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Familial Mediterranean Fever

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1. WHAT IS FMF

1.1 What is it?

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

1.2 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 ethnic groups. 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 years of age in approximately 90% of patients. In more than half of patients, the disease appears in the first decade of life.

1.3 What are the causes of the disease?

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

1.4 Is it inherited?

It is mostly inherited as an autosomal recessive disease, which means that parents usually do not show symptoms of the disease. This type of transmission means that to have FMF, both copies of the MEFV gene in an individual (one from the mother and the other from the father) are mutated; hence, both parents are carriers (a carrier has only one mutated copy but not the disease). If the disease is present in the extended family, it is likely to be in a sibling, a cousin, an uncle or a distant 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. In a minority of patients, one or even both copies of the gene appear to be normal.

1.5 Why does my child have this disease? Can it be prevented?

Your child has the disease because he/she carries the mutated genes that cause FMF.

1.6 Is it infectious?

No, it is not.

1.7 What are the main symptoms?

The main symptoms of the disease are recurrent fever accompanied by abdominal, chest or joint pain. Abdominal attacks are the most common, seen in about 90% of patients. Attacks with chest pain occur in 20-40% and joint pain occurs in 50-60% of 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. Patients recover fully at the end of an attack and feel well 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 FMF patients. During abdominal pain, the child is usually constipated but as the pain gets better, softer stools appear. The child can have very high fever during one attack and a mild increase in temperature in another. The chest pain usually only affects one side, and 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 one-third of patients, there is a red skin rash over the involved joint. Joint attacks may last somewhat longer than the other forms of attacks and it can take from four days to two weeks before the pain 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 5-10% of cases, joint involvement becomes chronic and may cause damage to the joint.
In some cases, there is a characteristic rash (skin eruption) of FMF called erysipelas-like erythema, usually observed over the lower extremities and joints. Some children may complain of leg pains.
Rarer forms of attack present with 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 periorchitis (inflammation surrounding the testicle).

1.8 What are the possible complications?

Some other diseases that are characterised by blood vessel inflammation (vasculitis) are seen more frequently among children with FMF, such as Henoch-Schönlein’s purpura and polyarteritis nodosa. The most severe complication of FMF in untreated cases is the development of amyloidosis. Amyloid is a special protein that deposits in certain organs, such as 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. Proteins in the urine may be a clue to the diagnosis. Finding amyloid in the gut or kidney will confirm the diagnosis. Children who are receiving a proper dose of colchicine (see drug therapy) are

safe from the risk of developing this life-threatening complication.

1.9 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.

1.10 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, such arthritis (joint inflammation) and myositis, are more common in childhood. The frequency of attacks usually decreases as the patient gets older. Periorchitis is detected more often in young boys than adult males. The risk of amyloidosis is higher among untreated patients with early disease onset.

2. DIAGNOSIS AND TREATMENT

2.1 How is it diagnosed?

Generally the following approach is followed:

Clinical suspicion: It is possible to consider FMF only after the child experiences 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. The parents should be asked to give a detailed description of previous attacks.

Follow-up: A child with suspected FMF should be monitored 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 assess the presence of inflammation. Generally, these tests become positive during an attack and return to normal or near normal after the attack subsides. Classification criteria have been designed to help recognize FMF. It is not always possible to see a child during an attack for various reasons. Therefore, the parents are asked to keep a diary and describe what happens. They can also use a local laboratory for blood tests.

Response to colchicine treatment: Children with clinical and laboratory findings that make the diagnosis of FMF highly probable are given colchicine for approximately six months and the symptoms are then re-evaluated. In case of FMF, attacks either stop completely or decrease in number, severity and duration. 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 might be involved in the diagnosis and management of FMF. These include general paediatricians, paediatric or general rheumatologists, nephrologists (kidney specialists) and gastroenterologists (digestive system).

Genetic analysis: Recently, it has been possible to perform 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 to date are found in about 70-80% of patients with FMF. That means there are FMF patients with one or even no mutation; therefore, the diagnosis of FMF still depends on clinical judgement. Genetic analysis may not be available in every treatment centre. Fever and abdominal pain are very common complaints in childhood. Therefore, it is sometimes not easy to diagnose FMF, even in high-risk populations. It might take a couple of years before it can be recognized. This delay in diagnosis should be minimized 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. Some of these diseases are also genetic and share some common clinical features; however, each has its own distinguishing clinical and laboratory characteristics.

