

Recognising and understanding cryopyrin-associated periodic syndrome in adults

René Williams, Philip Hawkins and Thirusa Lane

ABSTRACT

Cryopyrin-associated periodic syndrome (CAPS) is a group of rare hereditary autoinflammatory diseases characterised by recurrent flares of mild to severe systemic inflammation and fever. CAPS is the umbrella term for a spectrum of individual conditions, namely familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and neonatal-onset multisystem inflammatory disease (NOMID), also known as chronic infantile neurologic, cutaneous and articular (CINCA) syndrome. The flare symptoms include fever, fatigue, rashes, headaches, arthralgia and myalgia that can last for a few hours or for several days. These symptoms are debilitating, contributing to poor quality of life for patients if left untreated. Serious life-changing complications such as hearing loss, blindness and AA amyloidosis resulting in kidney failure can occur. Until recently, treatment of the disease was symptomatic using non-steroidal anti-inflammatory and immunosuppressant drugs with limited success. In contrast, biological treatments targeting interleukin 1 (IL-1) have proved remarkably effective, often associated with complete and sustained disease remission, vastly improved quality of life and avoidance of serious long-term complications.

Key words: Autoinflammatory disease ■ Cryopyrin-associated periodic syndrome ■ Interleukin 1 ■ Biological treatment

in the USA and 1 in every 360 000 in France (Cuisset et al, 2011). In the UK, the first known CAPS case presented at the National Amyloidosis Centre in 1993 (diagnosed posthumously) and the first anti-interleukin 1 (IL-1) therapy was successfully administered to a patient with CAPS in October 2002 (Hawkins et al, 2003). By the start of 2018, 121 CAPS patients, including children, were being treated under the UK CAPS Treatment Service, as part of the National Amyloidosis Centre.

The syndrome encompasses a continuum of three diseases: at the milder end of the spectrum is familial cold auto-inflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) is at the middle of the spectrum, and chronic infantile neurologic, cutaneous and articular (CINCA) syndrome, also known as neonatal-onset multisystem inflammatory disease (NOMID), is the most severe form (Figure 1). CAPS is caused by mutations in the NLRP3 gene, which codes for the protein cryopyrin; cryopyrin plays a key role in regulating the activity of interleukin-1 beta (IL-1 β). The mutation results in persistent and excessive production of IL-1 β by the cryopyrin inflammasome, rather than as a measured and controlled physiological response to inflammation, injury or infection (Autoinflammatory Alliance, 2017).

Patients usually develop symptoms from birth, but CAPS can also manifest later in childhood and early adulthood. Recent research has revealed that somatic NLRP3 mosaicism is present in some CAPS patients with an onset of symptoms in mid-late adulthood, ie that new CAPS-causing mutations in white blood cell lines have appeared during adult life. Rowczenio et al (2017) identified somatic NLRP3 mosaicism as the aetiology of CAPS in eight British adult patients who first developed typical CAPS symptoms late in life.

The disease responds remarkably well to treatments that block IL-1; in the UK these are the biological treatments canakinumab and anakinra. These IL-1-inhibiting therapies have been highly effective in most cases, providing complete and sustained disease remission (Koné-Paut et al, 2011). As with many rare diseases, awareness of CAPS among health professionals is limited, which often results in delayed diagnosis and initiation of appropriate treatment. The challenge for health professionals is therefore to recognise and piece together the symptoms to form a diagnosis, but this relies on a high index of suspicion. Early identification and treatment of the disease is of the utmost importance. Left undiagnosed and

Cryopyrin-associated periodic syndrome (CAPS) is a group of rare hereditary autosomal dominant autoinflammatory diseases characterised by recurring periods of systemic inflammation and fever (Touitou and Koné-Paut, 2008). The exact incidence is unknown and probably underestimated, but it is likely that 1 person per 1000 000 is diagnosed with CAPS

