Familial Mediterranean Fever

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ABSTRACT

Familial Mediterranean Fever (FMF) is an autosomal recessive hereditary disease that affects mainly the people of Jewish, Arabic, Turkish, and Armenian origins. FMF is a disease characterized by recurrent fever, abdominal pain, pleuritis, arthritis, and erysipelas-like skin lesion. The diagnosis of FMF is based on clinical manifestations; therefore, diagnostic difficulties are experienced in many FMF patients. This article is focused on a diagnostic approach to the FMF disease. *(JAREM 2015; 5: 89-93)*

Keywords: Familial Mediterranean Fever, diagnostic criteria, differential diagnosis

INTRODUCTION

Familial Mediterranean fever (FMF) is a disease accompanied by fever and is characterized by serous membranes with pain, non-infectious inflammation, seizures, and the development of amyloidosis with time (1). The disease is transmitted by autosomal recessive inheritance and is particularly common in certain societies (2). In addition to Jews, Armenians, and Arabs, Turks are among the ethnic groups most affected by this disease (3-6). The disease can also be encountered sporadically in different regions of the world (7, 8). The early diagnosis of FMF, which is a common health problem in our country, is important in terms of the treatment of the disease and the prevention of complications that may occur.

Common Features of FMF Seizure

Familial Mediterranean fever is characterized by distinct attacks of fever and pain. Recurrent attacks of fever and serositis generate the clinical picture of the disease. The frequency of attacks is variable, and the patient is completely healthy between attacks. Patients may spend a long period without any attacks. The first attack occurs before the age of 20 in 90% of patients (9, 10). Symptoms of the disease may be seen in 50% of the patients during the first decade of life and after the age of 30 in 5% (11). Although the duration of attacks varies between 2 and 4 days, there might be a longer or shorter period of seizures. Although the triggering factors are usually unknown, infections and stress are considered to play an important role. Attacks often occur suddenly without any signs and then spontaneously disappear (12). In some patients, various sensory and physical complaints such as nervousness, dizziness, increased appetite, and changes in taste may be prodromal symptoms (13). Although clinical symptoms in attacks may take various forms, the most common form of seizure is one in which fever, abdominal pain, and joint symptoms are seen together (12).

Fever

Although there may be attacks that progress with fever alone, it is often seen together with other clinical findings. Fever remains high during attacks (12). There is fever in any period of seizures in almost all patients. However, afebrile seizures have been identified in few patients. The severity of fever may range from mild to 40°C. Fever can remain high for a period ranging from a few hours to 4 days, but it usually subsides within 24 h (1). Fever may not increase in some patients and therefore can be missed. High and normal values of temperature may be measured in seizures in the same patient. It is possible that systemic fever is not seen in joint attacks (12). It is also possible that fever is not seen in episodes of patients receiving colchicine treatment (Recordati Pharmaceutical Industry and Trade Joint Stock Company, İstanbul, Turkey) (1).

Abdominal Attacks

The most common feature in FMF is abdominal pain in 95% of patients. Abdominal pain can be severe enough to require bed rest or diffuse or localized enough to imitate peritonitis (13). It usually begins a few hours before the start of fever and continues for 1–2 days after it subsides (14). Some patients may have signs of acute abdominal pain, and this may cause an unnecessary appendectomy or laparotomy to be performed in many patients (9, 10, 14, 15).

