FAMILIAL MEDITERRANEAN FEVER (FMF)

CLINICAL MANIFESTATIONS

Familial Mediterranean fever (FMF) is characterized by sporadic, and in most cases, recurrent attacks of fever and serosal inflammation as manifested by abdominal and chest pain. The onset of fever and pain (due to serositis at one or more sites) is usually abrupt, peaking soon after onset. Episodes last for one to three days and then resolve spontaneously. Patients are asymptomatic between attacks. The frequency of attacks is highly variable, even in a given patient.

Recurrent fever

Fever is one of the most constant characteristics of FMF and is present in almost all cases during attacks.

Abdominal pain

In Middle-Eastern populations where FMF is common, up to 95 percent of the patients with FMF have episodic abdominal pain. Abdominal pain and tenderness may initially be localized and then progress to become more generalized.

Chest pain

Painful FMF attacks are localized to the chest in 33 to 84 percent of patients, depending on the patient's ethnic origin. Armenian FMF patients are reported to have a higher rate of pleuritic involvement compared with other ethnic groups. Chest pain may be due to inflammation of the pleura or referred pain from subdiaphragmatic inflammation. Pleural inflammation typically manifests as unilateral chest pain that is worse with inspiration or coughing. Patients often have a small, transient pleural effusion.

DIAGNOSIS

The diagnosis of FMF is made on the basis of clinical symptoms and supported by ethnic origin and family history. Genetic testing for FMF serves to support the diagnosis in patients who meet clinical criteria for FMF and to counsel family members. In individuals who meet clinical criteria for FMF but in whom genetic testing is not diagnostic (only one or no pathogenic MEFV mutation), the diagnosis of FMF is supported by a six-month trial of colchicine therapy that results in a relief of attacks and recurrence after cessation of treatment. However, a definitive diagnosis of FMF can be made only on a genetic basis. This is based on the observation that additional autoinflammatory diseases (eg, tumor necrosis factor [TNF] receptor-1 associated periodic syndrome [TRAPS] and mevalonate kinase deficiency [MKD, hyperimmunoglobulin D syndrome]) may present clinically identical to FMF.

Classification Criteria

Classification criteria for FMF have been proposed. These criteria require the presence of confirmatory MEFV genotype and at least one of the following four clinical features: duration of episodes one to three days, arthritis, chest pain, or abdominal pain. Alternatively, in cases with no confirmatory MEFV genotype, the patient should have at least two of the above features. Confirmatory genotype means carriage of pathogenic or likely pathogenic mutations as homozygotes or compound heterozygotes. Non-confirmatory genotype means carrying a single mutation (heterozygotes).

Genetic Testing

Genetic testing is used to support the diagnosis of FMF and to exclude other autoinflammatory diseases that may clinically mimic FMF. FMF is usually inherited as an autosomal recessive trait. Five founder mutations, V726A, M694V, M694I, M680I, and E148Q, account for approximately 75 percent of FMF cases from typical cases in Armenians, Arabs, Jews, and Turks. Among them, M694V is the most frequent mutation in all four populations, with a prevalence ranging from 20 to 65 percent. The detection of two pathogenic mutations in the MEFV gene in an individual confirms the diagnosis. However, approximately 33 percent of patients who meet clinical criteria for FMF have only one identifiable mutation. Furthermore, 10 to 20 percent of patients who meet clinical diagnostic criteria do not carry any known mutation for FMF.

Phenotypic expression of FMF has been reported in a significant subset of patients who carry only one MEFV mutation. The fact that there are FMF patients who carry only a single mutation raises the question of whether the disease is also transmitted as an autosomal dominant trait. Some reports describe a dominant trait among patients with specific mutations such as M694VDel, a deletion mutation, and H478Y, T577N, and P373L, which are missense mutations.

Source: Eldad Ben-Chetrit, MD; Clinical manifestations and diagnosis of familial Mediterranean fever; Uptodate; Last updated Oct 2021