

Familial Mediterranean fever: An updated review

Ismail Sari¹, Merih Birlik¹, Timuçin Kasifoğlu²

Abstract

Familial Mediterranean Fever (FMF) is a hereditary autoinflammatory disorder characterised by acute attacks of fever and serosal inflammation. FMF primarily affects Jewish, Armenian, Turkish, and Arab populations. The disease is accompanied by a marked decrease in quality of life due to the effects of attacks and subclinical inflammation in the attack-free periods. Untreated or inadequately treated patients run the risk of amyloidosis, which is an important cause of morbidity and mortality. In this review, the current information available on FMF is summarised.

Key words: Familial Mediterranean fever, review, aetiology, amyloidosis, treatment

Introduction

Familial Mediterranean fever (FMF) is the most commonly seen fever syndrome and is significantly associated with ethnicity. It frequently occurs among Turks, Armenians, Jews and Arabs (1). Although it has been known about for a long time, it was first mentioned in the literature in 1908 by Janeway and Mosenthal, who reported recurrent fever and abdominal pain in a 6 year-old Jewish girl (2). Its first definition as a disease was based on a case report, published under the title "benign paroxysmal peritonitis" by the allergy specialist Siegal from New York, as a compilation of Jewish patients with similar complaints. The periodical fever definition was first used by Reimann in 1948, and Sohar et al. (2) defined the disease as FMF in 1955. Prior to the use of colchicine, the disease was fatal, but a new era in the treatment of FMF began with the introduction of colchicine in 1972. In a number of studies, it has been shown that this drug not only has an effect on the symptoms, but also affects the development of amyloidosis (3, 4). In 1992, it was reported that the abnormality associated with FMF is found on chromosome 16, and the gene responsible for the disease was identified in 1997 (5, 6). The disease is accompanied by a marked decrease in quality of life due to the effects of attacks and subclinical inflammation in the period between attacks (7). Untreated or inadequately treated patients run the risk of amyloidosis, which is an important cause of morbidity and mortality (3). In this review, the currently available information on FMF is summarised.

Epidemiology

Familial Mediterranean fever shows a marked ethnic distribution. The disease is most frequently observed in Turkish, Armenian, Jewish and Arabic communities. Geographically, the disease is more commonly observed among the nations of the Mediterranean region (1). Throughout the world, the disease is most frequently seen in Turkey with a prevalence varying between 1:150 and 1:10,000 (8-13). The second most frequently affected ethnic group is Armenians; studies carried out in Armenia report a prevalence of ca. 1:500 (14). In studies conducted in Sephardic Jews, the prevalence of FMF is reported to be between 1:250 and 1:1000 (15). It has been claimed that the rate is ca. 1:73,000 among Ashkenazi Jews (15). In studies conducted in Israel, it was claimed that FMF incidence varies according to the ethnic group being studied (Ashkenazi or non-Ashkenazi Jews), but that it is observed at a rate of 1:1000 on average (16). No precise information is available about the prevalence of FMF among Arabs. On the other hand, recent studies conducted in countries such as Greece, Cyprus and Italy indicate that this disease occurs more frequently than previously believed (17, 18). FMF has also been identified in other countries. In Brazil, in a study assessing 102 cases with hereditary periodic syndrome, 17 patients with suspected FMF were reported and a mutation in both alleles was identified in three of these patients (19). In a study carried out in countries in the Middle East and Eastern Europe, the incidence of FMF among individuals under 19 years of age was reported to be ca. 2:1,000,000 (20). In a nationwide study conducted in Japan in 2009, cases of clinical FMF were investigated. A number of hospitals did not participate in this study; however, in participating centres, around 170 FMF cases were identified (21).

Aetiopathogenesis

Familial Mediterranean fever is a member of the group of autoinflammatory diseases. In these diseases, the innate immune system is primarily affected (22). This disease group, including FMF, shows a genetical-



1 Department of Internal Medicine,
Division of Rheumatology, Dokuz
Eylül University Faculty of Medicine,
İzmir, Turkey

2 Department of Internal Medicine,
Division of Rheumatology, Osmaniye
University Faculty of Medicine,
Eskişehir, Turkey

Address for Correspondence:
Ismail Sari, Department of Internal
Medicine, Division of Rheumatology,
Dokuz Eylül University Faculty of
Medicine, İzmir, Turkey

E-mail: ismailsari35@gmail.com

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ly monogenic heredity, with mutations in the affected genes causing the multiprotein complex called the inflammasomes to function abnormally (23). Basically, the inflammasomes activate the caspase-1 enzyme, which causes interleukin (IL)-1 β to be released. It is believed that, in autoinflammatory diseases including FMF, IL-1 β release is uncontrolled (22, 24, 25).

FMF is an autosomal recessive hereditary disease and occurs as a result of point mutations (single substitutions) in the *Mediterranean Fever (MEFV)* gene on the short arm of chromosome 16. This gene encodes a protein called pyrine, with a weight of 95 kDa (26). The pyrine protein is essentially responsible for the regulation of apoptosis, inflammation and cytokines, and is mainly expressed in neutrophils, eosinophils, dendritic cells and fibroblasts (26). At present, no agreement exists about the physiological role of the pyrine protein. However, it is assumed that the primary function of this molecule is to suppress the inflammatory response. Structurally, the pyrine protein consists of the following domains: (i) the pyrine domain (PYD) located at the N-terminal end; (ii) the *B box zinc finger*; (iii) alpha helix (*coiled coil*); and (iv) B30.2 (PRYSPRY) located at the carboxy end (26). Each of these domains has its own specific protein-protein interactions. The PYD domain at the terminal end has a death domain fold (DDF) and forms homotypical bonds to the apoptosis-associated speck-like protein containing a CARD (ASC) protein, which plays a role in apoptosis (27, 28). Under normal circumstances, this link activates the nuclear factor kappa beta (NF- κ B) and pro-caspase-1, while suppressing IL-1 β production. It is presumed that the mutated pyrine molecule is theoretically not able to suppress, and thus the

inflammatory response develops (Figure 1) (27, 28). B30.2 at the C-terminal end is an important domain, and a significant number of mutations in the *MEFV* gene occur here. At the same time, this domain binds directly to caspase-1 (IL-1 transforming enzyme), independently of the apoptosis-associated speck-like protein containing CARD (ASC) protein, and inhibits this enzyme. Mutations in this domain are thought to eliminate physiological caspase-1 inhibition and cause uncontrolled IL-1 β release (22).