Joint Attacks

This is the third most frequent (75%) clinical sign that is seen after fever and abdominal pain. It may also occur without fever and abdominal pain. Joint involvement is observed in the form of arthritis in 70% of patients and in the form of arthralgia in 30%. Arthritis conventionally occurs in a non-mobile, mono- or oligoarticular style that does not damage the joints and cause sequelae. In general, it most commonly affects major and lower extremity joints. Joint attacks disappear spontaneously within a few days or 1–2 weeks. In 50% of cases of arthritis that occur in the ankle, erythema is observed on the back of the foot (1, 15). While acute attacks of arthritis are observed in 95% of patients, chronic arthritis can be seen in 5% (16). Events such as minor traumas and long walks may provoke attacks. The synovial fluid is sterile in acute attacks. According to the severity of synovitis in the joint, the appearance of joint fluid may change from mildly blurred to purulent (1). Changes that are irremediable or will require arthroplasty can be seen in 5% of cases of chronic arthritis that is spontaneous or disappears without sequelae and extends for a few months or up to 1 year (15). Although the hip and knee joints are usu-

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ally affected in chronic arthritis, the ankle, temporomandibular, or sternoclavicular joints may also be affected (1, 17).

Chest Attacks

Chest pain was reported at a rate of 30% in patients (13). Typical chest pain due to pleurisy is unilateral and violent. A decrease in lung sounds due to effusion, or sometimes rubbing, or fullness on percussion may be observed on physical examination, but there are no obvious physical findings (1). Recurrent pericarditis was reported in 0–5% of patients. In FMF, pericarditis tends to occur in late stages of the disease (14). Temporary effusion, blunting in the costophrenic sinus depending on effusion, and in rare cases, atelectasis may be seen in chest X-rays of patients (1, 14).

Skin Attacks

The most characteristic skin lesion in FMF is erythema similar to erysipelas, of which the incidence was reported to be 3–46% (4). It is most commonly seen in the lower extremities: on the front side of the leg, the ankles, the back of the foot, or the mallei. It occurs as unilateral pink-purple rashes in the form of erythema that are slightly raised on the skin and approximately 10–15 cm in diameter. The skin region where the lesion is found is stretched and edematous and has an increased temperature (10, 14, 16). Symptoms usually regress spontaneously within 2–3 days (14, 16). As well as rashes similar to erysipelas, purpura, subcutaneous nodules, maculopapular rash, and urticaria occurring in the lower extremities can also be seen (12).

Scrotal Involvement

This is more common in children and young adults. It is rare after the age of 20. It reveals itself by swelling, redness, and sensitivity. It recedes spontaneously without leaving any anatomical sequelae within 12–24 h. It usually occurs unilaterally in a testicle as a result of inflammation of the tunica vaginalis. Scrotal swelling alone can be the first sign of FMF in male patients (1, 10). FMF should be considered in the differential diagnosis of recurrent orchitis (12).

Muscle Findings

Muscle pains may occur in 25% of FMF patients. Muscle pains that occur in the patient can clinically present as spontaneously receding, exercise-induced occurrence, or prolonged febrile myalgia syndrome (10, 18). Pain, sensitivity, and loss of function are less severe in classic FMF myalgia, in contrast to prolonged febrile myalgia (1). Joint symptoms are mostly not found in prolonged febrile myalgia and muscle enzymes, electromyographic examinations, and muscle biopsy are found to be normal (12). Prolonged febrile myalgia, which is a dramatic clinical sign of FMF, may occur despite treatment with colchicine and requires therapy with corticosteroids (10, 12).

Vasculitis

It is known that vasculitis is an important group of disorders associated with FMF. Because of the similarities between vasculitis and FMF in terms of clinical and laboratory results, it should be kept in mind that vasculitis can be seen both as a differential diagnosis and with FMF (16). The most common form of vasculitis in FMF is Henoch–Schönlein purpura. Another vasculitis seen in FMF more commonly than in the normal population is polyarteritis nodosa (PAN). FMF must definitely be considered in PAN that occurs in childhood and youth (12).

Neurological Involvement

Neurological involvement can occur during FMF attacks, albeit rarely. The most common symptom of neurological involvement is headache. Episodes of aseptic meningitis may rarely be seen. Cases of pseudotumor cerebri and cranial nerve involvement sensitive to treatment with colchicine (Recordati Pharmaceutical Industry and Trade Joint Stock Company, İstanbul, Turkey) were also reported (10, 12).

