Autoinflammatory diseases: cryopyrinassociated periodic syndromes presenting in the newborn and first year of life

Autoinflammatory diseases are disorders of the innate immune system, characterised by recurrent attacks of fever and systemic inflammation in the absence of infection. This article focuses on a group of hereditary autoinflammatory conditions (or periodic fever syndromes), the cryopyrin-associated periodic syndromes (CAPS) that can have a neonatal onset, particularly chronic infantile, neurological, cutaneous and articular (CINCA) syndrome. The clinical presentation, diagnostic investigations, treatment and outcome of CAPS are reviewed.

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Key points

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- In neonates and infants with recurrent fever and rash consider the possibility of an autoinflammatory condition, specifically CAPS.
- 2. A strong index of suspicion for CAPS is required, with referral to an expert service.
- 3. Early diagnosis is vital, since timely treatment can prevent IL-1 mediated organ damage.
- 4. Treatment with an IL-1 blocker such as anakinra or canakinumab is extremely effective.

Autoinflammatory conditions

The autoinflammatory conditions (also known as periodic fever syndromes) are disorders of innate immunity. Innate immune responses provide the body with its first line of defence against infections. The concept of autoinflammation was introduced in 1999 when two of the hereditary conditions were distinguished from typical autoimmune conditions.¹ Unlike autoimmune conditions, which are characterised by abnormal T and B cell reactivity associated with autoantibody production, in autoinflammatory conditions there is a marked absence of autoantibodies and antigen-specific T cells.

Autoinflammatory conditions are characterised by:²

- 1. Recurring episodes of fever, rash and malaise with normal health in between
- 2. Systemic inflammation affecting the serosal surfaces, joints, skin and eyes.

Life expectancy can be reduced and there is a risk of developing amyloid A (AA) amyloidosis.³

Cryopyrin-associated periodic syndromes: an overview

CAPS are a group of autoinflammatory conditions with a common gene mutation, but a variable phenotype presenting at different ages. The disorders are caused by mutations in the *NLRP3* gene, formally called the *CIAS1* (cold induced autoinflammatory syndrome 1) gene.¹⁴ The spectrum of systemic inflammation, ranging from mild to severe, helps subdivide CAPS as follows:5

- familial cold autoinflammatory syndrome (FCAS)
- Muckle-Wells syndrome (MWS)
- chronic infantile, neurological, cutaneous and articular syndrome (CINCA), also known as neonatal onset multisystem inflammatory disease (NOMID).

Although this classification remains useful, increasingly these conditions are being labelled as mild, moderate or severe CAPS. CAPS are now considered to be one of the main hereditary autoinflammatory conditions. It is estimated that there are 1-2 cases per million in the USA and 1 in 360,000 in France.⁶⁷ CAPS predominantly



FIGURE 1 The key presenting signs seen in patients with CAPS. A) typical urticarial rash. B) frontal bossing, hypoplasia of the face, macrocephaly and flattening of the nasal bridge (saddle nose), with rash and a hearing aid. C) episcleritis. D) finger clubbing.

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affect northern Europeans with some cases noted in southern Asia.⁸ Males and females are affected equally.

Key presenting features

Fever with a non-pruritic urticarial rash and raised inflammatory markers are common to all three CAPS phenotypes (**FIGURE 1**). Clinical overlaps, particularly for MWS and CINCA have been reported⁹ and the conditions form a disease spectrum. However, there are distinct features that help differentiate the three disease entities, summarised in **TABLE 1**.

CINCA

Patients have mildly dysmorphic features including frontal bossing, facial hypoplasia,

macrocephaly and flattening of the nasal bridge (saddle nose), as shown in **FIGURE 1**.¹⁰⁻¹² Conjunctivitis or episcleritis may be seen (**FIGURE 1**), with uveitis or papillitis of the optic nerve on ophthalmological assessment. Intrauterine growth restriction (IUGR) may have been recognised and poor growth, with short stature, may persist. Finger clubbing may be seen (**FIGURE 1**), particularly in long-standing disease.

Three major criteria have been defined for the diagnosis of CINCA:¹⁰

- 1. Early-onset urticarial skin rash occurring with episodic fever
- 2. Central nervous system (CNS) involvement
- 3. Inflammatory or deforming arthropathy.

Neurological symptoms include headaches, seizures, irritability, vomiting, developmental delay and learning difficulties.

