



Familial Mediterranean Fever

What is it?

Familial Mediterranean fever (FMF) is a genetically disease. Patients will suffer from recurrent bouts of fever, accompanied by abdominal, chest, or joint pain and swelling. The disease generally affects people of Mediterranean and Middle Eastern descent, that is Jews (especially Sephardic), Turks, Arabs and Armenians.

How common is it?

The frequency of the disease in high risk populations is about one to three in 1000. It is rare in other parts of the world. However, since the discovery of the associated gene, it is being diagnosed more frequently, even among populations where it was thought to be very rare, such as Italians, Greek and Americans.

FMF attacks start before 20 year of age in approximately 90% of the patients. In more than half of them the disease appears in the first decade of life. Boys are affected slightly more often than girls (13:10).

What are the causes of the disease?

FMF is a genetic disease. The responsible gene is called the MEFV gene after Mediterranean fever and it affects a protein, which plays a role in the natural resolution of inflammation. If this gene carries a mutation, as in FMF, this regulation cannot be done properly and the patients experience attacks of fever.

Is it inherited?

It is inherited as an autosomal recessive disease (which means that it is not linked to the gender and that neither parent needs to show symptoms of the disease). This type of transmission means that to have FMF one needs two mutated genes, one from the mother and the other from the father. So both parents are carriers (a carrier has only one mutated copy, but not the disease) rather than patients. The disease in the extended family, for example, is usually detected in a sibling, a cousin, an uncle or a far relative. However, as seen in a small proportion of cases, if one parent has FMF and the other is a carrier, there is a 50% chance that their child will get the disease

Why has my child got this disease? Can it be prevented

The child has the disease because of the genes that cause FMF. In approximately one fourth of patients, the parents are of the same family tree (descendants of the same ancestors).

Is it contagious?

No, it is not.

What are the main symptoms?

The main symptoms of the disease are recurrent fever, accompanied by abdominal, chest, or joint pains. Abdominal attacks are the most common, seen in about 90% of patients. Attacks with chest pain occur in 20-40%, and joint pain in 50-60% of the patients.

Usually children complain of a particular attack type, such as recurrent abdominal pain and fever. Yet some patients experience different attack types, one at a time or in combination

These attacks are self-limited (meaning that they resolve without treatment) and last between one and four days. The patients recover fully at the end of an attack and are totally normal in between these bouts. Some of the attacks may be so painful that the patient or family seeks medical help. Severe abdominal attacks may mimic acute appendicitis and therefore some patients may undergo unnecessary abdominal surgery, such as an appendectomy.

However, some attacks, even in the same patient, may be mild enough to be confused with abdominal distress. This is one of the reasons why it is hard to recognize these patients. During abdominal pain, the child is usually constipated, but as the pain gets better, soft stools appear.

The child can have very high fever during one attack and a mild increase in temperatures in another. The chest pain usually only affects one side, but it may be so severe that the patient cannot breathe deeply enough. It resolves within days. Usually, only one joint is affected at a time (monoarthritis). It is commonly an ankle or a knee. It may be so swollen and painful that the child cannot walk. In about a third of these patients there is an erythematous rash over the involved joint. Joint attacks may last somewhat longer than the other forms of attacks.

It can take from four days to two weeks before it resolves completely. In some children, the sole finding of the disease may be recurrent joint pain and swelling, which is misdiagnosed as acute rheumatic fever, or juvenile idiopathic arthritis.

In about in 5-10% of cases joint involvement may become chronic and cause irreversible changes. There is a characteristic rash of FMF called erysipelas-like erythema, usually observed over the lower extremities and joints. Some children may complain of leg pains.

Among the rarer forms of attack are recurrent pericarditis (inflammation of the outer layer of the heart), myositis (muscle inflammation), meningitis (inflammation of the membrane surrounding the brain and spinal cord) and orchitis (testicular inflammation).

Some diseases characterized by blood vessel inflammation (vasculitis) are seen more frequently among children with FMF, such as Henoch-Schönlein's purpura and polyarteritis nodosa.

The most sever complication of FMF in untreated cases is the development of amyloidosis.