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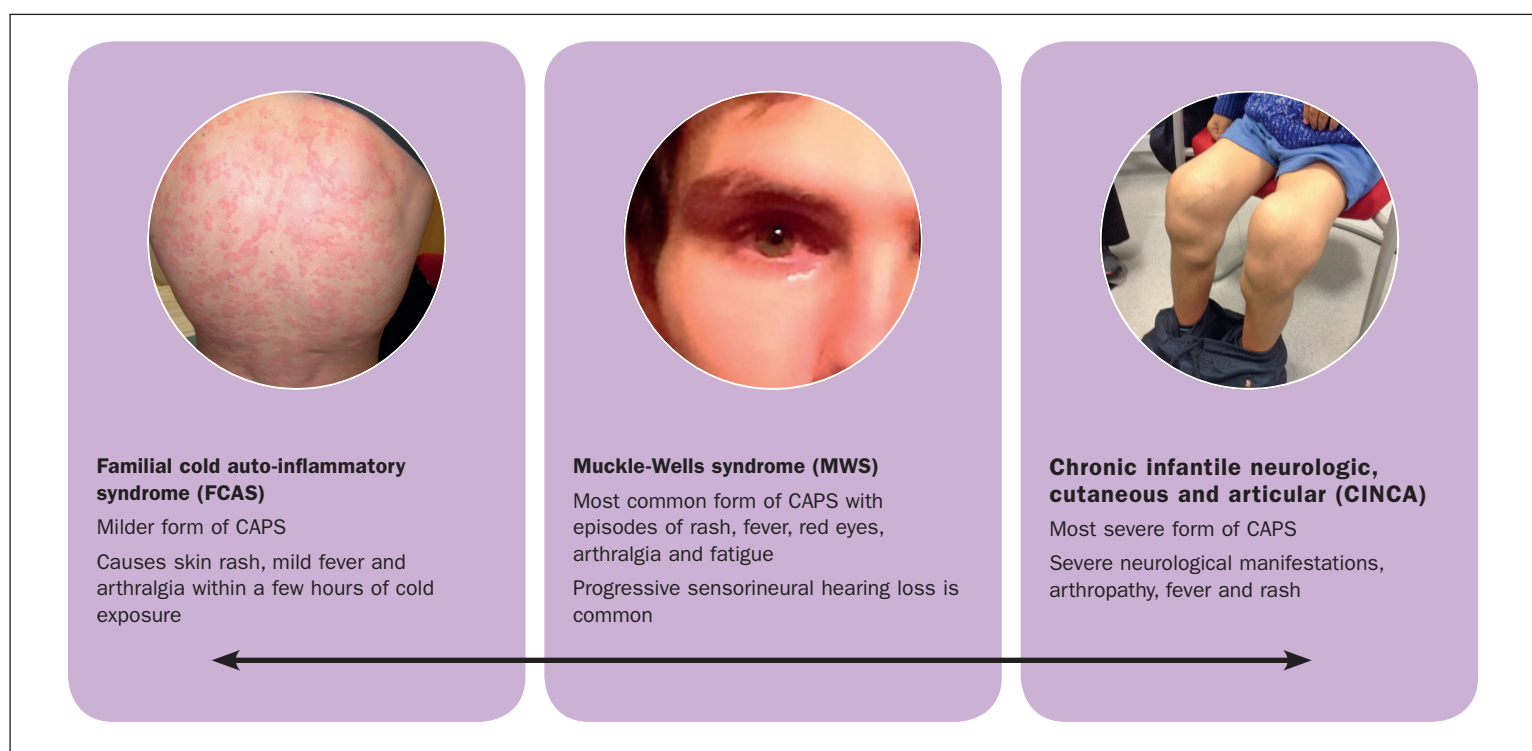


Figure 1. The clinical spectrum of cryopyrin-associated periodic syndrome (CAPS)

untreated, CAPS can have a profound adverse effect on the quality of life of sufferers and is associated with the risk of developing AA amyloidosis and, eventually, renal failure.

The innate immune system and the activation and regulation of IL-1

CAPS is a disorder of innate immunity. Innate immunity is a genetically encoded system that provides a rapid response to danger signals. The innate immunity is executed by two major classes of receptors: Toll-like receptors, which are membrane bound, and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), which are cytosolic. Both receptors are involved in identifying pathogen-associated molecular patterns (PAMPs), and the NLRs more specifically sense endogenous signals, referred to as danger-associated molecular patterns (DAMPs) (Jesus and Goldbach-Mansky, 2014).

