

Patient Information

Cryopyrin Associated Periodic Syndrome (CAPS)

What is CAPS?

Cryopyrin Associated Periodic Syndrome (CAPS) is an extremely rare genetic disease. It affects about 1 out of every 1 million people, and there are currently about 50 patients in England with confirmed CAPS, all of whom have been diagnosed at the National Amyloidosis Centre (the NAC). It is believed that there may be about 20 further cases as yet undiagnosed and that a child is born



A boy with CAPS with urticarial rash and impaired hearing

with CAPS about once every 2 years in England. Patients with this condition experience flu-like symptoms including severe fatigue, fever and muscle pains on a daily basis, often starting in early infancy. There are also several other associated complaints that may affect the skin, eyes, joints and brain. Untreated patients may develop severe long term disabilities such as blindness, deafness and, in about 1 in 4 cases, amyloidosis. A highly effective treatment for CAPS is now available, called canakinumab. When this drug is injected under the skin every 8 weeks, the symptoms of CAPS disappear completely.

How is CAPS diagnosed?

Clinical symptoms and findings may lead doctors to suspect CAPS. The diagnosis is confirmed if genetic testing shows a mutation in a gene known as NLRP3 or CIAS1.

CAPS is NOT amyloidosis



If you have been referred to us because of suspicion that you or your child may have a fever syndrome such as CAPS, this does NOT mean that you or your child have amyloidosis.

Very understandably, some patients and family members may become concerned when they are referred to us, for the following reasons:

1. We are based at the National Amyloidosis Centre (NAC), at the Royal Free Hospital.
2. Our consultants are specialists in amyloidosis as well as fever syndromes.

It is true that a few patients with longstanding, untreated periodic fever syndromes may eventually, after many years, develop amyloidosis.

However for the vast majority of our patients:

1. Referral to us is for the purposes of diagnosis and treatment of a fever syndrome.
2. Amyloidosis is not suspected at any time in the course of their illness.
3. Amyloidosis can be easily prevented by appropriate treatment.

What causes CAPS?

CAPS belongs to a category of diseases known as the “inherited periodic fever syndromes”. These syndromes are all believed to be caused by overactivity of part of the body’s natural defence system, the immune system. The immune system involves different types of blood cells and molecular messengers. These components interact together through a variety of complex mechanisms, known as pathways. The part of the immune system affected in inherited periodic fever syndromes is called innate immunity.

In healthy people, normal activation of the innate immune pathways occurs when the body encounters some type of tissue damage or disease. The consequent inflammation helps to fight disease and promote recovery.

In inherited periodic fever syndromes, such as CAPS, some of these pathways are overactive. This leads to an overly aggressive immune response. The body acts as if there was a serious infection even when there is no actual disease or tissue damage acting as a stimulus. There is a state of prolonged inflammation, known as auto-inflammation. Auto-inflammation itself leads to symptoms of disease and sometimes to tissue damage.

Different pathways are implicated in different types of inherited periodic fever syndromes. CAPS is caused by mutations in the gene for a newly discovered protein called cryopyrin. This leads to excessive production of an inflammatory messenger called interleukin 1 β (IL-1 β). IL-1 β is also responsible for many of the symptoms healthy people experience when they have flu.

Auto-inflammation is different from auto-immunity. Auto-immune diseases (such as childhood diabetes and rheumatoid arthritis) are caused by abnormal functioning of a different part of the immune system, so that the body produces antibodies against itself, causing tissue damage. They are far commoner than auto-inflammatory syndromes. In auto-inflammatory conditions the body does not produce antibodies against its own tissues.

How is CAPS treated?

Injected drugs called monoclonal antibodies which block IL-1 β are effective at treating CAPS. Canakinumab is the only one of these drugs licensed to treat CAPS.

When administered by injection under the skin every 8 weeks it leads to complete resolution of the symptoms and signs of CAPS. Since they began receiving this treatment, our patients with CAPS have experienced a remarkable turnaround in their lives. Canakinumab blocks the activity of IL-1 β and thereby simply “switches off” the excessive inflammation that is the hallmark of CAPS. Canakinumab has only become standard treatment for CAPS relatively recently, so we do not yet have information regarding the long term. But we hope that prolonged treatment with canakinumab will completely prevent the long term deformities and complications that were previously seen in patients with CAPS.