Amyloid is a special protein that deposits in certain organs, like the kidneys, gut, skin and heart and causes gradual loss of function, especially of the kidneys. It is not specific for FMF and it may complicate other chronic, inflammatory diseases that are not properly treated, but finding amyloid in the gut or kidney maybe a clue to diagnosis.

Children who are receiving a proper dose of colchicines (see drug therapy) are safe from the risk of developing this life-threatening complication.

Is the disease the same in every child?

It is not the same in every child. Moreover, the type, duration and severity of attacks may be different each time, even in the same child.

Is the disease in children different from the disease in adults?

In general FMF in children resembles that seen in adults. However some features of the disease like arthritis (joint inflammation) and myositis are more common in childhood and their frequency decrease as the patient gets older. Orchitis is detected more often in young boys than adult males. The age of onset of FMF is also important. The risk of amyloidosis is higher among untreated patients with early disease onset.

How is it diagnosed?

There is no specific tool for the diagnosis of FMF. Generally the following approach is followed:

a) Clinical suspicion: It is possible to consider FMF only after the child experience a minimum of three attacks. A detailed history of the ethnic background should be considered, as well as relatives with similar complaints, or renal insufficiency.

Also, the parents should be asked to give a detailed description of previous attacks.

b) Follow-up: A child with suspected of having FMF should be followed closely before a definite diagnosis is made. During this follow-up period, if possible, the patient should be seen during an attack for a thorough physical examination and for blood tests to look for the presence of inflammation.

Generally, these tests become positive during an attack and go back to normal, or near normal, after the attack subsides. There are classification criteria designed to help in recognizing FMF, which can be used at this stage of diagnosis.

It is not always possible to see a child during an attack for various reasons. Then the parents are kindly asked to keep a diary and describe what happens. They can also use a local laboratory for blood tests.

c) Response to colchicine treatment: Children with clinical and laboratory findings, which make the diagnosis of FMF highly probable, are given colchicine for approximately six months to evaluate the symptoms. If the patient has FMF, either there will be no attacks, or the number, severity and duration of attacks will be significantly less than expected.

Only after the above steps are completed can the patient be diagnosed as having FMF and prescribed life-long colchicine.

As FMF affects a number of different systems in the body, various specialists are involved in the diagnosis and management of FMF. These are in general pediatricians, pediatric or adult rheumatologists, nephrologists (kidney specialist) and gastroenterologists (digestive system).

d) Genetic analysis: For the last couple of years, it has been possible to perform a genetic analysis of patients to ascertain the presence of mutations that are thought to be responsible for the development of FMF

The clinical diagnosis of FMF is confirmed if the patient carries 2 mutations; one from each parent. However, the mutations that have been described, so far, are found in about 70-80% of patients with FMF. That means there are FMF patients with no mutations, therefore, the diagnosis of FMF still depends on clinical judgement. Genetic analysis may not be available in every treatment center.

Fever and abdominal pain are very common complaints in childhood. Therefore, it is not easy to diagnose FMF, even in high-risk populations. It takes a couple of years before it can be recognized. This delay in diagnosis is very important, because of the increased risk of amyloidosis in untreated patients.

There are a number of other diseases with recurrent bouts of fever, abdominal and joint pain. The Majority of these diseases are also genetic and share some common clinical features, however, each has its own distinguishing clinical and laboratory characteristics.

What is the importance of tests?

a) Blood tests: The laboratory tests, as mentioned before, are important in diagnosing FMF. Tests like erythrocyte sedimentation rate (ESR), CRP, whole blood count and fibrinogen are ordered during an attack to see the extent of inflammation.

These are repeated after the child becomes symptom-free, to observe if the results are back to normal, or near normal. In about a third of patients, the tests go back to normal levels. In the remaining two thirds, the levels decrease significantly, but remains over the upper limit of normal.

A small amount of blood is also needed for the genetic analysis. The children, who are on life-long colchicine treatment, have to give some blood and urine twice a year for observational purposes.

b) Urine test: A sample of urine is also tested for the presence of protein and red blood cells. There may be temporary changes during attacks. Patients with amyloidosis will have persistent levels of protein in urine tests. This warns the physician to do more tests to see if this is secondary to amyloidosis.

c) Rectal or renal biopsy: Rectal biopsy is when a very small piece of tissue is removed from the rectum and it is very easy to perform. If the rectal biopsy fails to show amyloid, a renal biopsy is necessary to confirm the diagnosis. For the renal biopsy the child has to spend a night at the hospital. The tissues obtained from the biopsy are stained and then examined for deposits of amyloid.