The inflammasome is a multimeric cytosolic complex involved in regulating the activation of caspase enzymes, which are responsible for converting interleukins from their inactive to their active forms. The NLRP3 inflammasome, consisting of cryopyrin and other sensing, adapting and activating molecules, plays a pivotal role in recognition of these danger signals and the subsequent immunological response (Lane and Lachmann, 2011; Kuemmerle-Deschner and Haug, 2013). Activation by PAMPs or DAMPs results in cryopyrin interacting with other protein components of the inflammasome, resulting in cleavage of procaspase-1 to caspase-1, which in turn cleaves inactive pro-IL-1 β to mature, active IL-1 β (Lane and Lachmann, 2011).

Cytokines are small signalling proteins secreted by cells when activated by PAMPs or DAMPs. Their role is to mediate the body's immune response to danger and injury. Cytokines may be

pro-inflammatory, functioning to up-regulate the inflammatory response, or anti-inflammatory, acting to inhibit the pro-inflammatory cytokine response (Zhang and An, 2007). IL-1 α and IL-1 β are pro-inflammatory cytokines. They activate cells by binding and signalling through the IL-1 receptor type I (IL-1RI). At the receptor level, the IL-1 receptor antagonist (IL-1RA) is the anti-inflammatory cytokine responsible for regulating IL-1 signalling, competing with IL-1 α and IL-1 β for IL-1RI binding, inhibiting the formation of a receptor signalling complex and terminating IL-1 α - and IL-1 β -mediated signalling (Jesus and Goldbach-Mansky, 2014).

IL-1 α is continuously expressed as a precursor in cells forming biological barriers, such as epithelial cells and keratinocytes as well as other organ cells. It does not rely on processing for activation and it is released from damaged or dying cells. IL-1 β , however, needs to be proteolytically cleaved into its active form. Active IL-1 β is predominantly produced in a subset of blood monocytes, dendritic cells and tissue macrophages, where its activation and release are tightly controlled (Jesus and Goldbach-Mansky, 2014). Once released, circulating IL-1 β binds to the IL-1 receptor, activating the inflammatory response (Dinarello, 1996).

In short, in patients with CAPS, the presence of mutant cryopyrin results in intense activation of IL-1 β and the innate immune system, to innocuous triggers that ordinarily do not have this effect. Anti-cytokine agents that inhibit the activity of IL-1 such as anakinra (a recombinant IL-1 receptor antagonist), rilonacept (an IL-1 Trap), and canakinumab (a fully humanised anti-IL-1 β monoclonal antibody) have dramatically changed the landscape for CAPS patients and have played a crucial role in our current understanding of the role of IL-1 β in these disorders (Lane and Lachmann, 2011).

Table 1. Clinical characteristics and disease manifestations	
Disease manifestations	% affected
Fever	64
Other constitutional symptoms*	20
Skin manifestations	97
Musculoskeletal manifestations	90
Neurological involvement	53
Eye involvement	85
Hearing impairment	34
Other:	52
■ Oral ulcers	40
■ GI manifestations	4
■ Pleurisy	3
■ Pericarditis	1
■ Growth stunting	3
■ AA amyloidosis	1

*Defined as fatigue, malaise or mood disturbances
Source: Lane, 2016

Clinical manifestations

The signs and symptoms of CAPS are due to multi-system inflammation and include the following clinical manifestations:

- Urticarial skin rash
- Arthralgia (joint pain)
- Myalgia (muscle pain)
- Headache
- Red eyes
- Fatigue
- Fever/chills
- Cold-induced symptoms
- Abdominal pain
- Oral ulcers

Some patients exhibit a chronic sustained disease pattern with daily or almost daily symptoms, with superimposed exacerbations; others have a more relapsing–remitting course, sometimes with quite prolonged asymptomatic periods between flares. *Table 1* depicts the clinical characteristics and disease manifestations of an analysis cohort from a single–centre experience by Lane (2016) where approximately 60% of patients described a chronic pattern with intermittent flares prior to starting treatment.