MEFV Gene Mutations

The *MEFV* gene on the short arm of chromosome 16 consists of 10 exons. Most of the mutations identified occur in exon 10 (e.g., M680I, M694V, M694I and V726A). Apart from this, mutations in exon 2 (E148Q) and other exons have also been identified (Figure 2). Most of the mutations are point mutations, known as missense mutations, and are characterised by single-nucleotide changes. To date, 288 mutations have been identified in Infervers (<http://fmf.igh.cnrs.fr/ISSAID/infervers>), which is an online databank for mutations that play a role in autoinflammatory diseases. The majority of these mutations are rare, without causing any clinical phenotype, and are mainly observed in populations in which FMF is not prevalent. It has been shown that the E148Q, M680I, M694V, M694I and V726A mutations are responsible for more than 80% of FMF cases in the Middle Eastern region (16). On the other hand, because E148Q has a high carrier rate (>10%) and does not cause an FMF phenotype, even in homozygous cases, some researchers have claimed that this should not be considered a mutation, but rather a polymorphism (29). Because of the autosomal recessive nature of FMF, it is emphasised that individuals with clin-

ical FMF should have two mutations (29, 30). Nevertheless, studies have not demonstrated a second allele in almost 30% of the individuals with an FMF phenotype (30). The absence of a second mutation in an autosomal recessive disease has attracted the interest of many researchers, and a number of hypotheses have been developed to account for this. The first and simplest hypothesis is that the mutation cannot be identified using the presently available laboratory methods (29, 30). Another explanation is that, even if there is a single mutation in a patient, the other functional allele is possibly not able to perform its function because of epigenetic mechanisms. The existence of polymorphisms occurring in the genes on the inflammatory cascade is claimed to be another possible explanation. Another important point in the occurrence of the disease phenotype in individuals with a single mutation is the effect of environmental factors on the abovementioned conditions (29). The incidence of mutations in the *MEFV* gene may differ between ethnic groups (Table 1). In the Turkish population, the most commonly seen mutation is M694V. This is followed by M680I and V726A (31). To a lesser extent, other mutations such as E148Q, M694I, R761H, K695R, E148V and P369S have been identified (31). Yilmaz et al. (32) reported the allele frequency in FMF patients to be 51.1% for M694V and 9.22% for M680I. Some studies have investigated the *MEFV* gene mutation carrier state of healthy individuals. In Turkey, the rate of carriers is reported to be 20% (32). This high rate is similar to the carrier rate determined among the Ashkenazi and North African Jews. In Turkey, the most frequent mutation determined in carriers is E148Q; this is followed by the M680I, M694V and V726A mutations (32).

The Phenotype-Genotype Relationship

Researchers have claimed that there is a relationship between FMF symptoms and the genotype. According to some researchers, those individuals who are homozygous for the M694V mutation present with a more serious and severe disease course (31, 34, 35). When considered from this point of view, the most serious complication of the disease, amyloidosis, is reported at a higher incidence in homozygous M694V cases (35-37). When patients are studied in terms of frequency of fever and abdominal pain, which are the most important clinical symptoms of FMF, studies provide contradictory data (31, 34, 38, 39). Whereas some studies did not demonstrate such a relationship (31, 34), others determined that these symptoms are more frequent in individuals with an M694V or M680I genotype (38, 39). When the age at onset of the disease is considered, some studies claim that the disease develops earlier in M694V mutation carriers (31, 40), whereas others

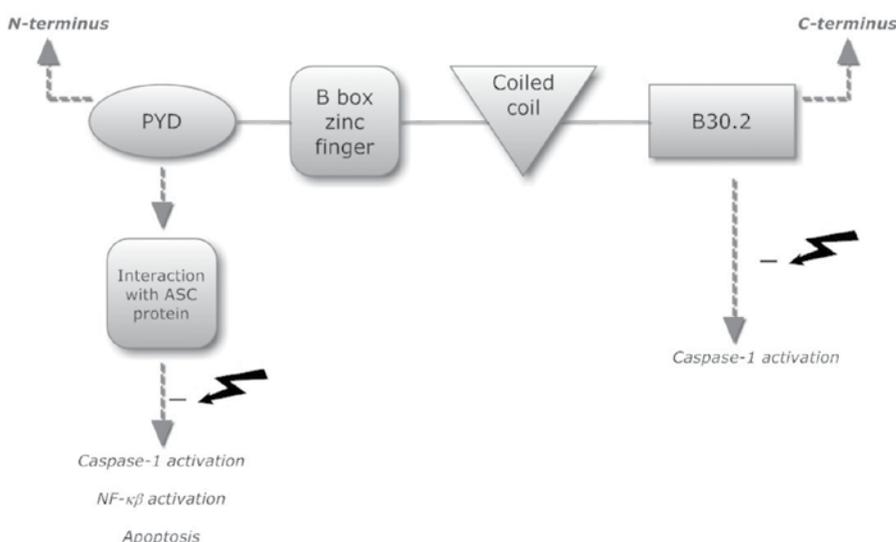


Figure 1. Structure of the pyrine protein and molecular interactions
PYD: Pyrin domain; ASC: Apoptosis-associated speck-like protein containing a CARD

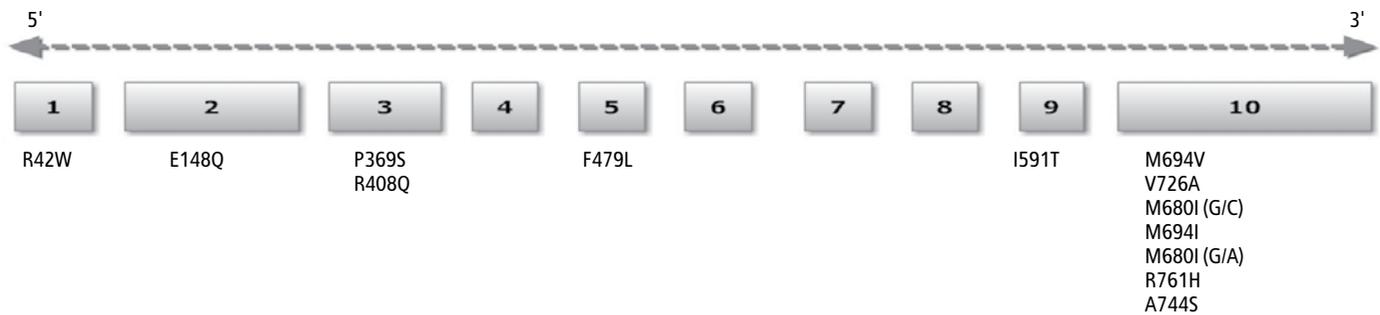


Figure 2. Distribution of MEFV gene mutations throughout the gene (33)

The MEFV gene consists of 10 exons. The mutations in this gene most frequently occur in exon 10. Nevertheless, mutations in other exons may also be seen. Mutations emphasised in bold are the most commonly identified in FMF at present; those shown in a lighter colour are less frequently observed. The majority of the mutations identified are not shown in this figure.

report that the disease occurs later in homozygous M694V patients (34). However, other studies could not determine a relationship between genotype and the age at onset of the disease (38). As a result, a considerable discrepancy exists between studies investigating the phenotype-genotype relationship. However, researchers seem to agree that the disease is more severe in M694V homozygous patients.

