvement. In some conditions, it may improve deafness and control amyloidosis. Unfortunately, it does not seem to be effective on overgrowth arthropathy. Doses required depend on disease severity. Treatment has to be started early in live, before chronic inflammation causes organ

irreversible damage as deafness or amyloidosis. It requires daily sub-cutaneous injection. Local reaction at injection site are frequently reported. Rilonacept (Arcalyst ®) is an other anti-IL-1 drug, approved by the FDA (Food and Drug Administration in USA) for patients older than 11 years, suffering from FCAS or MWS. Weekly sub-cutaneous injections are required. Canakinumab (Ilaris ®) is an other anti-IL-1 drug recently approved by the FDA and European Medicines Agency (EMA) for CAPS patients older than 4 years. In MWS patients this drug has been recently show to effectively control the inflammatory manifestations with a sub-cutaneous injection every 8 weeks. Due to the genetic nature of the disease, it is conceivable that the pharmacological blockade of IL-1 should be maintained for long periods, if not life-long.

How long will the disease last for?
CAPS is a lifelong disorder.

What is the long term prognosis (predicted outcome and course) of the disease?
Long term prognosis of FCAS is good but quality of live can be affected by recurrent episodes of fever. In MWS syndrome, long term prognosis may be affected by amyloidosis and impaired renal function. Deafness is also a significant long term complication. Children with CINCA may have growth disturbances during the course of the disease. In CINCA/ NOMID long term prognosis depends on severity of neurological, neurosensorial and joint involvements. Hypertrophic arthropathies may impose severe disabilities. Premature death is possible in severely affected patients.