FCAS is variable in its manifestations and is characteristically triggered following cold exposure such as wind, air conditioning or a light mist. Symptoms are intermittent, ie periodic, and self-limiting and include episodes of mild fever, skin rash (may appear erythematous, plaque like, often itchy and sensitive to touch), arthralgia, headache and conjunctivitis. The systemic inflammatory response usually begins a few hours after exposure to low temperatures with the duration of most flares being less than 24 hours. Deafness and AA amyloidosis are not usually observed, but despite the generally modest symptoms, may nevertheless develop (Autoinflammatory Alliance, 2017).

MWS is characterised by rash, fever/chills, arthralgia, myalgia, conjunctivitis and fatigue. These symptoms are typically experienced every day, are usually worse in the evening, and may be triggered by stress, exercise or other unknown factors. Progressive sensorineural hearing loss is present in about 70% of cases, and development of AA amyloidosis is not uncommon (Lachmann and Hawkins, 2009). It is estimated that AA amyloidosis would affect 25–33% of patients if left untreated (Aganna et al, 2002). Neurological impairment is not usually associated with MWS, although headache and papilloedema have been reported (Terrerri et al, 2015).

CINCA/NOMID is characterised by all of the features above along with chronic aseptic meningitis causing chronic headaches, cerebral atrophy, papilloedema and hearing loss; these patients may even die from disease complications in childhood. Bone and joint involvement may also vary in severity with the larger joints such as the knees being affected with oedema, deformity and functional disability (De Boeck et al, 2000). Growth and development during childhood and adolescent may be markedly delayed.

Diagnosis

Diagnosing CAPS can be difficult—the rarity of the disease means early diagnosis requires a high index of suspicion. A lack of awareness of CAPS among health professionals, together with what may appear to be expansive symptomatology, often leads to a delay in diagnosis, with symptoms being attributed to infection or autoimmune disease. These patients are often referred and re-referred to rheumatology, dermatology and immunology clinics and are frequently left frustrated by fragmented care and a lack of confirmed diagnosis despite many investigations while they continue to suffer the debilitating day-to-day symptoms.

A suspicion of CAPS would be prompted by the signs and symptoms found during a thorough physical examination and a detailed medical and family history, followed by a genetic test confirming a mutation in the NLRP3 gene. Acute-phase markers in the blood, such as C-reactive protein (CRP) and serum amyloid A protein (SAA) are useful for further evaluation of CAPS since they are often very raised, even at times when a rash or definite symptoms are absent. Due to the episodic nature of the disease serial measurements are recommended (Yu and Leslie, 2011).

Persistently elevated SAA, associated with any inflammatory disorder, places patients at risk of development of AA amyloidosis. In patients who develop this complication, which causes renal dysfunction, the ongoing degree of SAA elevation is the most important factor influencing the risk of death (Targońska-Stępnia and Majdan, 2014). SAA is the most sensitive blood biomarker for tissue injury and inflammation, but assays are available only in specialist centres. CRP is a more widely used and available test for estimating the acute phase response and, in the absence of amyloidosis, is generally sufficient for monitoring CAPS disease activity and response to therapy.

Treatment

Until 2003 no effective treatment for CAPS existed and patients tended to be treated with non-steroidal anti-inflammatory drugs (eg ibuprofen), antihistamines, disease-modifying anti-rheumatic

drugs (eg methotrexate, sulphasalazine), corticosteroids and other immunosuppressants (eg cyclosporine) in attempts to ameliorate symptoms. However, these treatments were ineffective and had many adverse effects; a great unmet need existed for targeted effective therapy that was safe over the course of a lifetime. In the last decade biological treatments targeting IL-1 (anakinra, canakinumab and rilonacept) have revolutionised the treatment of CAPS and have turned around the lives of these patients. Each therapy has a different mode of action and all are generally well tolerated by patients (Hawkins et al, 2003; Goldbach-Mansky et al, 2006; Hoffman et al, 2008; Lachmann et al, 2009).