Arthropathy is distinctive with frequent knee involvement. Overgrowth of epimetaphyseal cartilage is usually apparent by three years of age. Before this, premature ossification of the patella may be seen on X-ray. Severe deformities, contractures and leg length discrepancy may develop.¹³

Severity of CINCA is variable, but can include debilitating organ damage and death in young adulthood in 20% of patients due to infection, AA amyloidosis, or cachexia.¹⁴ Early diagnosis and treatment is essential to improve prognosis.

	CINCA	MWS	FCAS	
Severity	Severe	Intermediate	Mild	
Age of onset	Neonatal/infancy	Adolescence to adulthood	Infancy to adulthood	
Inflammatory markers	Raised CRP and ESR	Raised CRP and ESR	Raised CRP and ESR	
Length of attack	Continuous attacks with exacerbations but symptoms predominantly in the early mornings	1-2 days or continuous with flares usually occurring daily, often in the afternoon and evenings	30 minutes to 72 hours	
Trigger	No specific triggers	There may be a degree of cold exacerbation but this is less obvious than in FCAS	Typically precipitated by exposure to cold or damp conditions	
Neutrophilic urticarial rash	Rash persistent	Evanescent but more persistent than in FCAS	Typically triggered by cold, often occurring 2-3 hours after cold exposure	
General symptoms	Lymphadenopathy	Fatigue	Nil of note	
	Hepatosplenomegaly	Abdominal pain		
	Finger clubbing			
Sensorineural deafness	Present	Present: occurs in 60% of cases ¹⁷ Often missed in the early stages ¹⁵	Not recognised	
Neurological symptoms	Severe chronic aseptic meningitis leading to raised intracranial pressure, hydrocephalus and cognitive impairment due to cerebral atrophy	Intermittent aseptic meningitis leading to irritability and headache	Not recognised	
Musculoskeletal	Characteristic deforming arthropathy with overgrowth of epimetaphyseal cartilage, particularly of the long bones and patella overgrowth	Arthralgia and arthritis usually of the larger joints the larger joints		
Eye involvement	Uveitis and optic disc swelling. Possible loss of vision	Uveitis and papilloedema	Inflammatory eye disease, conjunctivitis and episcleritis	
AA amyloidosis	Develops with increasing age in 25% of patients	<25%	Not recognised	
Organ damage	Growth and puberty are adversely	Growth is normal	Very little if any permanent organ	

TABLE 1 Typical features of the different CAPS phenotypes. Key CINCA = chronic infantile, neurological, cutaneous and articular syndrome, MWS = Muckle-Wells syndrome, FCAS = familial cold autoinflammatory syndrome, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate.

Watch out for...

CAPS, specifically CINCA, presents almost directly after birth, with fever and rash. In neonatal medicine it is important to consider sepsis as an initial cause of these symptoms. Vigilance is needed to look for features suggestive of sepsis, immunodeficiency or malignancy. Assessment should include checking for raised intracranial pressure, particularly if acute meningitis is suspected. Aseptic meningitis is seen in CAPS. The classical urticarial rash associated with CAPS (**FIGURE 1**) may be mild and careful examination is needed.

A positive family history may be a key feature, or record of similar symptoms in parents (who may be undiagnosed). A family history of renal failure should also be sought, since this could be caused by AA amyloidosis.¹⁰ Absence of a family history does not exclude CAPS and sporadic cases can occur.

Differential diagnosis

Other causes of pyrexia of unknown origin need to be considered, most commonly: immunodeficiency

 malignancy, including acute lymphoid leukaemia (ALL), acute myeloid leukaemia (AML) or lymphoma.

One study noted that the most common diagnoses suspected prior to confirmation of CAPS (specifically MWS) were conjunctivitis (44%), unclassified rheumatic disease (41%), sensorineural hearing loss (32%), urticaria (26%) and uveitis (18%), implying that CAPS features may not always be considered together, adding to diagnostic delay.¹⁵

Important autoimmune diseases need to be ruled out such as neonatal lupus, atypical Kawasaki disease, systemic juvenile idiopathic arthritis (sJIA) and Behcet's disease.

Other autoinflammatory conditions can present in infancy and early childhood;¹⁶ more information can be found on the

website of the Eurofever Project at www.printo.it/eurofever/index.asp. Expert paediatric rheumatology advice should be sought if autoimmune or autoinflammatory conditions are suspected.

