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THE MAIN FACTORS IN THE ORIGIN OF FAMILIAL MEDITERRANEAN FEVER DISEASE

Muminova Kimsanxon Toxtasinovna

Andijan State Medical Institute

Annotation

Familial Mediterranean fever is an autosomal recessive disorder characterized by recurrent bouts of fever and peritonitis, sometimes with pleuritis, erysipelas-like erythema, arthritis, and, rarely, pericarditis. Amyloidosis may develop, sometimes leading to renal failure. People with genetic origins in the Mediterranean basin are more frequently affected than other ethnic groups. Diagnosis is based on clinical suspicion and genetic testing. Treatment with prophylactic colchicine prevents acute attacks as well as amyloidosis in almost all patients. Patients who are colchicine-resistant or -intolerant may be treated with interleukin-1 inhibitors (anakinra, canakinumab, rilonacept). Prognosis is excellent with treatment.

Key words

Fever, disease, autosomal recesseve, pericarditis, familial mediterranean fever.

Familial Mediterranean fever (FMF) is a disease of people with genetic origins in the Mediterranean basin, predominantly people who have Sephardic Jewish, North African Arab, Armenian, Turkish, Greek, or Italian ancestry. However, cases have occurred among enough other groups (eg, people who have Ashkenazi Jewish, Cuban, or Japanese ancestry), so the diagnosis should not be excluded solely on the basis of ancestry.

FMF is caused by

- Mutations in the MEFV gene on the short arm of chromosome 16

The mutation is classically inherited in an autosomal recessive manner, but heterozygotes may manifest a clinical phenotype. FMF mutations are gain-of-function, that is, they confer new or enhanced activity on a protein, with a gene dosage effect (ie, more copies of the abnormal gene convey a greater effect). The MEFV gene normally codes a protein named pyrin, which is expressed in circulating neutrophils.

Pyrin plays a role in innate immunity. It senses modifications in the activity of the small GTPase RhoA, a molecular switch that regulates a variety of signal transduction pathways including cytoskeletal organization. Pathogen virulence toxins (such as Clostridioides difficile, Burkholderia cenocepacia, and Vibrio cholera) downregulate RhoA activity and cause an assembly pyrin along with other proteins into a pyrin inflammasome, which eventually results in the production of the proinflammatory cytokine interleukin-1 beta (IL-1 beta). MEFV pathogenic variants favor the active state of pyrin and give rise to cell membrane rupture (pyroptosis) and the release of proinflammatory cytokines.

There is strong evidence that Yersinia pestis, the cause of bubonic plague, led to the positive selection of FMF-associated MEFV mutations. These mutations confer a survival advantage to certain people who harbor Yersinia pestis.

Onset of FMF is usually between the ages of 5 and 15 years but may be much later or earlier, even during infancy. Attacks have no regular pattern of recurrence. They usually last 12 to 72 hours but may last longer. Frequency ranges from 2 attacks/week to 1 attack/year (most commonly, once every 2 to 6 weeks). Physical and emotional stressors (eg, physical trauma, infection, menstruation) may trigger attacks (1). Severity and frequency tend to decrease during pregnancy and in patients with amyloidosis. Spontaneous remissions may last years.

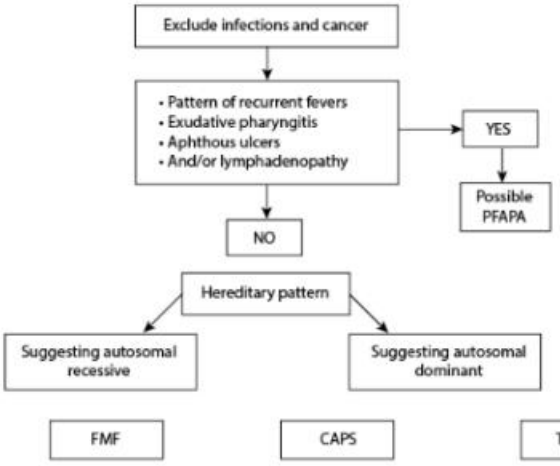
Fever as high as 40° C, usually accompanied by peritonitis, is the major manifestation. Abdominal pain (usually starting in one quadrant and spreading to the whole abdomen) occurs in about 95% of patients and can vary in severity with each attack. Decreased bowel sounds, distention, guarding, and rebound tenderness are likely to occur at the peak of an attack and cannot be differentiated from a perforated viscus by physical examination. Consequently, some patients undergo urgent laparotomy before the correct diagnosis is made. With pleural involvement, dyspnea due to pleuritic pain may occur.