Canakinumab (Ilaris)

Canakinumab is a fully humanised monoclonal antibody specifically targeting IL-1 β . Once bound to IL-1 β with high affinity, it neutralises the biological function of the cytokine, thereby blocking its interaction with the IL-1 receptor and preventing IL-1 β activation (Lachmann et al, 2009). Canakinumab was approved in 2009 by the US Food and Drug Administration (FDA) for the treatment of FCAS and MWS and by the European Medicines Agency (EMA) for the treatment of CAPS (Kuemmerle-Deschner and Haug, 2013).

Canakinumab has a mean half-life of 26 days, ie on average, it would take 26 days for the concentration of canakinumab in the body to reduce to half the initial value. It is administered by subcutaneous injection every 8 weeks at a starting dose of 2mg/kg for patients with a body weight between 15 kg and 40 kg or 150 mg for patients with a body weight over 40 kg. Kuemmerle-Deschner et al (2011) established that patients with a more severe phenotype have higher circulating concentrations of IL-1 and therefore require higher doses of IL-1 inhibitor. For these patients and those who have ongoing residual central nervous system or non-central nervous system symptoms with evidence of persistent serological inflammation, the dose can be increased to 600 mg every 8 weeks. Up-titration is done in increments of 150 mg until a satisfactory clinical and serological response is achieved. *Figure 2* shows the canakinumab up-titration protocol from the UK CAPS National Treatment Service.

Anakinra (Kineret)

Anakinra is a recombinant interleukin-1 receptor antagonist (IL-1RA). It inhibits IL-1 binding to the IL-receptor type1 (IL-1RI) thereby blocking the activity of IL-1. In 2013 anakinra was approved for the treatment of all forms of CAPS in the European Union (EU) and was approved for the NOMID form of CAPS in the USA by the FDA in early 2013. It has a very short half-life of 4–6 hours and is given as a daily subcutaneous injection. Anakinra comes in a prefilled graduated syringe of 100 mg/0.67 ml. The graduated syringe allows for dosage between 20 mg and 100 mg. It is administered at a recommended starting dose of 1–2 mg/kg and can be adjusted to a maximum of 8 mg/kg daily to regulate persistent inflammation (Swedish Orphan Biovitrum, 2012).

Rilonacept (Arcalyst)

Rilonacept is a dimeric fusion protein consisting of the IL-1 binding domains of IL-1RI and the IL-1 receptor accessory