What are the different types of CAPS?



CAPS includes three diseases that were previously thought to be different syndromes:

1. Muckle Wells syndrome (**MWS**)
2. familial cold urticaria (**FCU**)
3. chronic infantile neurological cutaneous and articular syndrome (**CINCA**) (also known in USA as neonatal onset multisystem inflammatory disease, **NOMID**)

These three diseases are part of a single spectrum:

- **FCU** is the mildest and causes attacks of itchy rash, red eyes and fever within hours of exposure to cold. Most affected patients come from North America.
- **MWS** is the type most often seen in the UK. It causes daily episodes of generalised ‘nettle’ rash, red eyes and fever. These symptoms usually appear soon after birth and are worst in the evenings. About a quarter of patients will become deaf later in childhood.
- **CINCA (NOMID)** is the most severe and causes chronic inflammation of the lining of the brain resulting in loss of hearing, poor vision and learning difficulties. Children with CINCA can also have problems with their bone growth, and also have the rash and fever seen in the other two conditions.



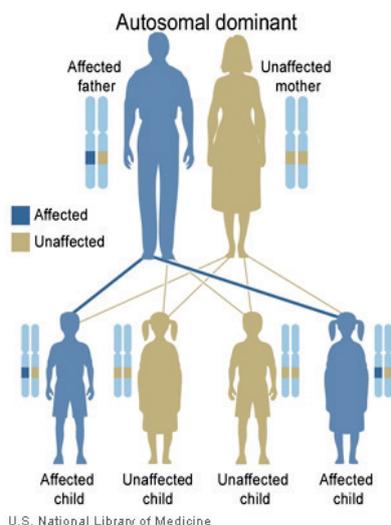
Typical CAPS rash in a patient before canakinumab treatment



The same patient's skin, after canakinumab treatment led to disappearance of the rash

How is CAPS inherited?

Inheritance of MWS and FCU is called “autosomal dominant”. This means that the presence of just one copy of a mutated gene can cause the disease. The principles of autosomal dominant inheritance are illustrated below. In the figure, the father has one copy of a mutated gene, and one copy of a normal gene. He therefore suffers from the disease. The mother, like the vast majority of the population, has two normal genes and is healthy. Each child gets one copy of each gene from their mother, and 1 from their father.



As the figure shows, when there is simple autosomal dominant inheritance of a condition:

- Each child has a 50% (1 in 2) chance of inheriting a mutated copy of the gene from the affected parent.
- Each child has a 50% (1 in 2) chance of inheriting a normal copy of the gene from the affected parent.
- Half of the children have a mutated gene and develop the disease. They can then pass the mutated gene and the disease on to half of their children.
- Half of the children have 2 copies of the normal gene. They are healthy and they cannot pass the disease on to their children.
- Brothers and sisters of people with the disease have a 50% (1 in 2) chance of having the mutated gene and developing disease.
- Men and women have equal chances of inheriting the mutated gene and of developing the disease.

Sometimes patients with CAPS have no known family history of disease. This may be because:

- A few people who have inherited a mutated gene never actually develop disease. The reason for this is not known.
- A parent may have suffered from mild disease and may not have sought medical attention.
- The mutation may have arisen in the patient themselves for the first time.

Although CINCA is due to mutations in the same gene, these mutations usually develop for the first time in the affected individual and so other family members are usually not affected. The principles behind inheritance of genetic diseases are explained in more detail in the appendix at the end of this factsheet.

The CAPS National Treatment Service

The physicians at the National Amyloidosis Centre in the Royal Free Hospital, London, have been managing patients with CAPS for over 14 years. During this time we have progressed from recognition that this syndrome exists to development of canakinumab as a profoundly effective treatment. The sequence of events that took place over this time is detailed at the end of this information sheet.

We are the only UK centre specialising in diagnosis and treatment of patients with CAPS. Our expertise in diagnosis, genetic analysis and clinical management of this extremely rare disorder is recognised internationally. We are now able to offer our patients highly effective treatment for this debilitating disorder. We have therefore been commissioned by the NHS National Commissioning Group since 2010 to provide the CAPS Treatment Service for the entire UK.