Pelvic Involvement

Familial Mediterranean fever can negatively affect fertility in female patients. The reason for this is thought to be that miscarriages occur as a result of pelvic adhesions or that abdominal attacks increase secondary to the inflammation that occurs (19, 20). Limited attacks in the pelvic region are known to stimulate the formation of pelvic inflammatory disease (PID) in FMF patients (10).

Liver–Spleen Involvement

Acute hepatitis and recurrent hyperbilirubinemia were reported in FMF patients treated with colchicine (10). Splenomegaly was described in 30–50% of patients. The fact that most of the examined rectal biopsies were negative for amyloid suggests that amyloid deposits did not occur as a result of enlargement of the spleen (14).

Ophthalmic Involvement

Optic neuritis was reported as a rare clinical indication of FMF (10).

Amyloid

The main feature that determines the prognosis of FMF is the presence of amyloidosis. It is believed that the protein called serum amyloid A (SAA) is produced by the liver and is the degradation product of an acute-phase reactant (APR) that is formed during infection, malignancy, tissue damage, FMF attacks, and other inflammatory conditions (21, 22). The first clinical sign associated with amyloidosis in FMF is proteinuria (13, 21). In the course of time, proteinuria may lead to nephrotic syndrome, uremia, and eventually kidney transplant or end-stage renal failure. Patients are often normotensive and non-hematuric. Owing to the widespread use of colchicine treatment, amyloidosis occurs in only a small number of patients with FMF. Studies revealed that ethnicity, heredity, and environmental conditions are the factors that affect the risk of getting amyloidosis (9, 21-24). Amyloid slowly accumulates in various organs and tissues and its accumulation in the kidney is the most obvious form of organ dysfunction (13). The average life expectancy is almost the same as that of a healthy person after treatment with colchicine, if amyloidosis has not developed at the time of diagnosis (9). A relationship could not be determined between the severity of inflammatory events and the frequency of amyloidosis in FMF. A history of past attacks does not exist in some of the FMF patients in whom amyloidosis developed and it presents with nephropathy. This condition explains the existence of subclinical inflammation in patients and the development of amyloidosis and nephrotic syndrome without acute attacks (23-26). The diagnosis of amyloidosis is made by demonstrating the accumulation of amyloid in a biopsy of the involved organ. Renal and rectal biopsies are used most frequently (16). Colchicine treatment should be continued at a level

of at least 2 mg/day in FMF patients with persistent proteinuria, dialysis treatment, or end-stage renal disease requiring kidney transplantation (13).

Clinical Diagnosis

There are no specific examination findings or laboratory tests for making a precise diagnosis of FMF. A diagnosis of FMF is made by the exclusion of clinical findings, family history, biochemical and genetic laboratory data, response to treatment, and other familial periodic fever syndromes. Although it supports the diagnosis, genetic analysis is not a certain diagnostic criterion in the diagnosis of FMF. If the patient is seen during an attack, the presence of concomitant inflammatory signs [increases in leukocytosis, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and/or fibrinogen] and their decrease to normal values at the end of the attack helps in diagnosis. It should be noted that a positive result of these tests is not specific to FMF and only indicates the presence of inflammation in the body. Some accepted diagnostic criteria are used for the diagnosis of the disease in clinical practice (Tables 1, 2) (13, 27-29).