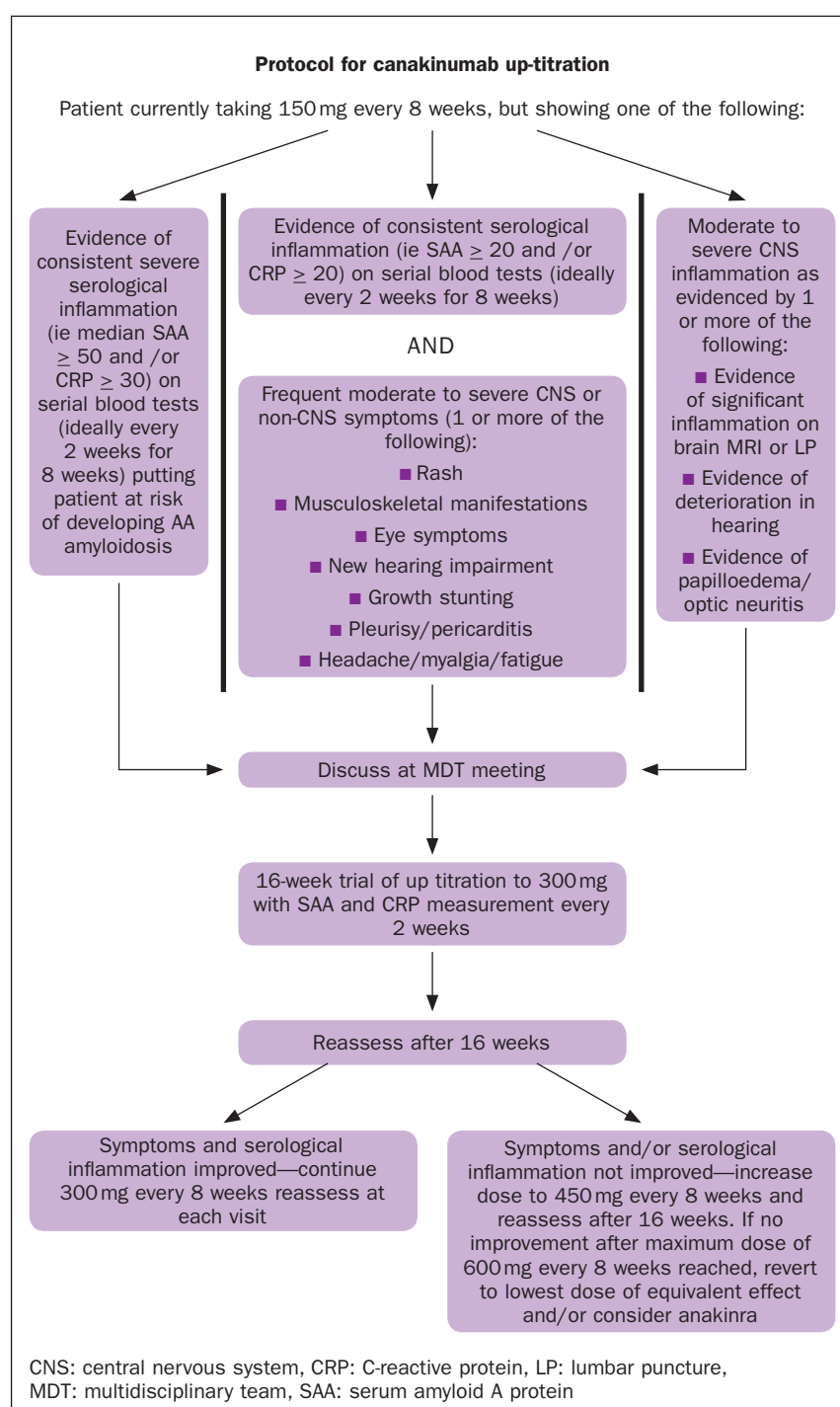


Figure 2. Canakinumab up-titration protocol used by UK National CAPS Treatment Service

protein (IL-1RAcP) attached to the human immunoglobulin G (IgG) molecule. Also known as IL-1 Trap, it acts as a soluble decoy receptor that binds IL-1 β preventing its interaction with cell surface proteins thereby preventing the cells from being triggered to increase production of inflammatory mediators (Gillespie et al, 2010). Rilonacept also binds IL-1 α and IL-1RA with lower affinity (Regeneron, 2016). Rilonacept was the first FDA-approved treatment for CAPS, specifically for FCAS and MWS in adults. It was approved for marketing in the EU in