Familial Mediterranean Fever Clinical Symptoms

Familial mediterranean fever is a disease that is characterised by recurrent fever and serositis (e.g., peritonitis, pleuritis, synovitis) symptoms. Individual and ethnic differences may be seen in both the frequency and course of the clinical symptoms. While a single sign may sometimes accompany high fever, at other times, more than one symptom can occur simultaneously. Even in the same patients, clinical symptoms may differ over time (1, 41). Attacks develop quite spontaneously and continue for at least 12 hours. Most symptoms resolve within 3-4 days, and the interval between attacks is clinically relatively symptom-free. However, arthritis and myalgia may have a prolonged course (1, 41). Disease onset is prior to 20 years of age in 90% of cases and, in 60% of cases, the age at onset is under 10 years. Nonetheless, the disease may develop after the first years of life (2). When the sex distribution of FMF is considered, a slight male dominance can be noted (31).

The prodromal phase

In approximately half of FMF patients, various constitutional and physical signs, including restlessness at the site where the symptom is about to occur, anxiety, irritability, increased appetite and taste alterations, accompany the onset of an attack. The period between the prodromal signs and the onset of the attack has been reported to average 20 hours (42).

Fever

High fever is the most important symptom of FMF and one of the essential symptoms in

the diagnosis. Body temperature is generally above 38°C. Fever typically emerges spontaneously, increases rapidly, and is followed by a plateau and a rapid decrease, which completes the cycle. This course generally lasts 1-3 days. Non-specific findings such as weakness, fatigue, myalgia, arthralgia, headache, lower back and back pain commonly accompany high fever (3). Most patients assess their fever subjectively. According to one view, patients who do not define high fever do not measure their body temperature and therefore report high fever as negative (2).

Gastrointestinal system symptoms

Peritonitis and related complications: Abdominal pain resulting from inflammation of the peritoneal lining is the most frequent clinical complaint in FMF. This is observed in more than 90% of patients. On the other hand, abdominal pain attacks were reported to be the most frequent baseline symptom of the disease in more than half of patients. Abdominal pain starts in any region and quickly spreads to the whole abdomen. In order to alleviate the pain, the patient lies without moving in the flexion position. Upon examination, there are signs relating to peritoneal irritation (such as abdominal swelling, tenderness, sensitivity, stiffness, a decrease in bowel sounds, defence and rebound), numerous air-fluid levels on direct graphs and leucocytosis in laboratory tests, and increased acute phase symptoms. These symptoms resemble a surgical acute abdominal picture. In some patients, haematuria may be determined in the urine, and this finding may lead to inaccurate clinical interpretations in individuals that are not diagnosed correctly. Although there is generally no gas or stool excretion, about 10-20% of patients may experience diarrhoea. Abdominal pain relief is achieved within 6-12 hours; however, it generally takes 24-48 hours for it to resolve completely (2, 3, 31). Patients describing abdominal attack experience various forms of pain on a

Table 1. The most frequently observed mutations in the MEFV gene, by various ethnic groups (16)

<i>Turks</i>	M694V, M680I, V726A, E148Q
<i>Armenians</i>	M694V, M680I, V726A, E148Q
<i>Jews</i>	
North African	M694V, E148Q
Iraq	V726A, M694V, E148Q, M680I
Ashkenazi	E148Q, V726A
<i>Arabs</i>	V726A, M680I, M694V, M694I, E148Q

MEFV: Mediterranean fever

mild to severe range throughout their lives. Some patients may undergo unnecessary surgery, due to misinterpretation of the acute abdominal clinical picture emerging during the course of the disease. In a retrospective study, it was found that abdominal surgeries in FMF patients predominantly occurred (ca. 90%) prior to the FMF diagnosis and that, after the diagnosis was made, this rate decreased to around 10% (43). According to the same study, whereas surgeries performed prior to the FMF diagnosis were mainly done with the suspicion of acute appendicitis, surgeries following FMF diagnosis were more frequently performed due to ileus (43). In a trial conducted in Turkey, it was determined that about one in five FMF patients was operated on for a suspicion of acute appendicitis (31). Although a number of researchers claim that elective appendectomy may protect FMF patients against unnecessary examinations and surgical intervention, this is not recommended and, moreover, can increase adhesions of the peritoneal lining (3). In previously performed studies, during an attack, hyperaemia in the peritoneal lining and, in some patients, fluid accumulation in the peritoneum was shown. This fluid was found to be rich in fibrin and polymorphonuclear leukocytes and exhibits exudate characteristics. On the other hand, in a computed tomography examination, peritoneal fluid may even be detected during the asymptomatic period (44).

Recurrent accumulations of the exudative fluid and its resolution may cause adhesions in the peritoneal lining over time, and may thus lead to complications such as mechanical bowel obstruction, volvulus and strangulation (2). Too many neutrophils in the peritoneal fluid are believed to increase the risk of adhesion (45). Studies have demonstrated that mechanical bowel obstruction is seen more commonly in FMF patients compared with the normal population (46). In FMF patients with no previous surgery, the occurrence of intestinal obstruction is reported to be 3% (43). As a result of recurrent attacks, some patients develop sclerosing peritonitis (encapsulated peritonitis), which may lead to acid development (3).

Spleen and lymph node symptoms: Splenomegaly was reported in various series at different rates, with an incidence between 10% and 60% (3). In general, this occurs as a result of reactive changes secondary to the inflammation. However, although rare, it may also occur as a result of amyloid accumulation (47). In some cases, peripheral and abdominal lymphadenopathy (LAP) secondary to the inflammatory response was identified, with an incidence of ca. 14%. Sometimes, cases undergoing laparotomy due to an enlargement of the mesenteric lymph node have also been reported. The biopsy assessment of the lymph nodes revealed non-specific lymphoid hyperplasia (44).

Hepatic symptoms: During the course of FMF, hepatomegaly might occur, and this is identified to a lesser degree compared with splenomegaly (approximately 5%) (44, 48). A number of observational studies have indicated that, as cryptogenic hepatic cirrhosis is more frequently observed in FMF patients, there might be a relationship between the diseases (49). Another study revealed that non-alcoholic steatohepatitis (NASH) is observed in FMF at a higher rate than expected and associated this with the effects of proinflammatory cytokines and *MEFV* gene mutations on the liver. In the same study, it was suggested that NASH might have caused the increase in cryptogenic cirrhosis mentioned earlier (50). Although an increase in the incidence of cholelithiasis in FMF was shown in some studies (3), others do not support this finding (47).

Mesothelioma: Observational studies produced data indicating that mesothelioma is increased in FMF. According to these researchers, over time, chronic inflammation causes malignant transformations in the serous membrane. However, other observational studies do not confirm the finding of increased mesothelioma in FMF (47).

Other gastrointestinal system symptoms: About 5% of FMF patients are reported to have irritable bowel syndrome as an accompanying disease (47). This might lead to abdominal pains that are not related to the attacks. Another condition causing abdominal pain is colchicine intolerance, which may also be accompanied by diarrhoea (47). Although rare, another condition is diarrhoea and malabsorption due to the accumulation of amyloid in the small intestine (3).