Table 1. Diagnostic criteria for FMF by Livneh et al. (13)

Major Criteria: Typical attacks (repeated ≥3 times in the same form, attack lasts 12–72 h, and fever of 38°C or above)
1. Common peritonitis
2. Pleuritis (unilateral) or pericarditis
3. Monoarthritis (hip, knee, or ankle)
4. Fever only
5. Incomplete abdominal attacks
Minor Criteria: 1–3. include incomplete forms; one or more of the following attacks
1. Chest
2. Abdominal
3. Joint
4. Leg pain emerging due to exercise
5. Good response to treatment with colchicine
Supporting Criteria:
1. FMF in the family
2. Ethnicity
3. Attacks beginning before 20 years of age
4. Requirement for intensive bed rest due to attacks
5. Spontaneous recovery from attacks
6. Lack of symptoms between attacks
7. Abnormal test response indicating temporary inflammation (increase in leukocytosis, ESR, fibrinogen, sAA)
8. Recurrent proteinuria or hematuria
9. History of unnecessary laparotomy or appendectomy
10. Consanguineous marriage
Definitive diagnosis: 1 major criterion or at least 2 minor criteria; 1 minor and 5 supporting criteria; or 1 minor and 4 of the first 5 supporting criteria are required.

sAA: serum amyloid A; ESR: erythrocyte sedimentation rate; FMF: Familial Mediterranean fever

Treatment

Colchicine, which is a plant-based phenanthrene derivative, stops cell division in the mitotic metaphase and reduces chemotaxis of monocytes and neutrophils. It inhibits lysosomal degranulation, increases cAMP levels in leukocytes, and strengthens cell walls. It reduces levels of SAA, i.e., of the acute-phase protein (12, 30, 31). It was shown that regular treatment with colchicine not only reduces the number and severity of attacks in the vast majority of FMF patients but also prevents the development of amyloidosis in all patients (9, 16). Lifetime use of colchicine is required for it to be effective (12). Treatment with colchicine is started at a dose of 1 mg/day regardless of age or body weight. Until remission is achieved, this dose is increased in increments of 0.5 mg/day to 1.5 mg or 2 mg. Treatment with doses of 1.5 mg and higher should be divided into two within each day; sometimes, a single dose of 1.5 mg/day can be given for compliance (13, 32). There are also some who propose adjusting the doses according to body weight or surface area (32). There is no consensus on the dose of colchicine that could be used in children. A divided adult dose may be used for children with a body surface

Table 2. Tel-Hashomer diagnostic criteria for FMF (27)

Major criteria
• Recurrent episodes of fever progressing with polyserositis
• sAA-type amyloidosis not attributable to another cause
• Positive response to continuous colchicine treatment
Minor criteria
• Recurrent febrile attacks
• Erysipelas-like rash
• Presence of FMF in first-degree relatives
Possible Diagnosis: 1 major + 1 minor criteria
Definitive Diagnosis: 2 major or 1 major + 2 minor criteria

sAA: serum amyloid A; FMF: Familial Mediterranean Fever

Table 3. Recurrent periodic fever syndromes (39)

1. Tumor necrosis factor receptor-associated periodic syndrome (TRAPS)
2. Hyperimmunoglobulin D periodic fever syndrome (HIDS)
3. Neonatal onset multisystem inflammatory disease/Chronic infantile neurological cutaneous and articular syndrome (NOMID/CINCA)
4. Familial cold urticaria-associated syndrome (FCAS)
5. Muckle–Wells syndrome (MWS)
6. Pyogenic arthritis, pyoderma gangrenosum, acne-related syndrome (PAPA)
7. Periodic fever, aphthous stomatitis, pharyngitis (PFAPA)