Logistics

Patients with CAPS need long-term surveillance, with canakinumab administration and specialist follow up every 8 weeks. Our consultants provide on-going direct management at the Royal Free Hospital for adults and at Great Ormond Street Hospital for Children. When patients live far away, it may be possible to arrange for some treatments to be administered at their local hospitals or at other regional centres.

In these cases, we can help by providing:

- regular advice to patients and doctors involved in their treatment
- regular reviews at the Royal Free Hospital or Great Ormond Street Hospital for Children
- arrangements for hotel accommodation during visits

Children

Our consultants share a specialist paediatric fever clinic with Dr Paul Brogan and Professor Nigel Klein at the Great Ormond Street Hospital for Children. The atmosphere and environment there is child-friendly, with fun activities to occupy children while waiting for their appointment. The specialist paediatric nurses are expert at taking blood from children and putting them at ease. Therefore, most children and parents prefer to attend this clinic.



Occasionally we see children at the Royal Free Hospital if this location is more convenient, especially in the case of older children coming for repeat visits. This option should be discussed with our consultants before making the appointment.

Children with CAPS under age 4

There are no licensed drugs for children under age 4 with CAPS at present, although there is an on-going trial of canakinumab. Children in this age group may be prescribed off label canakinumab or anakinra, another drug of the same class.

Overseas and non-NHS entitled patients

The Royal Free Hospital welcomes overseas patients. European Union residents may be entitled to an NHS assessment in the UK under EU reciprocal arrangements for medical care that is not available locally (EU 112 form). Non-NHS entitled patients are welcome but are usually liable to charges.

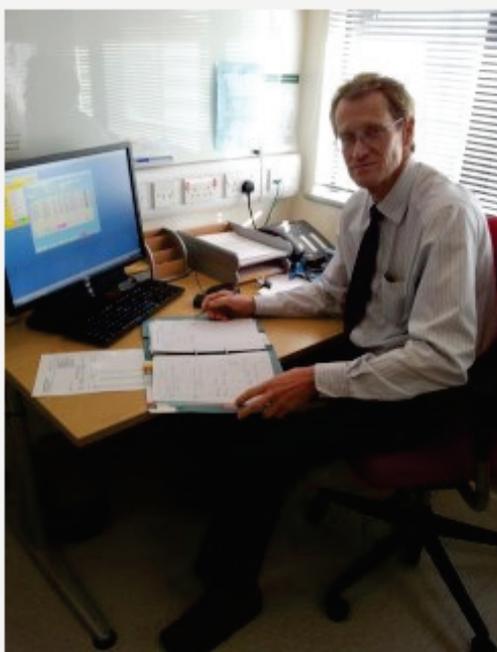
Inherited Periodic Fever Service

The Inherited Periodic Fever Service is the only centre in the UK dedicated to the needs of patients with inherited fever syndromes. We are based at the National Amyloidosis Centre. We have “state-of-the-art” clinical and research facilities and a team of highly qualified clinical, research and support staff. We are funded by the Department of Health to provide a diagnostic and management advice service for the UK’s national caseload of patients with inherited periodic fevers and related disorders. The clinical service includes:

- Detailed clinical assessment
- Genetic testing and counselling
- Recommendations for treatment and monitoring response
- Measurement and monitoring of specialised biochemical (blood) tests for C-reactive protein (CRP) and serum amyloid A protein (SAA)
- 3-12 monthly follow-up to assess response and further treatment requirements
- Providing information and support to fever patients, their families and health providers
- Systematic evaluation of existing and new treatments



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Professor Philip Hawkins



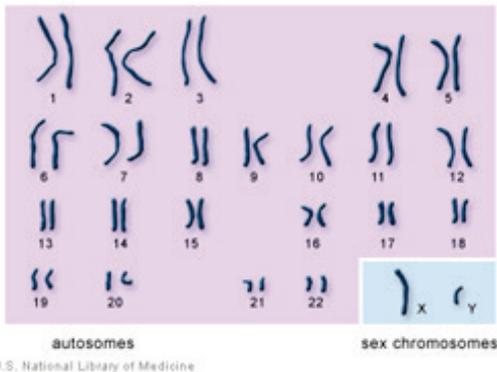
Dr Helen Lachmann

Appendix

Basic genetics - understanding inheritance

The human body is made up of millions of tiny cells, each of which contains identical copies of the genes which we inherit from our parents. These genes function like an instruction manual, or a recipe book for the cells to construct the proteins which make up the body.