Can it be treated or cured?

It cannot be cured, but it can be treated with life-long use of colchicine. In this way, recurrent attacks and amyloidosis can be prevented. If the patient stops taking the drug, the attacks and the risk of amyloidosis come back.

What are the treatments?

The treatment for FMF is simple, cheap and without any major drug side-effects. Today Colchicine is the only drug that is used in the treatment of FMF. After the diagnosis is made, the child has to take the drug for the rest of his life. If taken properly, the attacks disappear in about 60% of patients, a partial response is obtained in 30%, but it is found to be ineffective in 5-10% of patients.

This treatment not only controls the attacks, but also eliminates the risk of amyloidosis. Therefore, it is crucial for the doctors to explain to parents and the patient over and over again how vital it is to take this drug in the dose prescribed. Compliance is very important. If this is established, then the child can live a normal life with a normal life-expectancy. The dose should not be modified by the parents without consulting the physician.

The dose of colchicines should not be increased during an already active attack, as such an increase is ineffective. The important thing is to prevent attacks from coming.

What are the side effects of drug therapy?

It is not easy for parents to accept that their child has to take these pills forever. They are usually worried about the potential side effects of colchicine. It is a safe drug with minor side effects which usually respond to dose reduction. The most frequent side effect is diarrhea.

Some children cannot tolerate the given dose because of frequent watery stools. In these cases, the dose should be reduced till it is tolerated and then slowly with small increments it should be increased back to the appropriate dose.

Other side effects are nausea, vomiting, and abdominal cramps. In rare cases, it may cause muscle weakness. The number of peripheral blood cells (white and red blood cells and platelets) may decrease occasionally, but recover with dose reduction.

A decrease in the number of sperms is very rare in treatment doses. Female patients do not have to stop taking colchine during pregnancy or breast-feeding.

How long should treatment last for?

It is a life-long preventive treatment.

What about unconventional or complementary therapies?

There is no such therapy.

What kind of periodic check-ups are necessary?

Children being treated should have blood and urine tests for at least twice yearly.

How long will the disease last for?

It is a life-long disease.

What is the long term prognosis (predicted outcome and course) of the disease?

If treated properly with life-long colchicines, children with FMF live a normal life. If there is a delay in diagnosis, or lack of compliance with treatment, the risk of developing amyloidosis increases, which is related to a poor prognosis. The children who develop amyloidosis, may need a kidney transplant.

Growth retardation is not a major problem in FMF. In some children, growth development at the time of puberty is recovered only after colchicine treatment.

Is it possible to recover completely?

No, because it is a genetic disease. However, life-long therapy with colchicine gives the patient the opportunity to live a normal life, without restrictions and with no risk of developing amyloidosis.

Everyday life

How could the disease affect the child and family's daily life?

The child and the family experience major problems before the disease is diagnosed. They have to take the child to a hospital frequently because of severe abdominal, chest or joint pain. Some

children undergo unnecessary surgery due to misdiagnosis. After the diagnosis is made, both the child and the parents lead an almost normal life. Some even forget that the child has FMF. This may be dangerous, because it can foster complacency with regard to taking the colchicine. The only problem may be the psychological burden of life-long treatment. This can be overcome with patient-parent education programs.

What about school?

Frequent attacks cause problems with school attendance. After the colchicine treatment is initiated, this is no longer a problem.

The teachers should be informed about the disease and what to do in case an attack starts at school.

What about sports?

The patients with FMF who are receiving life-long colchicine, can do any sport they wish. The only problem can be protracted joint inflammation, which may cause limitation of motion at affected joints.

What about diet?

There is no specific diet.

Can climate influence the course of the disease?

No, it cannot.

Can the child be vaccinated?

Yes, the child can be vaccinated.

What about sexual life, pregnancy, birth control?

Patients with FMF do have fertility problems before colchicine treatment, but after colchicine has been prescribed, this problem disappears. The drug must be taken during pregnancy.