Familial Mediterranean Fever (FMF)

What causes FMF?

FMF is the most common inherited periodic fever syndrome

FMF is caused by changes (mutations) in a gene called MEFV. These mutations lead to production of an abnormal form of a white blood cell protein called pyrin.

The mechanism whereby these mutations cause FMF is not fully understood. It is believed that the abnormal pyrin may make white blood cells ‘overactive’ so that attacks of inflammation occur spontaneously.

FMF is usually inherited by autosomal recessive inheritance. This means that people with FMF have two abnormal copies of the MEFV gene and both parents are asymptomatic carriers of the condition.

More rarely, FMF may be inherited by autosomal dominant inheritance. This means that one abnormal copy of the gene can cause the disease, and people with FMF may have one affected parent.

Autosomal dominant inheritance of FMF usually occurs only when the M694 mutation is present. For a more detailed explanation of genes, mutations and autosomal recessive and dominant inheritance, see the appendix below.

FMF 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 FMF, 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.
Symptoms of FMF

FMF attacks usually last up to three days. Common symptoms include:

- high fever
- severe stomach pain
- joint pain
- leg swelling
- rash (usually round the ankles)

Less common symptoms include:

- severe chest pain
- testicular pain and swelling in children

These attacks usually start in childhood, but 10% of patients with FMF begin experiencing symptoms only after age 40. Attacks of FMF may occur without apparent cause, or may be precipitated by stress, menstruation or diet.

The pain may be so severe that the first attack is thought to be appendicitis. Between attacks, affected individuals feel entirely well and grow and develop normally.

Some patients experience muscle pain on exertion between attacks, usually affecting the calves.

The frequency of the attacks varies from once every week to several times a year. The symptoms and severity vary between different patients, sometimes even amongst members of the same family.

Blood test results always suggest that there is a lot of inflammation, and include:

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

Doctors in countries where FMF is common may be familiar with this condition and quick to raise the possibility.

However, most doctors in the UK have seen few patients with FMF and it may take some time before the condition is diagnosed. In some parts of the country there are large immigrant communities from countries where FMF is common. Doctors in these areas may become more familiar with FMF.

Sometimes patients know that there is a family history and recognise the symptoms themselves.

Treatment

The treatment for FMF is a drug called colchicine. Colchicine originally came from a flower called the autumn crocus or meadow saffron.

This flower has been known to possess medicinal powers since the time of ancient Greece. Interestingly, it grows mainly in the Mediterranean region, as well as parts of Asia.

Colchicine has been used successfully to treat FMF since 1972. Nowadays colchicine tablets are synthesized in the laboratory rather than being extracted from the flower. It is effective at preventing attacks in the vast majority of patients, so long as sufficient doses are taken. It is taken as tablets once or twice a day.
Colchicine has been very widely used and more than 40 years of experience in FMF has shown it to be very safe at the usual doses of 0.5 to 2 mg per day. It may be safely given to children with FMF even before the age of 1 year. Children taking colchicine grow and develop completely normally. It is also safe during pregnancy.

The main side effect of colchicine is a bowel upset with diarrhoea. This can usually be avoided by increasing the dose slowly. In some people it may be helpful to cut out consumption of milk products for a period of time. Colchicine is dangerous if overdose is taken and it should always be kept out of reach of children. During acute attacks, analgesic (pain killing) drugs may also be helpful.

### Colchicine in pregnancy

FMF is usually diagnosed in childhood or young adulthood.

Many patients are concerned about the effect on childbearing potential both of FMF itself and of FMF treatment.

Some women with FMF enjoy a period free from attacks while pregnant. Others actually experience severe attacks during pregnancy that are worse than their usual attacks. These attacks may endanger the pregnancy itself, by causing miscarriage, if the FMF is not treated.

Colchicine use in pregnancy has been studied extensively in hundreds of women. The results are clear:

- The chances of successful pregnancy outcome are actually **better** in women with FMF who are careful to take their colchicine.
- A comprehensive review of the medical literature on the use of colchicine during pregnancy may be found at http://www.amyloidosis.org.uk. This review is in the fever syndromes section of the website, under “the inherited periodic fever syndromes – information on each syndrome”.

### Who should have genetic testing for FMF?

- Anyone with symptoms and laboratory findings suggestive of FMF should have genetic tests performed, even if they are not from an ethnic background where FMF is common, as FMF can occur in any ethnic group.

- We perform these tests at the Inherited Periodic Fever Service at the National Amyloidosis Centre.

- We are happy to discuss genetic testing with siblings of FMF patients even if they do not report any symptoms.

### FMF and AA amyloidosis

A serious complication of FMF is development of AA amyloidosis, which may lead to kidney failure. As well as preventing FMF attacks, regular colchicine treatment is effective in preventing development of AA amyloidosis in most patients with FMF. Some FMF patients taking colchicine may have on-going auto-inflammation despite experiencing few attacks. SAA is a very sensitive marker of inflammation, so we monitor the SAA levels regularly in all our FMF patients. This is the best way to ensure that they are receiving sufficient doses of colchicine to suppress inflammation and prevent development of AA amyloidosis.

Colchicine is usually effective in treatment of FMF patients who have already developed AA amyloidosis. It can lead to regression of AA amyloid deposits and improved kidney function.
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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Appendix

FMF was first recognised as a distinct condition in 1945. In 1997 it was discovered that mutations in a gene called MEFV cause FMF.

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 FMF?

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.

FMF is caused by mutations in a gene called MEFV, located on chromosome number 16. This gene is responsible for production of a protein called “pyrin”. The mechanism whereby abnormal pyrin causes fever is not fully understood. It is thought that pyrin may make white blood cells ‘overactive’ so that attacks of inflammation occur spontaneously.

FMF is usually inherited by autosomal recessive inheritance.

Autosomal recessive inheritance

Autosomal recessive inheritance is illustrated in the following 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) that each person inherits, one from each parent.

When a condition is autosomal recessive, 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 the disease, but they can pass it 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 inherited periodic 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 receiving the mutated genes, and of developing disease or being carriers.

**Autosomal dominant inheritance**

Rarely, FMF may be inherited by autosomal dominant inheritance (when the M694 mutation is present).

Autosomal dominant inheritance is illustrated in the following 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) that each person inherits, one from each parent.

When a condition is autosomal dominant, the presence of just one copy of a mutated gene can cause the disease.

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. Half the children inherit the mutated gene from the father and suffer from the disease. The other half are healthy.

When there is simple autosomal dominant inheritance of a condition:

- Each child has a 50% (1 in 2) chance of receiving a mutated copy of the gene from the father.
- Each child has a 50% (1 in 2) chance of receiving a normal copy of the gene from the father.
- 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 receiving the mutated gene and of developing disease.

Sometimes patients with a hereditary periodic fever syndrome 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.
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