Laboratory findings/investigations

Investigations may initially be expansive to rule out differential diagnoses. Fever is a common symptom in children, usually due to infections.¹⁰ A septic screen should be carried out that may include as a minimum:

- full blood count and blood film
- C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) or plasma viscosity
- blood cultures
- chest X-ray
- urine dipstick, microbiology, culture and sensitivity
- lumbar puncture, cerebrospinal fluid analysis
- viral infection screen and serology.

If symptoms of fever, rash and raised inflammatory markers persist despite treatment for sepsis, it is logical to consider an immune deficiency or autoimmune condition. Expert advice should be sought.

In the case of CAPS, an immune deficiency and autoimmune condition will not be evident. Blood tests show a leukocytosis and elevated acute-phase reactants – ESR, CRP and serum amyloid A (SAA) – during attacks.⁵ CRP and SAA can be strikingly elevated by 100- to 1,000fold, underlying the high risk of AA amyloidosis.¹⁷ Normalisation of CRP and SAA between attacks is typical of autoinflammatory conditions, aiding diagnosis, as well as demonstrating control of subclinical inflammation as part of treatment monitoring.¹⁸

CAPS should be considered particularly if fever and rash is associated with conjunctivitis, lymphadenopathy or raised intracranial pressure. Investigations should be carried out looking for organ specific associations, and may include:

- 1. CT scan/MRI brain, for
- ventriculomegaly, cerebral atrophy 2. Lumbar puncture, typically aseptic
- meningitis (may be normal) 3. Ophthalmology review – uveitis, chronic
- papilloedema, optic nerve atrophy, loss of vision
- 4. X-ray of knees, patella overgrowth or premature ossification of patella
- 5. Audiology review sensorineural hearing loss.

Specific diagnosis relies on recognising clinical manifestations and identification of the gene. Necessary genetic technologies are not widely available and genetic testing needs to be carried out in a specialist centre. In the UK, this is performed at the National Amyloidosis Centre, University College Hospital London (www.ucl.ac.uk/ amyloidosis/nac). Genetic testing is available within Europe for patients where there is a strong clinical suspicion by enrolment in the Eurofever Project (www.printo.it/eurofever/ index.asp).

Treatment of CAPS Symptomatic control

Initial treatment of a first attack should be in response to fever and potential for sepsis. Intravenous antibiotics should be commenced while awaiting microbiology results. However, attacks will be unresponsive to antibiotics and treatment is symptomatic. Antipyretics should be given (although may be ineffective) and intravenous fluids if needed.

Overview and aims of treatment

The rarity of these diseases poses important limitations to trials,¹⁶ with few randomised controlled trials available. Frequently, the observation period is short and so knowledge of long-term safety and

IL-1 blocker	Mechanism of action	Length of action/administration	Licensing in CAPS
Anakinra (Kineret)	Blocks IL-1α and IL-1β binding to the IL-1 receptor	Short-acting Daily SC injection (1-2mg/kg/day)	Available for children >8 months of age with a body weight ≥10kg
Rilonacept (Arcalyst)	Binds IL-1α and IL-1β	Long-acting Weekly SC injection	Not currently licensed in UK/Europe for CAPS
Canakinumab (Ilaris)	An anti-IL-1β monoclonal antibody that selectively binds soluble IL-1β	Long-acting SC injection (8mg/kg) once every eight weeks	Available for children >2 years of age with a body weight of ≥7.5kg

TABLE 2 IL-1 inhibitors used in the treatment of CAPS. Key: IL-1 = interleukin-1, SC = subcutaneous.

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efficacy is limited.¹⁹ The published evidence for most autoinflammatory conditions is derived from small series and case reports. Treatment aims to:¹

- Improve disease symptoms and/or reduce attack frequency and duration, thereby improving health-related quality of life
- 2. Reduce/normalise the systemic inflammatory response markers in the blood (CRP, ESR, SAA)
- 3. Prevent inflammation-related progression of organ damage and death from multiorgan failure.

Anti-histamines are ineffective for the urticarial rash due to its non-pruritic nature. Corticosteroids and other immunosuppressants demonstrate a limited improvement in the inflammatory markers but not necessarily the organ damage.

IL-1 inhibitors in CAPS

Targeted therapy by interleukin-1 (IL-1) blockade causes a rapid and dramatic improvement of clinical symptoms accompanied by a decrease in acute phase reactants, implying that the clinical features are indeed mediated by IL-1.¹⁷ However, it is not known if there is complete suppression of inflammation at the cellular level.