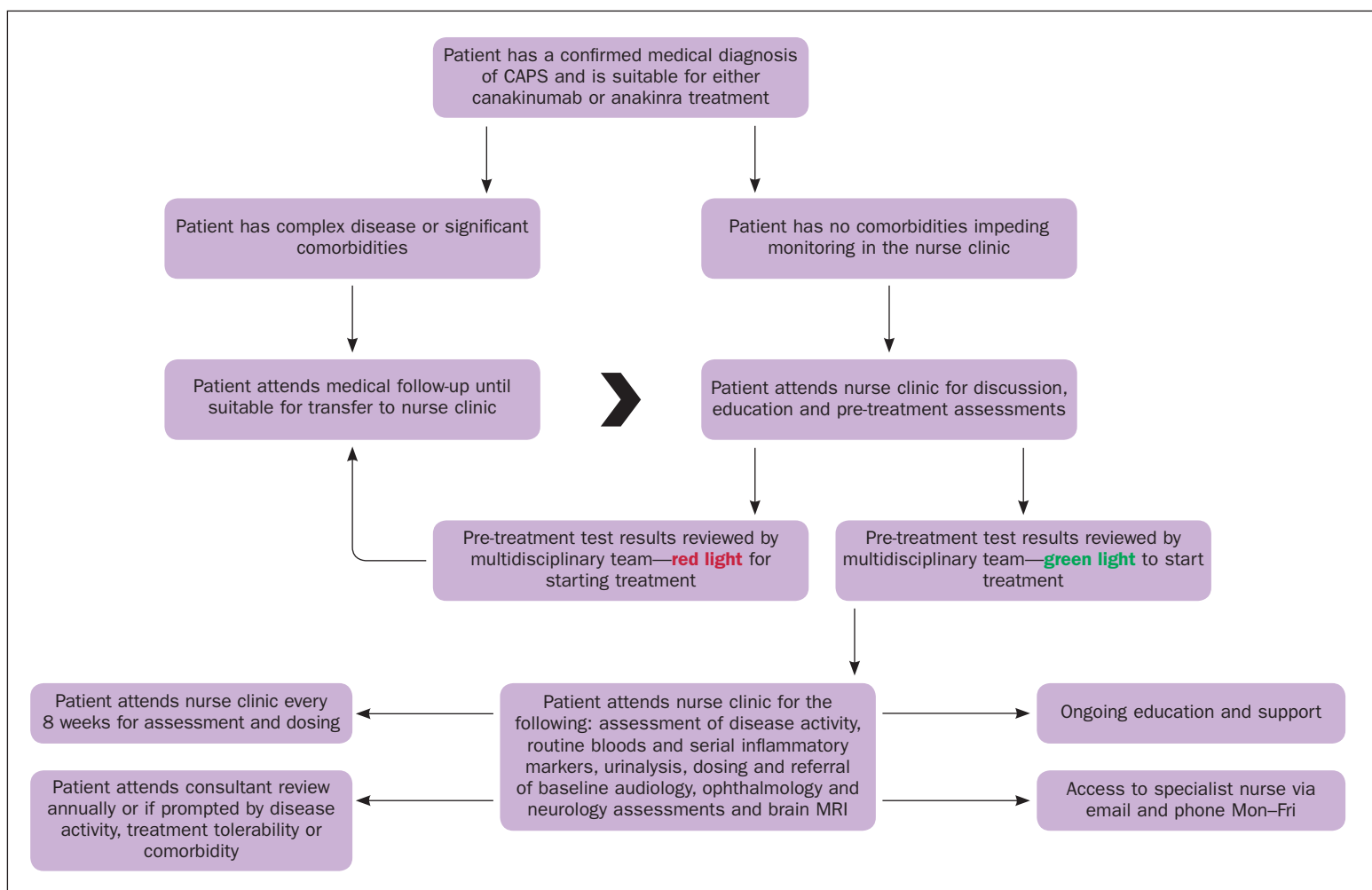


Figure 3. Patient pathway at the UK National CAPS Treatment Service (adapted from Lane, 2016)

2009, but is not available for prescription in the UK. It has a half-life of 8.6 days and is given as a weekly subcutaneous injection. Treatment is initiated with a loading dose of 320 mg administered as two separate 2 ml injections of 160 mg on the same day. Thereafter dosing is continued on a once-weekly basis of 160 mg/2 ml subcutaneous injection (Russell et al, 2003; Regeneron, 2016).

Patient care pathway

Following initiation of treatment, it is important that these patients are monitored regularly, the frequency depending on disease activity and treatment regimen. These patients should be followed up by a specialist medical facility focusing on the care of patients with auto-inflammatory diseases. In the UK, the CAPS National Treatment Service, commissioned in 2010, is based at the Royal Free London NHS Foundation Trust, where the adult patients and older children are seen. Young children are seen and treated at Great Ormond Street Hospital in London at the specialist paediatric fever (autoinflammatory disease) clinic, working closely with the Royal Free team. The service provides diagnosis, assessment, treatment and monitoring of patients. Furthermore, it is solely through this service that CAPS patients in England have access to canakinumab, which is funded centrally by NHS England.