Human cells each contain about 25,000 different genes. Each cell contains two copies of each gene, one from each of our parents. Within each cell, the genes are arranged into 46 long strings, called chromosomes. 23 chromosomes come from the father and 23 from the mother. Complicated interactions between the two copies of each gene determine how the body is composed, inside and out. External traits, like hair colour, eye colour and height and internal traits like blood group are all a consequence of which genes we inherit from our parents.



How do mutations cause CAPS?

The genes act like an instruction manual or a recipe for protein production inside every cell of the body.

Sometimes an alteration or error may arise within a gene. This is called a mutation.

Anyone who has ever baked a cake knows that a single error in the recipe may have a number of different effects on the final product. It may lead to complete disaster (if you put in salt instead of sugar, or forgot the baking powder). Alternatively, there may be little effect on the final product (if you used margarine instead of butter).



Similarly, a mutation in a gene may have a number of different effects. Some mutations have minimal effects or no effects either on the proteins produced or on the person's health. Other mutations may lead to abnormal ("variant") protein production, causing a wide variety of diseases.

CAPS is caused by mutations in a gene known as NLRP3 or CIAS1. This gene is responsible for the production of a protein known as NALP3 or cryopyrin. Cryopyrin is involved in controlling inflammation. The gene mutations that cause CAPS lead to faulty regulation of inflammation. There is an over aggressive immune response, whereby the immune system behaves as if there was a constant serious infection. There is excessive production of an inflammatory messenger called interleukin 1 β (IL-1 β). IL-1 β is also responsible for many of the symptoms healthy people experience when they have flu.



Brief history of CAPS and the National Amyloidosis Centre

1998: We began to recognise CAPS as a distinct clinical syndrome.

2000: We performed a genome wide genetic linkage study.

2001: We discovered the abnormal gene that causes CAPS.

2002: We undertook seminal scientific studies that implicated excessive IL-1 production as the cause of the disease.

2002: We treated the first patients in the world with an IL-1 inhibitor. This completely “switched off” the disease.

2003: We began collaboration with the Novartis pharmaceutical company to investigate their completely novel super-potent IL-1 blocking drug (canakinumab).

2003: We performed the first into man treatment of CAPS with canakinumab. Further studies demonstrated virtually 100% efficacy of canakinumab in CAPS.

2010: The NAC was commissioned by the NHS National Commissioning Group to provide the CAPS Treatment Service for the entire UK.

The physicians at the National Amyloidosis Centre have been working closely with patients with CAPS from all around the UK throughout this period, offering general help and support and conducting clinical research. The physician-patient relationships that have developed are rather unique, and many of the patients who are now benefiting from canakinumab treatment can claim much credit in its development. These patients universally describe the extraordinary efficacy of this drug, and the remarkable manner in which the treatment has turned their lives around.

Services offered by our team

If patients are referred to us because of suspected CAPS, we offer:

- expert clinical assessment
- genetic testing to confirm or rule out CAPS, or other hereditary fever syndromes if relevant

After diagnosis of CAPS, we offer the following services:

- expert clinical evaluation of disease
- assessment of suitability for canakinumab therapy (in almost all patients aged over 4 years, this treatment is deemed suitable)

Baseline assessment before starting canakinumab includes:

- audiometric hearing test
- ophthalmic assessment by ophthalmologist
- brain MRI and neurological assessment if there is neurological disease
- quality of life assessment
- entry of details into CAPS registry
- SAP scan in selected individuals

Subsequent treatment involves:

- visits to the Royal free CAPS clinic every 8 weeks for:
 - administration of canakinumab by injection under the skin
 - blood tests
 - quality of life assessment
- monthly measurements of serum amyloid A (SAA) protein in blood samples. We provide blood tubes and the blood can be drawn at the patient’s local clinic and sent to the Royal Free by post (SAA is the most sensitive marker of disease activity in CAPS, and a predictor of the development of amyloidosis)
- annual assessment:
 - audiometry
 - ophthalmic assessment
 - follow up brain MRI in selected cases
- long term surveillance and follow up at the NAC

It may become possible to reduce frequency of visits to the NAC to four monthly. This depends on the availability of adequate local arrangements to formulate and deliver canakinumab and to perform the necessary monitoring.

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