2.2 What is the importance of tests?

The laboratory tests are important in diagnosing FMF. Tests such as erythrocyte sedimentation rate (ESR), CRP, whole blood count and fibrinogen are important during an attack (at least 24-48 hours after the start of the attack) to assess the extent of inflammation. These tests are repeated after the child becomes symptom-free to observe if the results are back to or near normal. In about one-third of patients, the tests return to normal levels. In the remaining two-thirds, the levels decrease significantly but remain above the upper limit of normal. A small amount of blood is also required for the genetic analysis. Children

who are on life-long colchicine treatment must provide blood and urine samples twice a year for observational purposes. A sample of urine is also tested for the presence of protein and red blood cells. There may be temporary changes during attacks but persistent elevated protein levels in urine may suggest amyloidosis. The physician may then perform a rectal or kidney biopsy. Rectal biopsy involves the removal of a very small piece of tissue from the rectum; it is very easy to perform. If the rectal biopsy fails to show amyloid, a kidney biopsy is necessary to confirm the diagnosis. For a kidney biopsy, the child must spend a night at the hospital. The tissues obtained from the biopsy are stained and then examined for deposits of amyloid.

2.3 Can it be treated or cured?

FMF cannot be cured but it can be treated with life-long use of colchicine. In this way, recurrent attacks can be prevented or decreased and amyloidosis can be prevented. If the patient stops taking the drug, the attacks and the risk of amyloidosis will recur.

2.4 What are the treatments?

The treatment for FMF is simple, inexpensive and does not involve any major drug side effects, as long as it is taken in the right dose. Today, a natural product, colchicine, is the drug of choice in prophylactic treatment of FMF. After the diagnosis is made, the child must take the drug for the rest of his/her 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 repeatedly explain to parents and the patient how vital it is to take this drug in the dose prescribed. Compliance is very important. If this is established, the child can live a normal life with a normal life expectancy. Parents should not modify the dose without consulting the physician. The dose of colchicine should not be increased during an already active attack as such an increase is ineffective. The important thing is to prevent attacks. Biologic agents are used in patients resistant to colchicine.

2.5 What are the side effects of drug therapy?

It is not easy to accept that a child must take pills forever. Parents are often worried about the potential side effects of colchicine. It is a safe drug with minor side effects that usually respond to dose reduction. The most frequent side effect is diarrhoea. Some children cannot tolerate the given dose because of frequent watery stools. In such cases, the

dose should be reduced until it is tolerated and then slowly, with small increments, increased back to the appropriate dose. The lactose in the diet could also be reduced for about 3 weeks and the gastrointestinal symptoms often disappear. Other side effects include 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.

2.6 How long should treatment last?

FMF requires life-long preventive treatment.

2.7 What about unconventional or complementary therapies?

No complementary therapy is known for FMF.

2.8 What kind of periodic check-ups are necessary?

Children being treated should have blood and urine tests at least twice a year.

2.9 How long will the disease last?

FMF is a life-long disease.

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

If treated properly with life-long colchicine, 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 results in a poor prognosis. Children who develop amyloidosis may require a kidney transplant. Growth retardation is not a major problem in FMF.

2.11 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.

3. EVERYDAY LIFE

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

The child and the family experience major distress already before the disease is diagnosed. The child needs frequent consultations because of severe abdominal, chest or joint pain. Some children undergo unnecessary surgery due to misdiagnosis. After the diagnosis is made, the goal of the medical treatment should be to obtain, for both the child and the parents, an almost normal life. FMF patients need long-term regular medical treatment and compliance with colchicine may be low; this may put the patient at risk of developing amyloidosis. A significant

problem is the psychological burden of life-long treatment. Psychosocial support and patient and parent education programs may be of great help.

3.2 What about school?

Frequent attacks cause major problems with school attendance and colchicine treatment will improve this problem. Information about the disease at school may be useful, in particular to provide advice on what to do in the event of an attack.

3.3 What about sports?

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

3.4 What about diet?

There is no specific diet.

3.5 Can climate influence the course of the disease?

No, it cannot.

3.6 Can the child be vaccinated?

Yes, the child can be vaccinated.

3.7 What about sexual life, pregnancy, birth control?

Patients with FMF might have fertility problems before colchicine treatment but once colchicine has been prescribed, this problem disappears. A decrease in the number of sperm is very rare at treatment doses. Female patients do not have to stop taking colchicine during pregnancy or breast-feeding.