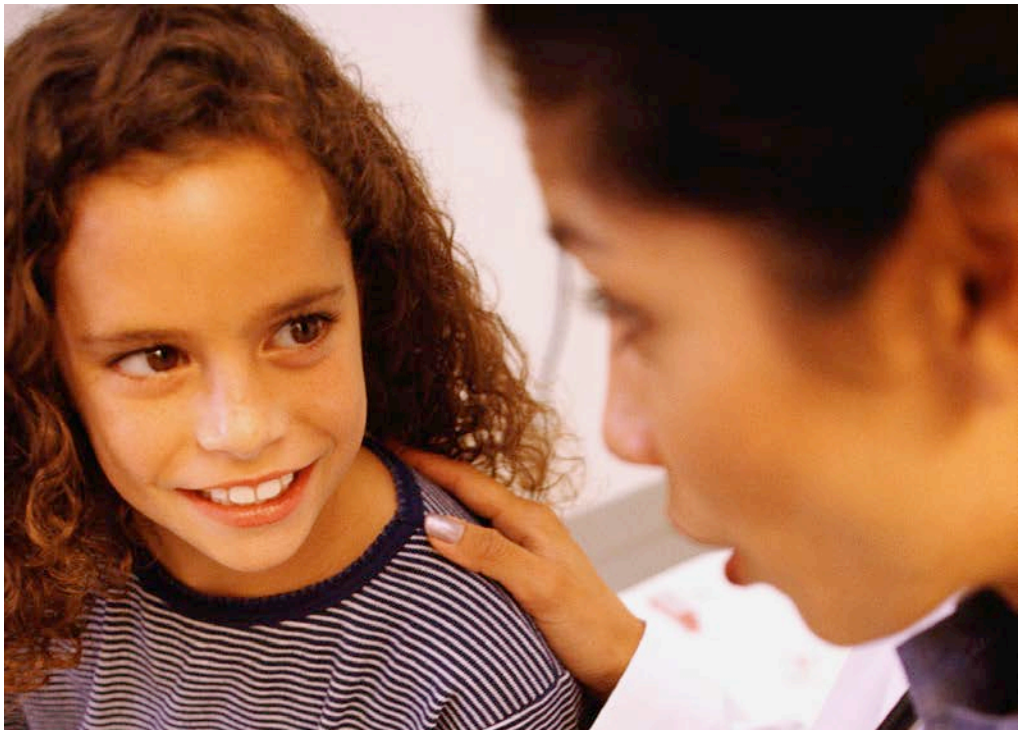

Familial Mediterranean Fever

FMF most often occurs in individuals of Mediterranean and Middle Eastern descent, and the first episodes typically begin in childhood

Fast Facts

- FMF causes episodic fevers with abdominal pain, chest pain or joint pain.
- FMF is a clinical diagnosis that can be confirmed by a gene mutation in the majority of cases.
- Treatment of FMF can prevent long-term injury to internal organs.
- The fever of FMF is not contagious.

What is Familial Mediterranean Fever?

Familial Mediterranean Fever (FMF) is a genetic disorder that causes recurrent episodes of fever that are typically accompanied by pain in the abdomen, chest or joints. It most often occurs in individuals of Mediterranean and Middle Eastern descent, and the first episodes typically begin in childhood.

Who gets FMF?

The disease generally affects people of Mediterranean and Middle Eastern descent, typically Sephardic Jews, Turks, Arabs and Armenians. Since the discovery of the gene defect, it is being diagnosed more frequently, even among populations where it was thought to be very rare, such as Italians, Greeks Ashkenazi Jews and even among Asian populations. FMF episodes start before the age of 20 years in approximately 90 percent of the patients. In about 75 percent of patients, fever appears before the age of 10 years. FMF can appear or be active in adults, but often the disease is milder and less obvious (and harder to diagnose) than in children.

What are the main symptoms of FMF?

The main symptoms of FMF are recurrent episodes of fever, accompanied by abdominal, chest or joint pain. Not all children will have all the symptoms, and symptoms may change over time. Episodes usually last 1-3 days and resolve without treatment. Most children look and feel healthy between episodes, but some children have such frequent episodes they do not fully recover or do not grow properly. Some of the episodes may be so painful that the patient or family seeks medical help in the emergency department. Severe abdominal pain may look like appendicitis, and some patients may undergo surgery to remove the appendix. The chest pain may be so severe that it is difficult to breathe deeply. Joint pain may accompany the episodes of fever. Usually, only one joint is affected at a time, most commonly an ankle or a knee. The joint may be so swollen and painful that the child cannot walk. One-third of patients may have a red rash over the lower extremities, usually near the ankles and feet. In some children, the only finding of the disease may be episodes of joint pain and swelling, which can be misdiagnosed as acute rheumatic fever or juvenile idiopathic arthritis. Usually the joint swelling resolves over 5-14 days, but sometimes may become chronic. Some children report muscle pain in the legs, especially after physical exertion. Rarely, children have recurrent pericarditis (inflammation of the outer layer of the heart); myositis (muscle inflammation); meningitis (inflammation of the membrane surrounding the brain and spinal cord); or orchitis (testicular inflammation). Younger children (less than 5 years old) may present only with episodes of recurrent fever, without other symptoms.

What causes FMF?