There are three currently available IL-1 inhibitors, shown in **TABLE 2**. In the UK, anakinra and canakinumab are the most commonly used agents. Before initiating treatment, tuberculosis (TB) should be



FIGURE 2 Case 1 before and after treatment with IL-inhibitor. A) Before: cachexia, rash and misery pre-treatment. B) Response to treatment: improved growth and weight gain as well as improved mood.

	Case 1 (FIGURE 2)	Case 2
Diagnosis	Diagnosed with possible CINCA aged two years (genetic test not available at that time)	Diagnosed with CINCA aged two years
Symptoms prior to diagnosis	 Recurrent urticarial rash Slow development Head circumference acceleration with small left- sided subdural hemorrhage needing a ventriculo- peritoneal shunt Lost to follow up and re-presented at 11 years of age Urticarial rash since birth Anaemia Raised SAA Delayed motor development Poor growth (wearing clothes for age 5-6) Wheelchair user Wearing nappies Frontal bossing, saddle nose Arthritis Clubbing 	Rash since birth Recurrent fevers Abdominal pain Bloodshot eyes (FIGURE 1C) Elevated ESR, CRP, SAA Low haemoglobin Frontal bossing, saddle nose Skin biopsy revealed inflammatory changes Knee X-ray revealed premature ossification of patella
Treatment	Anakinra started at age 11 years	Anakinra started at age two years
Response to treatment	Temperatures, rash, arthritis, headaches completely resolved Clubbing resolved Good mood, alert and happy No longer sleeping in day Gained weight and now wears the correct clothes for his age Walked into clinic; no longer using wheelchair Uses the toilet normally	Rash, arthritis, temperatures resolved Better mood, increased energy Developmentally normal No hearing loss Normal ophthalmology review Inflammatory markers normal Re-occurrence of symptoms if missed dose/given late/growth spurts
Progress	After several years of treatment with anakinra, chose to change to canakinumab. Good response maintained	Maintained on anakinra. Dose increased over time. Good response maintained

TABLE 3 Case histories illustrating the impact of IL-1 inhibition in CAPS. Key: CINCA = chronic infantile, neurological, cutaneous and articular syndrome, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, SAA = serum amyloid A.

excluded, due to risk of reactivation of latent TB with biologic therapies.

Dosing

The dose of IL-1 blockade therapy needed to suppress systemic and organ inflammation in CAPS patients depends on disease severity and extent of organ involvement. It is recognised that anakinra does not always normalise the acute phase reactants at standard doses (1-2mg/kg/day) and it may be necessary to increase the dose over time (up to 10mg/kg/day) to induce and maintain complete remission.^{1,20} Similar findings have been noted with canakinumab (**TABLE 2**).²¹

Management

CAPS patients need a multidisciplinary team (MDT) and multiprofessional approach. Physiotherapy is particularly important for rehabilitation due to frequency of pain, presence of myalgia and joint limitations associated with this condition.²²

Prognosis and long-term complications of CAPS

The disease course and disease-associated disability is variable. Patients with FCAS primarily experience episodic attacks with very little, if any, permanent organ damage, while patients with CINCA usually have continuous disease resulting in debilitating organ damage. Treatment with anakinra or canakinumab has significantly improved outlook and long-term prognosis: **TABLE 3** gives two case histories that illustrate the impact of IL-1 inhibition in CAPS.

Complications of chronic inflammation, most severe in CINCA but also seen in MWS, may include:²³

- sensorineural deafness
- blindness due to optic atrophy or uveitis
- bone and joint deformities
- CNS damage leading to cognitive deficits and developmental delay
- poor growth due to inflammation
- AA amyloidosis leading to renal failure and early death.

Conclusion

Autoinflammatory diseases are rare conditions of which CAPS is one of the

groups described. It is important to be aware of CAPS in neonatal and infantile medicine, since CINCA can have an early onset with fever and non-pruritic urticarial rash that can be mistaken for infection. Key clinical features and raised acute phase response with episodes of fever should arouse suspicion. There is no single diagnostic test, but genetic techniques are advancing. IL-1 blockade allows for control of systemic inflammation, decreasing risk of permanent organ damage, thereby improving long-term prognosis.

Patient consent

The authors received written consent to publish this report from the patients' representatives.

Conflict of interests

Dr Beverley Almeida – no conflict of interests.

Dr Liza McCann has participated in two clinical advisory boards for Sobi (Swedish Orphan Biovitrum AB), 2013-2014.

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