Musculoskeletal system symptoms

Arthralgia and arthritis: Arthralgia and arthritis are the most common clinical symptoms of FMF. Arthritis generally develops in childhood, with an incidence ranging between 20% and 70% (51, 52). In some cases (approximately 10%), it can be the baseline symptom of the disease (53). Arthritis attacks are usually accompanied by fever; they demonstrate a monoarticular characteristic and manifest themselves in the large joints of the lower extremities (knee > ankle) (2). In arthritis cases, a rash is frequently observed (2, 54). However, some studies indicate that erysipelas-like erythema (ELE) may also accompany up to 40% of cases (55). Arthritis attacks tend to resolve within a week (53). Upon examination of synovial fluid, fluid accumulation that is more predominant in neutrophils and with an inflammatory characteristic is detected. In some cases, leukocyte numbers in the synovial fluid may increase dramatically, and this may be confused with septic arthritis (56). Despite recurrent arthritis attacks, erosion in the joints is not expected (51, 55). Some 5-10% of FMF patients may experience protracted arthritis attacks lasting more than a month, sometimes even years (55-57). In protracted arthritis, mainly the knees and, to a lesser extent, the hip joints are affected (57). The inflammation in the knee joint is usually resolved without sequelae, with massive fluid accumulation (57, 58). However, protracted hip arthritis may exhibit destructive characteristics. In trials, it has been shown that approximately 30% of patients with hip manifestation required a total hip arthroplasty operation (56, 57).

Clinical manifestations in the axial spine: Studies indicate that the incidence of sacroiliitis is increased in FMF patients. As already known, sacroiliitis is a common characteristic of the spondyloarthropathy (SpA) disease category, and it seems that FMF might also be in this spectrum. Moreover, as arthritis in FMF tends to manifest itself in the large joints of the lower extremities and may cause manifestations in the root joint, such as the hip joint, FMF is similar to the SpA group of diseases in terms of the arthritis pattern. The association of FMF with SpA was first pointed out in the 1960s, and this relationship

was further explored through case reports and various other studies. In a study in which approximately 3000 FMF patients were evaluated, SpA prevalence was reported to be 0.4% (59). In a study conducted in Turkey, 503 FMF patients were evaluated, and sacroiliitis was detected by x-ray in up to 10.5% of these patients (60). When FMF patients with sacroiliitis were assessed, these patients are generally determined to be HLA-B27 negative, whereas in HLA-B27-positive cases, the axial manifestation symptoms were observed to be more severe (61). In addition, it is interesting to see that *MEFV* gene mutations (particularly M694V) that play a role in FMF pathogenesis are significantly increased in ankylosing spondylitis (AS) patients, with negative FMF clinical symptoms (62, 63).

Muscle symptoms: During the course of FMF disease, various muscle symptoms may emerge, and the incidence in this patient series is about 20-40% (31, 64). Types of myalgia that may occur during the course of FMF can be categorised as (i) muscle pain occurring in childhood after exercising; (ii) disseminated muscle pain due to fibromyalgia; (iii) protracted febrile myalgia (PFM); (iv) muscle pain accompanying the attack; and (v) myalgia and myopathy related to colchicine treatment. Post-exercise muscle pains occur particularly in the lower extremities. These are not accompanied by fever or acute phase response, last for 2-3 days on average, may follow a severe course, and usually begin in the evening (3). The incidence of fibromyalgia syndrome, which causes generalised pain, has increased in both paediatric and adult FMF patients. The basic cause of this situation is that the pain threshold decreases as a result of chronic illness. Acute phases and muscle enzymes in myalgia resulting from this are normal, and trigger points with pain can be detected during examination (65, 66). Generalised muscle pain that accompanies fever and other clinical findings during attacks is another type of myalgia. This situation ends when the attack ends (67). Another finding relevant to muscles is myopathy, which develops due to colchicine treatment. As is previously known, colchicine is the gold standard treatment for FMF. This risk increases in those with renal failure and who use cyclosporine. In colchicine myopathy, in addition to weakness of proximal muscles, an increase in laboratory muscle enzyme levels, a myopathic pattern in electromyographic (EMG) examination, and autophagic vacuoles histopathologically visible in non-necrotic muscle fibrils, and lysosomal storage will probably be observed (68).

Another type of muscle pain is PFM. Its incidence has been stated to be 1-3% in various

case series (54, 69). It occurs particularly in the lower extremities, continues with intense pain and sensitivity, and seriously affects the patient's quality of life. Contrary to most FMF clinical findings, PFM can last for up to 6 weeks. Some authors have suggested that to be able to say that a pain is PFM, it should last for at least 5 days (70). PFM can occur before or after a serositis attack. Approximately 70% of cases are accompanied by fever (71). In PFM, muscle enzymes are at normal levels, and no abnormality is detected in muscle biopsy and EMG (3). However, in magnetic resonance imaging (MRI) examinations, findings of oedema have been reported in the involved muscles (72). A higher ratio of female patients in the case series is noteworthy (64). Studies of the genotype-phenotype relationship suggest that PFM is seen more frequently in M694V homozygous individuals (73). Some authors suggest that Antistreptolysin O (ASO) titres are high in these patients and, therefore, recent streptococcal infection may trigger the condition (74). Because some cases are accompanied by a skin rash, the existence of hyperglobulinaemia in laboratory tests, and symptoms that respond to high-dose (1 mg/kg) corticosteroids, it has been suggested that autoimmunity may be involved in the pathogenesis of PFM (3, 64). On the other hand, the fact that the storage of immunoglobulin and complements is observed in skin biopsies from some patients supports this hypothesis (75).

Pulmonary findings: Pleural involvement occurs in approximately 40% of FMF patients. Pain is usually one-sided, gets worse with breathing and can expand to the shoulder. Similar to the other attacks, it lasts for 1-4 days. Sometimes the right pleura and sometimes the left pleura is affected. In a direct graphy of the patient, closure of the costophrenic sinus due to fluid can be observed during attacks. Fluid analysis is exudative and neutrophils are dominant. In some patients, thickening and adhesion have been reported in the pleura as a result of repeated attacks. Pleural inflammation can be accompanied by atelectasia and, where pleurisy and fever co-exist, this situation can be diagnosed as pneumonia by mistake. As with peritoneal involvement, some authors have suggested an increased risk of pleural mesothelioma; however, there is insufficient evidence to prove this. In some patients, albeit rarely, pulmonary involvement due to amyloid has been reported, and other organ involvement due to amyloid is seen as well. On the other hand, some systemic vasculites can be seen together with FMF, and naturally, in such cases, pulmonary findings of the disease can also accompany the clinical picture. In some cases, especially in nephrotic syndrome cases resulting from amyloidosis,

the risk of hypercoagulopathy increases, and this situation, albeit rare, may cause pulmonary thromboembolism (2, 31, 76).