FMF is traditionally thought to be an autosomal recessive genetic disease. That means for FMF to occur, children must inherit two abnormal copies of the MEFV gene, one from the mother and one from the father. The parents are then called carriers. Often, someone in the extended family has the disease. If one child has the disease and the parents are carriers, there is a 25percent chance that another child will get FMF. If one child and one of the parents have FMF, there is a 50% chance of another child getting FMF.

However, the definitive mode of transmission of the disease from one generation to the next has recently been brought into question since about 30 percent of FMF patients are found to have only one or even no abnormal copies of the gene.

The responsible gene is called the MEFV gene, which affects a protein called pyrin. Pyrin plays a role in the natural control of inflammation. When the MEFV gene has a defect, inflammation gets out of control, and patients experience episodes of fever and pain. Infection, trauma, strenuous exercise, menstrual periods or psychological stress may trigger episodes of fever in FMF.

How is FMF diagnosed?

A test to look for gene mutations will be done in cases where FMF is suspected. If these tests are positive, the diagnosis of FMF is definite. However, it is possible to have FMF with a defect in only one gene copy or even without any gene defect. In the United States, more than 30% of the patients with FMF do not have mutations in both gene copies.

Therefore, the diagnosis of FMF is still based on symptoms and physical examination by the physician and can be difficult. FMF is suspected in children with episodic fever with an ethnic origin typical for FMF. A family member may have FMF or unexplained kidney failure. Often children, especially those younger than 5 years of age, initially have episodes of fever without the other symptoms, so it takes careful observation to make a diagnosis. Families can help by keeping a diary documenting the episodes. Examining the child during an episode and obtaining laboratory tests showing signs of inflammation can be helpful.

In some cases a specific medication, colchicine, will be given for 3-6 months as a test. If episodes of pain and fever are less frequent on colchicine treatment, this may make the diagnosis of FMF.

How is FMF treated?

FMF cannot be cured, but it can be well controlled with life-long use of colchicine, a medication that is taken by mouth 1-2 times a day. Colchicine prevents episodes from starting, but does not treat an episode that has already started. Therefore, the dose of colchicine should not be increased during an active episode. If the patient stops taking the medicine, episodes may return (often after missing only one dose!). If colchicine is taken regularly, the vast majority of children with FMF can live a normal life with a normal life expectancy. Do not change the medication dose without first discussing it with your doctor.

The most common side effects of colchicine are abdominal pain and diarrhea. If this occurs, the dose can be reduced until it is tolerated and then slowly increased back to the appropriate dose. Reducing the intake of milk or other dairy products, or consuming lactose-free milk may help. Other side effects are nausea, vomiting and abdominal cramps. In rare cases, colchicine may cause muscle weakness, especially when taking antibiotics from the erythromycin (macrolide) family or statins (cholesterol medications). Therefore, these medications need to be given with caution with colchicine. The blood counts (white and red blood cells and platelets) may decrease occasionally and there may be mild elevations in liver enzymes, but these usually recover with dose reduction. Children taking colchicine grow normally. Female patients do not have to stop taking colchicine during pregnancy or breast-feeding, but amniocentesis (obtaining fluid from the fluid surrounding the fetus) is recommended by most authorities. Children treated with colchicine should have blood and urine tests at least twice yearly.

About 10 percent of patients do not respond adequately or cannot tolerate colchicine. Recent research has found that medications that block interleukin-1, an important molecule involved in the inflammatory process, may be effective for the majority of these patients. These medications include rilonacept (*Arcalyst*), anakinra (*Kineret*), and canakinumab (*Ilaris*).

Broader health impacts of FMF and how to prevent them

The most severe complication of untreated FMF is the development of amyloidosis. Amyloid is a protein that deposits in the organs of children who have chronic inflammatory diseases that are not well controlled. The most common organ involved is the kidney, but amyloid can deposit in the intestines, skin and heart. Eventually, amyloid causes a loss of function, especially in the kidneys. If this occurs, dialysis or a kidney transplant might be necessary. Children who are properly treated with colchicine are safe from the risk of developing this life-threatening complication, but stopping treatment even for a short while can allow amyloidosis to occur. Patients with amyloidosis in the kidney will have high levels of protein in urine tests. Patients with FMF should have urine tests at least twice a year.

Living with FMF

Some children initially need psychological support to cope with a disease that means taking medications for their entire lives. Frequent episodes can affect the both the child and family life, including school attendance, so involvement of teachers, social workers, tutors, and other community members may be helpful. Most children, however, adapt to the treatment, and when well controlled, FMF should not interfere with a normal education and productive adult life.

Long-term outcome

If treated properly with life-long colchicine, the vast majority of children with FMF live a normal life.

Points to remember

- FMF is diagnosed in children with episodic fevers, often with pain in the abdomen, joints or chest.
- FMF is an inherited disorder, not an infectious one.
- Life-long treatment for inflammation can prevent the complication of organ failure from amyloidosis.

To find a rheumatologist

For more information about pediatric rheumatologists, visit www.rheumatology.org.

For a listing of pediatric rheumatologists in your area, click here.

For additional Information

The American College of Rheumatology has compiled this list to give you a starting point for your own additional research. The ACR does not endorse or maintain these websites, and is not responsible for any information or claims provided on them. It is always best to talk with your rheumatologist for more information and before making any decisions about your care.

Familial Mediterranean Fever

http://ghr.nlm.nih.gov/condition=familialmediterraneanfever

The Rheumatology Research Foundation

www.rheumatology.org/Foundation

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