What is TRAPS?

TRAPS is the second commonest of the inherited fever syndromes. It was originally thought to be commonest in North Western Europe, and was first called familial Hibernian fever, reflecting the Irish/Scottish ancestry of patients in early reports. We now know that it can affect people from all around the world. TRAPS is equally common in men and in women.

What are the inherited periodic fever syndromes?

These are a group of disorders in which patients experience recurrent fevers and other symptoms, although there are no signs of infection or of any other apparent cause. 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 a wide variety of 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 the inherited periodic fever syndromes, 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. Treatment aims to “switch off” the overactive inflammatory pathway and depends on precise identification of the particular syndrome, and pathway affected.

Auto-inflammation is quite different to auto-immunity. In auto-immune diseases, the body produces antibodies against its own tissues, which then cause damage. In auto-inflammatory conditions the body does not produce antibodies against its own tissues. Auto-immune diseases are far commoner than auto-inflammatory syndromes. Auto-immune diseases include conditions such as childhood diabetes and rheumatoid arthritis.

**What causes TRAPS?**

TRAPS, like most other inherited periodic fever syndromes, is a genetic disease. TRAPS is caused by mutations in a gene called TNFRSF1A, which lead to production by white blood cells of an abnormal form of their cell surface protein which responds to a powerful inflammatory signal called tumour necrosis factor. This causes overactive inflammation.

**How is TRAPS inherited?**

Inheritance of TRAPS 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 one from their father.

As the figure above 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 two 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 disease.

About half of all patients with TRAPS have no known family history of disease. This may be because:

- A parent may have the mutation but may never actually develop disease. This is called “incomplete penetrance”. 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.
See the appendix at the end of this factsheet for a more detailed explanation of basic principles of genetics and inheritance.

**What are the symptoms of TRAPS?**

The symptoms in TRAPS can be very variable and may be hard to distinguish from the symptoms of other periodic fever syndromes. Patients with TRAPS experience recurrent or continuous attacks, usually starting in childhood, before age 4. Symptoms during attacks may include:

- fever lasting around 1 to 4 weeks
- abdominal pain
- joint or muscle aches and swelling
- rash

More rarely there may also be:

- headache
- chest pain
- enlarged glands in the neck
- painful, red eyes

There have also been reports of nervous system abnormalities and appearances on imaging studies that are similar to multiple sclerosis.

For 1 in 3 patients, symptoms are nearly continuous.

**How is TRAPS diagnosed?**

The diagnosis of TRAPS, and of other periodic fever syndromes is often delayed because:

- The signs and symptoms are not specific and vary greatly.
- These syndromes are rare.

Some doctors have never heard of these syndromes, and may have seen few if any cases. So it may take time before the possibility is raised that a patient may have a periodic fever syndrome.

The presentation varies tremendously from patient to patient, but certain specialist blood tests can support the possible diagnosis. In these diseases symptoms are always accompanied by blood tests suggesting a lot of inflammation, including:

- high white cell count
- high CRP (C-reactive protein)
- high SAA (serum amyloid A protein)
- high ESR (erythrocyte sedimentation rate)

Ultimately the diagnosis is usually made by a combination of suspicious symptoms and blood tests plus a finding of an abnormal genetic result. For TRAPS this means a mutation in the TNFRSF1A gene. Genetic testing is difficult to do and expensive, so we are one of only a very limited number of laboratories in the world offering the tests.

**How is TRAPS treated?**

Steroid therapy can be beneficial during attacks. Injected drugs which block messenger of inflammation (cytokines) are very effective in more severe disease. These drugs are usually given under the skin or into a vein. The one we use most at present is called anakinra. This drug blocks a molecule called IL-1 which is involved in the overactive auto-inflammatory pathway.

Anakinra has to be given at home every day. Other, similar drugs may be injected every week. In the future we may be able to give drugs only every one or two months.

The side effects of these drugs include:

- stinging
- skin redness at the injection site, in some people
- increased risk of infection

In general the infections reported have been mild but we screen all patients for tuberculosis and ask about a history of other infections before starting such drugs.
Logistics

Patients with TRAPS need long-term surveillance, with regular administration of medications and specialist follow up.

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.

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

Clinical Director/Consultant  Professor Philip Hawkins  +44 (0)20 7433 2815/2816
Reader/Consultant  Dr Helen Lachmann  +44 (0)20 7433 2804
Clinical Research Nurses  Thirusha Lane  +44 (0)20 7433 2759
- Darren Foard  +44 (0)20 7433 2814
- Lisa Rannigan  +44 (0)20 7433 2732
- Rene Williams  +44 (0)20 7433 2797
Clinic Coordinator  Eleanor Pyart  +44 (0)20 7433 2738
Clinic Nurses  Alica Bangova  +44 (0)20 7433 2799
- Annie Hughes  +44 (0)20 7433 2730
Genetic requests and results  Dr Alison Bybee  +44 (0)20 7433 2751
- Rose Coughlan  +44 (0)20 7433 2753
General enquirers  +44 (0)20 7433 2725
Fax  +44 (0)20 7433 2817

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 TRAPS?

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.

TRAPS is caused by mutations in a gene known as TNFRSF1A. This gene is responsible for the production of a protein receptor for an inflammatory messenger called tumour necrosis factor alpha or TNFα. The exact way abnormal TNFα receptors cause spontaneous attacks of inflammation and fever is not fully understood.
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