Cardiovascular findings

Pericardial involvement: Inflammation of the pericardial membrane in FMF is less frequent compared with other serosal involvements. Kees et al. (77) have reported the incidence of pericarditis as 0.7% in a series of approximately 4000 patients. Pericarditis attacks last for 1-14 days (average 4.2 days), and patients often experience more than one pericarditis attack. Pericardial inflammation and other serous membrane involvement can also be seen during the course of the disease. Kees et al. (77) have reported that pericardial attack follows a benign course, and no sequelae remain in any patients. Dabestani et al. (78) evaluated 30 patients whom they chose randomly among their cohort of 210 patients, and reported that the findings of pericarditis were found in eight patients (27%) echographically. In this study, the existence of pericardial thickening was also observed in some patients. On the other hand, the aforementioned study had various methodological weaknesses, and the definition of pericarditis was based on effusion and/or thickening findings determined by echocardiography. Therefore, various authors have stated that this situation does not reflect the actual incidence of pericarditis (77, 79). A prospective study investigated the incidence of pericardial effusion during FMF attacks, and reported that 3.6% of patients have pericardial effusion during attacks (79). It was observed that the amount of effusion determined in this study was around 5 mm on average (79). According to the current data, FMF involves the pericardium less compared with other serosal membranes, and this finding appears as a relatively later clinical finding of the disease may cause pericardial thickening, and fluid is not expected in massive amounts.

Other cardiovascular system findings: As is known, inflammation causes atherogenic effects, and increased cardiovascular (CV) mortality due to early atherosclerosis is observed in some inflammatory rheumatic diseases (80). In recent years, various papers have been published on atherosclerosis in FMF patients. The earliest step in atherogenesis is endothelial cell damage (81). Various biomarker studies in FMF have demonstrated findings of endothelial cell damage both during and between attacks (82, 83). Additionally, some studies have pointed out the existence of endothelial dysfunction in ultrasonography during the subclinical period (84). However, some imaging studies have reported that the existence of carotid plates,

which are used to show atherosclerotic load, do not increase in FMF patients compared with healthy control subjects (85, 86). According to a very important and noteworthy study conducted by Langevitz et al. (87), in FMF patients who regularly use colchicine, their CV mortality is lower than that of those control subjects with another inflammatory disease. This study also used another control group consisting of relatives of FMF patients, and no difference in terms of CV mortality was found between the groups (87). As a result, although there are data regarding endothelial damage in FMF disease, this situation is not considered to cause an increase in the risk of CV mortality. The major reason for this is that, in contrast to the inflammation seen in rheumatoid arthritis and systemic lupus erythematosus, inflammation in FMF follows a course in attacks, and there is the possible atheroprotective effect of colchicine (82). In FMF, abnormalities in both atrial and ventricular transmission systems have been investigated, and no transmission system abnormality has been detected in patients without amyloidosis (88-90). On the other hand, a study of patients with amyloidosis reported that QT variability, which assesses the ventricular transmission abnormality, increases (91). Ventricle functions have been investigated in various studies. Accordingly, while no abnormality is detected in systolic functions, both right and left ventricle diastolic function has been detected in periods between attacks in FMF patients, and this function has been associated with inflammation (92-94). Some researchers have found abnormalities in the variables of aortic stiffness and arterial pulse wave velocity, which are parameters of atherosclerosis (93, 95). The clinical significance of these findings is not yet known.

Renal findings other than amyloidosis: In 22% of FMF patients, defined kidney problems other than amyloidosis involvement have been defined. These include temporary or permanent haematuria and/or proteinuria, recurring acute pyelonephritis, tubulointerstitial nephritis and glomerulonephritis (GN) (31, 96-98). However, vasculitic manifestations that accompany FMF may also cause different types of kidney involvement. Various types of GN such as diffuse proliferative, membranous and mesangiolproliferative GN may occur during the course of FMF (31, 96-98). Some researchers have suggested that colchicine prevents glomerular disease, and that the irregular use of this drug triggers GN attacks (96).

Dermal findings: Various rashes have been defined during the course of FMF. The primary dermal findings are urticaria, diffused erythema on the palms and soles, subcutaneous nodules,

angioneurotic oedema, pyoderma, Raynaud's phenomenon, dermal findings related to accompanying vasculites and EBE (99). Among these rashes, EBE is not considered to be typical of the disease. This finding usually accompanies fever or arthritis, and involves the front side of the leg, ankle or dorsum of the feet. It is usually triggered by walking or standing for a long time (99). The lesion is 15-50 cm in size, painful, warm, swollen and has sharp boundaries, and fades within approximately 1-3 days before disappearing (2). It is usually on one side, but it may sometimes involve both extremities (99). No specific anomaly has been defined in the histopathological examination of such lesions (99).

Other clinical findings: Inflammation of the tunica vaginalis, which is an extension of the peritoneum, may lead to acute scrotal attack. This mostly occurs in children and young adults. It is usually one-sided, and inflammation findings such as redness, pain and swelling can be observed (3). Various nervous system findings have been defined in the course of FMF. However, these findings are quite rare, and have usually been reported as case reports. Some observational studies have investigated the relationship between FMF and multiple sclerosis, and have suggested that this condition is seen 2- to 4-fold more in FMF patients than in the normal population (100-102). Involvement of the eye is quite rare. There are publications, usually as case reports, of findings of eye involvement, scleritis, pre-uveitis, pan-uveitis, papillitis, and objects similar to retinal colloid (103-105). Another study has reported that ocular surface anomalies are more common in FMF (106).

Amyloidosis in Familial Mediterranean Fever

The most important factors determining the prognosis of FMF are the development of amyloidosis and subsequent progression to end-stage renal failure of the patient. The most important factor in the development of amyloidosis is the increase in production of the SAA protein, which is synthesised in the liver (107). Increased synthesis of this insoluble protein, and hence decreased elimination of it, leads to accumulation of the molecule in extracellular areas and the development of amyloidosis (108). In the pre-colchicine period, in FMF patients aged 40 years and above, the incidence of amyloidosis has been reported to be at quite high levels of 60-75% (109). The incidence of amyloidosis has decreased markedly with the regular use of colchicine. Nevertheless, amyloidosis complications are still a problem, especially in communities where the disease is common. In two studies conducted in Turkey on many patients, the frequencies of amyloidosis have been reported as 12.9% (31)

and 8.6% (35). Although FMF carries a potential risk of amyloidosis, not everyone with FMF develops amyloidosis. Various publications have investigated the risk factors for amyloidosis. The fact that the development of amyloidosis is more common in Sephardic Jews compared with Ashkenazi Jews indicates that the genetic background of patients is important in this respect. The incidence of amyloidosis is also very different between people of the same ethnicity living in different geographic areas. While the incidence of amyloidosis in Armenian FMF patients living in Armenia is 24%, the incidence of amyloidosis in Armenians living in California is 0% (110). Various publications have reported the risk of amyloidosis in FMF patients who are homozygous for the M694V mutation in the *MEFV* gene (35, 37, 111). Kaşifoğlu et al. (35) performed a study conducted on 2246 patients, and reported that FMF patients who are M694V homozygotes carry a 6-fold risk of amyloidosis compared with FMF patients carrying other *MEFV* gene mutations. Additionally, male gender (35, 112), a family history of amyloidosis (112), and the existence of a homozygous SAA 1.1/1.1 genotype are also other defined risk factors for amyloidosis.