area of greater than 1 m^2 (9). The effective dose for children is 0.02–0.03 mg/kg/day (maximum 2 mg/day) (8, 10). Even one day of negligence in the treatment of FMF may cause a new attack of FMF (32). Maintaining regular daily treatment with colchicine enables attacks to end up in remission in 65% of patients with FMF. However, a significant reduction in the frequency of attacks is seen in 30% of patients. Although the frequency and severity of attacks remain unchanged in 5% of patients treated, treatment with 2 mg/day colchicine is continued for the prevention of amyloid formation in these patients (32). Colchicine should also be given to patients with amyloidosis. Colchicine should be administered at a dose of 2 mg/day in patients with renal amyloidosis. In addition, colchicine therapy should be continued in patients with secondary amyloidosis who had undergone kidney transplantation (16). Colchicine and its metabolites are excreted via urine and bile and it is a relatively safe drug (10). The side effects of colchicine are extremely rare and usually mild. The side effects most commonly observed are gastrointestinal cramping, abdominal pain, nausea, and diarrhea and they particularly occur at high doses (9, 10, 13, 31, 32). In the treatment of arthritis, nonsteroidal anti-inflammatory drugs should be added to the treatment in addition to colchicine (12). In patients who do not respond to colchicine treatment, intravenous colchicine and interferon-alpha treatment can be used (10, 13, 32). Alternative treatment approaches include IL-1 antagonists and anti-TNF therapy (31). The use of etanercept (Wyeth Pharmaceuticals, Havant, UK) and infliximab (Schering-Plough Medicinal Products Tic. A.Ş., İstanbul, Turkey) was shown to be beneficial in FMF attacks. Thalidomide (Erkim Pharmaceutical Industry and Trade Joint Stock Company, İstanbul, Turkey) was found to be effective in a small patient group but its side effects such as peripheral neuropathy and teratogenicity limited its use (13, 31).

Mutation Analysis

Pyrin, which is encoded by the MEFV gene, is a 781 amino acid protein. This protein is found in leukocytes, monocytes, and fibroblasts in small amounts. Pyrin is autoregulatory on leukocytes. A relationship is thought to exist between some cytokines such as IL-1β that play an important role in inflammation with this protein and signaling molecules such as NF-κB that are responsible for apoptosis. In FMF, a mutation in the MEFV gene causes the emergence of inflammatory attacks by stimulating the production of IL-1β and suppressing apoptosis (12). Seventy-five mutations have been identified so far. Mutations were most commonly detected in exon 10. Four of the five most common mutations are in exon 10 (M694V, V726A, M694I, and M680I) and one of them is in exon 2 (E148Q). These mutations, in particular those in exon 10, were found in all patients carrying a risk of disease, albeit at different rates (15, 16, 25, 33-37).

Laboratory Findings

There is no laboratory diagnostic test for FMF. Routine blood tests performed during acute attacks are not specific. During an attack, elevated levels of APRs including leukocytosis, ESR, CRP, fibrinogen, haptoglobin, C3, C4, and SAA are found. An APR that shows a significant increase during the attack either returns to normal in the period without attacks or shows a significant reduction in at least two-thirds of attacks, although it does not return to normal. CRP increases in all patients during an attack, ESR in 90%, and fibrinogen in 60%, and leukocytosis occurs in 50% of patients. It was reported that the secretion of inflammatory mediators such as IL-1, IL-6, IL-8, and TNF increased during attacks in FMF and a decrease occurred in interferon activity. In particular, serous fluid in the peritoneal cavity or the activity of the C5a inhibitor in the synovium decreased. Thrombocytosis is not seen during an attack, and ferritin levels do not increase. Increases in protein levels and neutrophil dominance occur in the synovial fluid of patients examined during acute attacks. Hematuria occurs in 5% of FMF patients with PAN or glomerulonephritis. Proteinuria should remind one of the possibilities of renal amyloidosis. Transient hematuria and albuminuria can be observed during FMF attacks (10, 12, 14, 28, 29, 38).

Differential Diagnosis

Although FMF may be confused with many diseases owing to clinical and laboratory similarities, the diagnosis can be made easily by a good clinician via the clinical features of typical attacks (13). The differential diagnosis of FMF is mainly made by considering periodic fever syndromes. Periodic fever syndromes are a group of autoinflammatory diseases characterized by recurrent fever and inflammatory attacks and diseases in which autoantibodies, as well as T cells specific to antigens, do not exist in the blood (Table 3) (39). FMF must be excluded in our country, no matter which periodic fever syndrome the patient's clinical features match other than FMF (40).

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