Patients who are referred to the National Amyloidosis Centre for review are initially seen by a medical consultant in the fever clinic where they undergo a thorough clinical assessment. *Figure 3* illustrates the patient pathway. Should there be a strong suspicion of CAPS, the likely diagnosis and suitable treatment options available, ie canakinumab or anakinra, are discussed with the patient. Genetic testing is performed to confirm a diagnosis of CAPS and a viral screen and QuantiFERON test are performed to rule out any serious infections before initiation of treatment. Patients are introduced to the CAPS clinical nurse specialist (CNS) who will hold a separate consultation with the patients, answering any questions patients may have about treatment. The CNS thereafter becomes the patients' first point of contact. After initiation of therapy, patients are routinely followed up in the CAPS CNS clinic. Here patients undergo clinical assessment and dosing with canakinumab approximately every 8 weeks. If anakinra is determined to be the treatment of choice, the patient is taught to self-administer the daily injection and will attend the CNS clinic every 3–6 months. The follow-up appointments include an assessment of disease activity, monitoring the effects of therapy by blood tests, questioning and examination, discussing medication up-titration if needed and provision of ongoing patient education and support.

Box 1. Sources of further information on CAPS and treatments available

- <http://www.ucl.ac.uk/amyloidosis/nac/fever-syndromes>
- <http://www.periodicfevers.com>
- <http://www.nomidalliance.net>

Patient-reported disease activity is assessed using a scoring tool. Patients are asked whether they have experienced any of a list of symptoms since their last clinic visit, and are asked to grade the symptoms from mild, moderate to severe. The symptoms are then given a score out of 20. Symptoms of a mild or moderate nature are each assigned 1 point and severe symptoms are each assigned 2 points. A score greater than 3 out of 20 suggests some degree of CAPS activity. Disease activity scoring is of importance when evaluating response to treatment and making decisions concerning up-titration of the medication. Patients who are on treatment may have persistent or occasional breakthrough symptoms and disease activity is sometimes triggered by factors such as viral infections and stress. Patients are therefore requested to make a note of their symptoms or keep a symptom diary that can be reviewed at appointments. In addition to scoring the patient-reported disease activity, serum CRP and SAA are measured at each visit.

Due to the possibility of central nervous system complications, patients have neurology, ophthalmology and audiology assessments at diagnosis and then annually. A routine brain magnetic resonance imaging (MRI) scan is also performed as a baseline assessment.

The disease may have a significant impact on the physical, social and psychological health and quality of life of sufferers. It is often the case that people with CAPS have not been able to complete their education, have had difficulty in gaining and maintaining employment and partaking in normal social activities, due to the debilitating symptoms and/or the social stigma of the disease. Providing psychosocial support is therefore important and is assessed on an individual basis. Measuring patient's health-related quality of life using the Medical Outcomes 36-item Short Form Health Survey (SF-36) is a reliable and validated means of monitoring disease and success of therapy (Maruish, 2011). Patients are asked to complete the survey at diagnosis, 3 months post treatment, 6 months post treatment and annually thereafter.

Although ongoing support and information is provided to patients at the National Amyloidosis Centre, their relatives and healthcare providers, the websites listed in *Box 1* provide further help and insight on CAPS and the treatments available.

Conclusion

Awareness and understanding of CAPS have significantly increased over the years with safe and effective treatment therapies now available that provide sustained and safe remission of systemic inflammation and CAPS symptoms. Nurses and other health professionals are on the front line of patient care and are well-placed to raise suspicion of CAPS so that a specialist referral can be made to confirm the diagnosis. Recognition of patients with these symptoms, although difficult, is possible

KEY POINTS

- Cryopyrin-associated periodic syndrome is an umbrella term for a group of rare inherited life-long autoinflammatory diseases
- Symptoms include fever, urticarial rash, arthralgia, fatigue, headaches and conjunctivitis
- Interleukin 1 (IL-1) blockers canakinumab, anakinra and riloncept are effective treatments licensed for CAPS
- Early diagnosis and treatment leads to complete remission of the disabling systemic inflammation and profound improvement in quality of life.

and prompt treatment will avoid the long-term complications associated with this disease. Referring patients to a specialist centre such as the National Amyloidosis Centre facilitates early diagnosis, appropriate management of symptoms, and overall improvement of quality of life. **BJN**

Declaration of interest: none

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CPD reflective questions

- Why is it important to identify patients with a potential CAPS diagnosis early and refer for specialist assessment?
- Reflect on the impact physical and psychosocial issues associated with CAPS have on the patient and their significant others
- What are the key presenting symptoms and which two blood tests would contribute to recognising CAPS?

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