Amyloid structures first accumulate in the spleen, liver and kidneys, and then in various tissues such as testicles, adrenal glands, the gastrointestinal system and the nervous system (107). The development of nephrotic syndrome and renal failure due to damage to the renal structure caused by amyloid fibrils is the most common clinical course. While absorption failures and diarrhoea resulting from involvement of the gastrointestinal system with amyloid can be seen, many patients can be asymptomatic. Storage of amyloid in the testicles can cause azoospermia and infertility. Transmission anomalies and cardiac failure can be seen as a result of cardiac storage. Storage in joints can lead to amyloid arthropathy (2, 3, 15).

All patients followed up with the diagnosis of FMF should also be regularly examined for amyloidosis by urinalysis. Tissue diagnosis can be required in patients with proteinuria between attacks. Renal biopsy is the most sensitive method. An increased disposition to bleeding due to amyloid storage can be limiting for renal biopsy. Although rectal biopsy is less sensitive, it is also a less invasive method, and can therefore be considered an alternative. Some studies have reported that the sensitivity of renal biopsy for diagnosis of amyloidosis is 88%, and the sensitivity of rectal biopsy is 75%, and gingival biopsy material is 19%. Other alternatives are bone marrow biopsy and fat tissue biopsy. It has been reported that the sensitivity

of bone marrow biopsy is closer to the sensitivity of rectal biopsy for the diagnosis of amyloidosis, and that the sensitivity of subcutaneous fat tissue is not very high for the diagnosis of amyloidosis (15, 113, 114).

Clinical findings regarding amyloidosis are usually seen at ages below 40 years. There is another clinical subgroup called phenotype II. In this clinical group, patients first have the AA amyloidosis diagnosis confirmed by biopsy, and the clinical manifestation of FMF occurs after the diagnosis. In some cases with phenotype II, the clinical manifestation of FMF may not occur; however, there are patients with clinical manifestation of FMF in the families of these cases (115).

Relationship between Familial Mediterranean Fever and Vasculitis

Studies have found that vasculites such as polyarteritis nodosa (PAN) and Henoch-Schönlein purpura (HSP) are more common compared with the normal population. According to some researchers, Behçet's disease (BD) is also more common in FMF; however, this relationship is less common than that observed with PAN and HSP.

Polyarteritis nodosa

Polyarteritis nodosa is a vasculitis that causes necrotising inflammation in small and medium-sized arteries. There are various publications regarding the concurrence of PAN and FMF. In a comprehensive study, the incidence of PAN in FMF was reported to be 0.9%. If we assume that the incidence of PAN in the normal population is 6 in 100,000, in that case, the incidence of PAN in FMF has increased approximately 200 times (31, 116). In cases of PAN associated with FMF, first, the clinical manifestation of FMF occurs, and then the clinical manifestation of PAN is added (116). In terms of the symptoms, both diseases have common findings such as abdominal pain, fever, muscle pain, articular symptoms and skin rashes (67). It has been reported that there are some differences between the PAN that accompanies FMF and classic PAN. One of these is the age at which the disease presents. Classic PAN usually emerges at ages 40-60 years. However, FMF-related PAN occurs at younger ages (116). In another study, the average age at which PAN accompanying FMF presents has been reported to be 14.9 years of age (117). Another difference is the gender distribution among patients. While classic PAN is usually seen in men, FMF-related PAN is seen equally in men and women (31). Another difference between the groups is that spontaneous perirenal hematoma, which is rarely seen in classic PAN

cases, accompanies almost half of PAN cases with FMF (117). The two groups are different in terms of mortality. It has been reported that FMF-related PAN cases follow a better course (117). Another interesting point is that, in contrast to classic PAN cases, in the concurrent cases of FMF-PAN, glomerular involvement can be seen (118, 119). Intensive myalgic complaints are observed in patients in cases of PAN that accompany FMF. Some clinicians have suggested that this could be a hint to suggest the possibility of PAN; however, it should be kept in mind that intensive muscle pain can also be seen in FMF in PFM and colchicine-related myopathy (117).

Henoch-Schönlein purpura

Henoch-Schönlein purpura is a vasculitis of small vessels that involves skin, kidneys, joints and the gastrointestinal system, and is the most common vasculitis of childhood. In various series, the incidence of HSP accompanying FMF has been given as 2.7-7.2% (31, 119). In this respect, it is also the vasculitis that most commonly accompanies FMF. Considering that the incidence of HSP in childhood is 0.8%, the incidence of this vasculitis has increased almost 4-fold (116). Researchers have stated that classic HSP and FMF-related HSP are not clinically different from one another (119).

Behçet's disease

Behçet's disease is an idiopathic inflammatory disease seen more commonly in the countries on the historic Silk Road, which is defined as between the Mediterranean region and the Far East (120). Although some studies have reported that the incidence of BD increases in FMF, others have not confirmed this (121, 122). It is suggested that the clinical picture in FMF-related BD cases is not different from that in classic cases (116).

Reproductive System and Pregnancy in Familial Mediterranean Fever

As FMF especially affects individuals in fertile age groups, it raises various concerns among both patients and doctors regarding reproduction and pregnancy. The first of these concerns is that FMF can cause infertility (123, 124). Another important concern is that it can lead to peritonitis, and fever can lead to uterine contractions, thus leading to undesired complications such as abortion or premature birth (125, 126). Another concern is the possible teratogenic effect of colchicine, which is the gold standard treatment for FMF (123).

Concerns about infertility

There are various studies on the relationship between FMF and fertility. In a study conducted in Israel, infertility was reported in approx-

imately one-third of fertile women with FMF not getting treatment for their disease, and it was suggested that ovulatory dysfunction could be responsible for this (127). Another study was conducted on women who received colchicine treatment for a long period of time, and it was also reported in this group that infertility was more common than in the normal population; this was because of ovulatory insufficiency (128). In another study conducted in Italy, it was suggested that infertility in women with FMF was twice that observed in the general population, and that ovary dysfunction and peritoneal adhesions were the cause of infertility (125). Another important conclusion from this study was that the majority of infertile women in this group consisted of women who had not been receiving colchicine treatment (125). Considering the literature data, particularly in untreated women, increased infertility is seen as a result of ovulatory insufficiency and peritoneal adhesions (because of attacks or operations). Fertility can be achieved, and the development of peritoneal adhesions can be decreased with colchicine treatment (129). It has been reported that artificial insemination techniques such as *in vitro* fertilisation in infertile FMF patients are quite successful (126).

It has also been reported that male infertility can be increased in FMF. The primary cause of this is that the attacks occurring as a result of inflammation of the tunica vaginalis can lead to testicular insufficiency or amyloidosis, which is a complication of FMF that can negatively affect spermatogenesis (123, 124). Sperm count investigations may be suggested for men who have amyloidosis and want to have children.

