

Patient Information

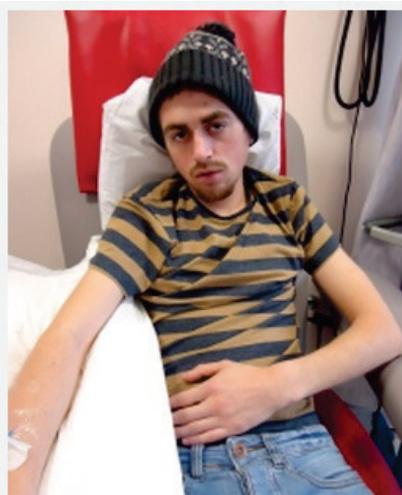
Mevalonate Kinase Deficiency (MKD)

What is MKD?

MKD is an extremely rare inherited condition. It is also known as hyperimmunoglobulin D syndrome and periodic fever syndrome (HIDS). This condition was first described in Dutch children in 1984 and is most common in North West Europe, especially in the Netherlands. It is equally common in boys and in girls.

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



A patient with MKD, during an attack

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.

MKD 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 MKD, 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.

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.

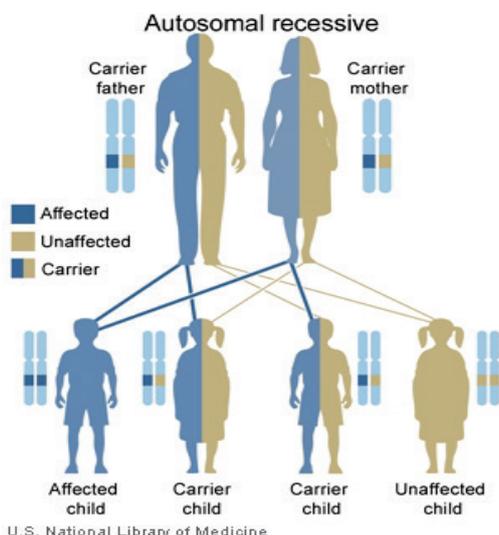
Auto-inflammation is quite different to auto-immunity. In auto-immune diseases, the body produces antibodies against its own tissues, which then cause damage. In auto-inflammatory conditions the body does not produce antibodies against its own tissues. Auto-immune diseases are far commoner than auto-inflammatory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

What causes MKD?

MKD, like most other periodic fever syndromes, is a genetic disease. MKD is caused by mutations in a gene called MVK. This gene is responsible for production of an enzyme called mevalonate kinase.

How is MKD inherited?

Inheritance of MKD is called “autosomal recessive”.



What are the symptoms of MKD?



Children with MKD usually develop recurrent attacks of fever in their first year of life, each typically lasting 3 to 7 days. These are often accompanied by:

- headache
- enlarged lymph nodes (glands) in the neck
- joint pains
- diarrhoea
- vomiting
- rash

Attacks often occur within hours of immunisations or minor infections, trauma, surgery or stress. The disease may get milder in adolescence.

This means that only people with two copies of a mutated gene develop the condition. People with just one mutated copy of the gene are known as “asymptomatic carriers.” This means that they feel well and exhibit no symptoms of disease but they can pass the condition on to their children. Both parents must be asymptomatic carriers in order to have a child affected by this type of disease.

Brothers and sisters of patients with an autosomal recessive condition also have:

- a 50% chance of being asymptomatic carriers
- a 25% chance of getting the disease
- a 25% chance of being healthy non-carriers

In the hereditary fever syndromes, carriers of gene mutations are usually completely well. It is very rare for them to develop the disease and if they do it tends to be milder.

Men and women have equal chances of inheriting the mutated genes, and of developing disease or being carriers.

Autosomal recessive inheritance is illustrated in the figure. The yellow-brown box represents an unaffected gene and the blue box represents an affected gene, carrying a mutation. The two columns next to each person in the figure represent two identical chromosomes (strings of genes) each person inherits, one from each parent.

How is MKD diagnosed?

The diagnosis of MKD, 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 most 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 all the periodic fever syndromes

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)

In addition to these findings, in MKD there are often high levels of antibodies called IgD and IgA.

Ultimately the diagnosis is usually made by a combination of suspicious symptoms and blood tests plus a finding of an abnormal genetic result. For MKD this means a mutation in both copies of the MVK gene.

Genetic testing is difficult to do and expensive so only a very limited number of laboratories in the world (including ours) offer the tests.

How is MKD treated?



Treatment of MKD involves avoiding immunisations as these are well known to precipitate attacks. Drug treatment is difficult although there is now evidence that injected drugs, such as anakinra, that block certain inflammatory proteins (cytokines) may be effective. Anakinra has to be given at home every day. Another drug of this type, etanercept, may also be helpful.

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 MKD 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



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Professor Philip Hawkins



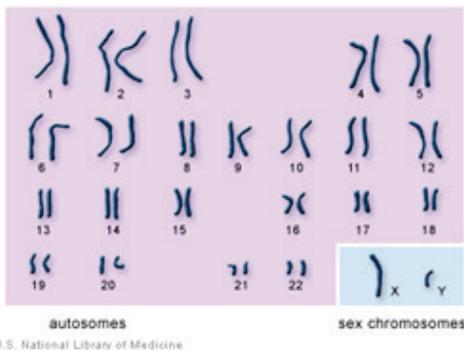
Dr Helen Lachmann

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 MKD?

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.

MKD is caused by mutations in a gene known as MVK. This gene is responsible for the production of an enzyme called mevalonate kinase. The exact way abnormal mevalonate kinase causes spontaneous attacks of inflammation and fever is not fully understood.



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