Other manifestations of FMF include arthritis (in 25%), usually involving the knee, ankle, and hip; an erysipelas-like rash of the lower leg; and scrotal swelling and pain caused by inflammation of the tunica vaginalis of the testis. Pericarditis occurs rarely. The pleural, synovial, and skin manifestations of FMF vary in frequency among different populations (2).

Despite the severity of symptoms during acute attacks, most patients recover swiftly and remain free of illness until their next attack.

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	FMF	CAPS	TRAPS
Age of onset	5–15 years	< 1 year (0–3 years)	< 20 years
Duration of flare-ups	12–72 hours	< 2 days (continuous)	7–21 days
Triggers	Stress, menstruation, infection	Cold	Physical or emotional stress, fatigue, injuries, infection, vaccination
Dermatologic findings	Erysipelas-like rash of the lower leg	Urticarial rash	Rash over migratory myalgias
Musculoskeletal findings	Monoarthritis	Arthralgia, arthritis, abnormal bony growth (with NOMID)	Migratory myalgias, arthralgia
Gastrointestinal findings	Severe abdominal pain	—	Abdominal pain
Ophthalmologic findings	—	Uveitis, optic disk edema	Periorbital edema, pain, conjunctivitis
More specific findings	Erysipelas-like rash of lower leg, pleuritic pain, scrotal swelling	Urticarial rash, chronic aseptic meningitis, sensorineural hearing loss	Rash over migratory myalgias, periorbital edema
Gene	MEFV	NLRP3	TNFR1
Therapy	Colchicine, canakinumab, anakinra, rilonacept	Canakinumab, anakinra, rilonacept	Corticosteroids, anakinra, canakinumab

Pict

ure 1. Autoinflammatory Periodic Fever Disorders

CAPS = cryopyrin-associated periodic syndromes; FMF = familial Mediterranean fever; NOMID = neonatal-onset multisystem inflammatory disease; PFAPA = periodic fevers with aphthous stomatitis, pharyngitis, and adenitis; TRAPS = tumor necrosis factor receptor–associated periodic syndrome.

Complications of familial Mediterranean fever

The most significant long-term complication of FMF is

- Chronic renal failure caused by deposition of amyloid protein in the kidneys

Amyloid may also be deposited in the gastrointestinal tract, liver, spleen, heart, testes, and thyroid.

FMF may cause infertility or spontaneous abortion in up to one third of untreated women because peritoneal pelvic adhesions form, interfering with conception.

Diagnosis of familial Mediterranean fever is mainly clinical based on Tel HaShomer criteria (see table Tel HaShomer Criteria for the Diagnosis of Familial Mediterranean Fever) (1), but genetic testing is available and is particularly useful in evaluation of atypical cases. However, current genetic testing is not infallible; some patients with phenotypically unmistakeable FMF have only a single mutated gene or occasionally no evident mutations in the MEFV gene. About 10 to 20% of patients who meet the diagnostic criteria for FMF do not have MEFV mutations, which suggests epigenetic and environmental factors contribute to the disease pathogenesis (2).

Nonspecific findings include elevations in white blood cells with neutrophil predominance, erythrocyte sedimentation rate, C-reactive protein, and fibrinogen. Urinary excretion of > 0.5 g protein/24 hours may suggest renal amyloidosis.

Differential diagnosis includes acute intermittent porphyria, hereditary angioedema with abdominal attacks, relapsing pancreatitis, and other hereditary relapsing fevers.

- Daily colchicine
- In patients who are colchicine-resistant or -intolerant, interleukin-1 (IL-1) inhibitors

Daily prophylactic colchicine should be initiated as soon as the diagnosis is made to prevent attacks as well as amyloidosis (1). Colchicine provides complete remission or distinct improvement in almost 95% of patients. If attacks or subclinical inflammation persist, the colchicine dose should be increased. Initiation of colchicine at the peak of an attack is not beneficial. Children require a dose adjustment for colchicine that is typically based on age, weight, and severity of phenotype and genotype (2). Dose adjustments should also be made for patients with liver or kidney dysfunction. Widespread use of prophylactic colchicine has led to a dramatic reduction in the incidence of amyloidosis and subsequent renal failure.

Colchicine does not add to the increased risk of infertility or spontaneous abortion among affected women; when taken during pregnancy, it does not increase the risk of teratogenic events. Lack of response to colchicine is often caused by poor adherence to the regimen.

Patients who are colchicine-resistant or -intolerant may be treated with IL-1 inhibitors (anakinra once a day, rilonacept weekly, or canakinumab every 4 weeks) (3, 4). However, the role of IL-1 inhibitors in preventing amyloidosis remains unknown, and patients taking IL-inhibitors should continue taking colchicine if tolerated.

Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen are sometimes needed for analgesia.

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