Concerns about pregnancy

Various studies have been conducted to investigate the risk of premature birth and spontaneous abortion in FMF. According to the literature data, the incidence of spontaneous abortions before colchicine treatment is around 25-30% (128). This is probably because FMF attacks (both peritonitis and fever) cause or increase uterine contractions (123, 126). Additionally, some studies have reported that premature births and spontaneous abortions are also increased in patients treated with colchicine (126). There are various studies on the course of pregnancy in women with amyloidosis. According to these studies, pregnancy in these patients can occur with spontaneous abortion, stillbirth and worsening of kidney functions (130, 131). Some authors suggest that fertile women with amyloidosis complications should not become pregnant (123). Looking at the course of the disease during pregnancy, no definite remarks can be made on

this matter. According to some researchers, the incidence of attacks increases during pregnancy; while, according to others, the incidence of attacks decreases during pregnancy (129, 132).

Teratogenicity

At present, the gold standard treatment for FMF is colchicine. This drug acts on the microtubular structure of cells. Therefore, colchicine use may affect various cellular processes such as mitosis. Laboratory studies have reported that chromosome aberrations could be observed due to the negative effect of colchicine on mitosis (133). Demonstration of the passage of colchicine through the placenta (134) and reports of trisomy in the children of women using colchicine in some case presentations have resulted in serious concerns on this issue (129). As a result, the manufacturing company has added a statement to the package leaflet stating that it should not be used during pregnancy (123, 129). As a result of these concerns, physicians have recommended the discontinuation of colchicine treatment for at least 3 months before pregnancy (123, 129). Some physicians have continued with this drug, suggesting that the frequency of abortion increased due to the non-use of colchicine; however, they recommended amniocentesis and karyotyping for their patients within the fifth gestational month because of the possibility of foetal malformation (123, 129). Subsequent animal studies have found that colchicine did not result in any chromosome aberrations (129). Analysis of large-scale monitoring data showed that no difference in cytogenetic abnormalities was observed in patients taking colchicine during pregnancy compared with those not taking colchicine (135-137). As amniocentesis is an invasive procedure with a risk of miscarriage and infection, some investigators have questioned the need for this procedure and reported that amniocentesis was not required in patients taking colchicine during pregnancy (124, 129, 135).

There are also some concerns about the negative impact of colchicine on spermatogenesis. This attracted attention because some animal studies have reported the toxic effect of colchicine on sperm (138). In fact, the colchicine dose used in these studies was 30- to 50-fold greater than the human dose (124). In addition, various studies have reported that there was no abnormality in the hormone values and sperm counts of patients on regular colchicine treatment (123, 124). Some studies evaluated the children of males on regular colchicine treatment born to healthy women, and reported that there was no difference between the groups in terms of abortion and foetal malformation development compared with control groups (123, 124, 139). Therefore,

the present opinion is that female patients with FMF should continue taking the optimal dose of colchicine during their pregnancy and that there is no need for amniocentesis during pregnancy. On the other hand, although data from animal and laboratory studies suggest that colchicine can affect sperm motility and sperm count, human doses do not have any reducing effect on sperm count and do not result in foetal malformations.

Lactation and postpartum period

Colchicine may be excreted into breast milk. Studies have reported that the drug reached the maximum level in breast milk 1-2 hours after administration. On the other hand, when the amount passed to the child was analysed, it was observed to be only one-tenth of the maternal dose (140). When children of mothers taking colchicine were evaluated, no side-effects were reported relating to the drug (140, 141). Accordingly, it was suggested that breastfeeding is safe in women taking colchicine. There is a limited number of studies relating to the course of disease in the postpartum period. Available data show that breastfeeding does not increase the frequency of episodes (140, 142).

Diagnosis of Familial Mediterranean Fever

Familial Mediterranean fever disease is diagnosed clinically. People with an appropriate ethnic origin, with recurrent findings and fever accompanied by serositis ongoing for 1-4 days are diagnosed with FMF (16). In the past, various criteria were suggested for diagnosis. One of the most commonly used criteria includes the Tel-Hashomer criteria (143) and diagnosis sets recommended by Livneh et al. (144). According to Tel-Hashomer, two or more major or one major plus one minor finding was sufficient for FMF diagnosis (Table 2) (143).

Both the sensitivity and the specificity of the diagnosis criteria adopted later, which were generated based on patient data in the records of the Sheba Medical Center, were reported to be 99% (144). These diagnosis criteria suggested by Livneh et al. (144) defined the episodes as typical and incomplete and also included supportive findings such as ethnicity and some laboratory data. As this set of criteria was very detailed, the same working group recommended using a simplified version (Table 3) (144).

In some cases, patients do not meet the clinical diagnosis criteria (144). Genetic diagnosis tests can be used to detect *MEFV* mutations that are frequently observed in patients with symptoms suggesting FMF but without a certain diagnosis. In countries where the disease is

observed frequently with an accordingly high rate of carriers, the presence of two mutations in the *MEFV* gene is interpreted in favour of the disease. However, the initiation of colchicine treatment (1.5 mg/day; 6-12 months) is recommended for cases with no detected mutations or with a single mutation. Then, colchicine is discontinued and the response is evaluated in these cases. Any response to treatment and occurrence (or increased occurrence) of episodes after discontinuation is evaluated in favour of FMF (16, 67). In some situations, there may be cases without any clinical signs of FMF which were studied for *MEFV* mutation analysis for another reason. Concerning the cases without clinical signs, the presence of a single or even a double mutation in the *MEFV* gene does not result in a treatment indication for these patients. It is recommended to follow-up the cases that are positive for two mutations concerning FMF clinical signs (67).

Laboratory Tests in Familial Mediterranean Fever

No laboratory tests specific to FMF are available at present. Acute phase markers such as the erythrocyte sedimentation rate (ESR), C-reactive protein, fibrinogen and serum amyloid A (SAA) are frequently increased during episodes (145, 146). Among these tests, CRP was reported to increase during almost every episode, accompanied by an increase in ESR, fibrinogen and leukocyte counts (90%, 60% and 50% of cases, respectively) (145). However, it was reported that albumin, a negative acute phase protein, remained unchanged during episodes,

and this was attributed to the short duration of episodes (145). Similarly, it was reported that there was no significant change in platelet levels in the acute episode period (145). On the other hand, acute phase proteins may also remain higher in the inter-episode period, called the subclinical period. The investigators reported that CRP levels were higher than normal in nearly half of the cases within this period (145, 147). On the other hand, SAA levels, which are considered to be related to amyloidosis, were reported to be high in nearly 30% of cases in the inter-episode period (146, 147). Interestingly, the level of acute phase proteins in healthy control subjects with an *MEFV* gene mutation was found to be higher than in healthy individuals with no mutation. This was explained by the incorrect pyrine protein activating the cytokine pathway and triggering the acute phase response (146, 148). Various cytokine levels were studied in patients with FMF both during episodes and in the inter-episode period. It was reported that levels of IL-6, which stimulated the production of acute phase proteins from hepatocytes, increased during the episode. However, data from the subclinical period were controversial and reported to be high in some studies and normal in others (149, 150). IL-1, which has a major role in disease pathogenesis at a molecular level, has been studied by various investigators; however, as the blood levels of this cytokine could not be determined using the routine enzyme-linked immunosorbent assay (ELISA), the investigators stated that more sensitive assay methods were needed for this

Table 2. Tel-Hashomer diagnosis criteria (143)

Major criteria	Minor criteria
Recurrent febrile episodes with serositis (peritonitis, synovitis or pleuritis)	Recurrent febrile episodes
Amyloidosis of AA type without a predisposing disease	Erysipelas-like erythema
Favourable response to regular colchicine treatment	FMF in a first-degree relative

Definitive diagnosis: 2 major or 1 major and 2 minor criteria. Probable diagnosis: 1 major and 1 minor criteria

Table 3. Simplified FMF diagnosis criteria suggested by Livneh et al. (144)

Major criteria	Minor criteria
Typical attacks (1-4)	Incomplete attacks involving either or both of the following sites
1- Generalised peritonitis	1- Chest
2- Unilateral pleuritis or pericarditis	2- Joint
3- Monoarthritis (hip, knee, ankle)	
4- Fever alone	
5- Incomplete abdominal attack	3- Exertional leg pain
	4- Favourable response to colchicine

FMF: familial Mediterranean fever

The requirements for the diagnosis of FMF have been defined as the presence of: at least 1 major; or at least 2 minor criteria. Typical attacks must include all the following: recurrent (at least 3 episodes), febrile (rectal temperature $\geq 38^{\circ}\text{C}$) and short in duration (12 hours to 3 days). Incomplete attacks (must be recurrent) are defined as differing from typical attacks in 1 or 2 features as follows: (1) temperature $<38^{\circ}\text{C}$; (2) attack duration longer or shorter than a typical attack (but no less than 6 hours and no more than 7 days); (3) no signs of peritonitis during the attacks; (4) localised abdominal attacks; and (5) arthritis in a location other than the hip, knee, or ankle

purpose (149). Some investigators performed studies on autoantibody frequencies. Thus, the levels of rheumatoid factor, anti-nuclear antibody, anti-CCP, and ENA in patients with FMF showed no difference between patients and healthy control groups (151, 152). Some case presentations suggested that there was an increase in bilirubin levels during FMF episodes. This was also confirmed in a subsequent case-control study. Thus, it was reported that there was a slight increase in both direct and indirect bilirubin levels in nearly 25% of cases during episodes, and this was reduced to normal limits in the subclinical period (153). In the abovementioned study, transaminase measurements were performed and no difference was observed (153). Urinalysis was performed both during episodes and in the inter-episode period in patients with FMF, and it was reported that transient haematuria and proteinuria might occur during episodes (145). Ozdogan et al. studied patients during episodes prospectively and detected the presence of occult blood in faeces in nearly half of cases during episodes. The authors attributed this finding to an increase in vascular permeability during episodes (119).

Treatment of Patients with Familial Mediterranean Fever

The targets in the treatment of FMF patients are: (i) treatment of acute episodes; (ii) prevention of episodes; (iii) suppression of subclinical inflammation in the inter-episode period; (iv) prevention of amyloidosis development and stopping progression in amyloidosis cases; and (v) treatment of other clinical findings accompanying FMF.

Colchicine has been used in the treatment of FMF since the 1970s and still remains unrivalled in this respect. The efficacy of colchicine in preventing acute episodes has been demonstrated in various randomized controlled studies (154-156). There is no consensus for the optimal dose of colchicine. However, it is recommended to treat adult patients with a dose of at least 1 mg and increase the drug dose to 1.5 and 2 mg for patients with ongoing episodes on the previous dose. It is also recommended to give the total dose once and divide the dose in case of side-effects (157). In a study performed with children, it was reported that complete remission was achieved in two-thirds of patients and partial remission was achieved in one-third of cases with the use of an appropriate colchicine dose, and that a lack of response to colchicine was observed in only 5% of patients (158, 159). In other studies, the lack of response to colchicine was also reported to be 5-10% (160). It was reported that no

amyloidosis complications developed in the cases using regular and appropriate doses of colchicine (161). In addition, in the cases who developed amyloidosis but did not progress to end-stage renal failure, disease progression and the decrease in proteinuria was reported with the use of colchicine at a dose of 1.5 mg or higher (162, 163). In amyloidosis cases (also referred to as high-risk cases) and in patients with prior progression to end-stage renal failure due to FMF-related amyloidosis undergoing renal transplantation, it was recommended to use 2 mg/day colchicine if tolerated by the patient, without taking the clinical symptoms into consideration (157). In cases with serious renal failure (GFR<10 mL/min), the colchicine dose should be reduced by 50% because of possible colchicine toxicity (157). The first action in cases with a suspected lack of response to colchicine is to evaluate drug compliance. The studies performed reported that the majority of cases classified as lacking response to the drug were in fact not taking colchicine regularly (164). In conclusion, colchicine is an indispensable drug for the treatment of this disease. Even if it does not reduce FMF episodes to the desired level, the drug should not be discontinued because of its protective effect against amyloidosis.

There are a limited number of actions to be performed during FMF episodes. As there is no effective therapy for acute episodes, supportive therapies such as bed rest, paracetamol or non-steroidal anti-inflammatory drugs can be administered. It was suggested that increasing the colchicine dose during an episode did not provide any benefit and might even lead to diarrhoea, resulting in the worsening of gastrointestinal complaints (157). In several studies with a limited number of cases, alternative therapies were tested for the treatment of acute episodes. In a study by Erken et al. (165), it was reported that a single intravenous dose of 40 mg of methylprednisolone administered in the initial phase of an FMF episode was significantly more efficient than placebo in reducing symptoms. In some case studies, although it was reported that interferon alpha treatment administered in the early phase of an episode had partial efficacy on clinical symptoms, a randomised controlled study demonstrated that this treatment was not superior to placebo in terms of attack symptoms (166). In some studies with a limited number of patients, it was suggested that blocking the IL-1 cytokine, one of the molecules involved in disease pathogenesis, could be effective in the treatment of acute episodes in colchicine-resistant cases (167).

Currently, there is no alternative treatment for cases that are resistant to, or intolerant of, colchicine. However, there are several drugs being tested to fill this gap. The most promising group of drugs appears to be the anti-IL-1 therapies. According to the data from case presentations, it was reported that anakinra (a human IL-1 receptor antagonist binding competitively to IL-1 α and IL-1 β) and canakinumab (an anti-IL-1 β monoclonal antibody) treatments had a positive effect on both the development and the intensity of episodes (167, 168). In a randomised study with rilonacept (a dimeric fusion protein consisting of the extracellular domains of IL-1 type 1 receptor and IL-1 receptor accessory protein joined to the Fc region of human Ig G1), this drug was reported to significantly reduce episode frequency compared with placebo (169). In some case presentations, it was suggested that anti-tumour necrosis factor (TNF) drugs were effective in reducing episode frequency in patients unresponsive to colchicine, and another study reported that thalidomide, with TNF inhibition as the main mechanism, also had positive effects on episodes (170, 171). A significant point to remember is that colchicine treatment should be maintained whilst administering alternative treatments to colchicine-resistant patients.

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