

Familial Mediterranean Fever (FMF) in Turkey

Results of a Nationwide Multicenter Study

Turkish FMF Study Group*

Abstract: Familial Mediterranean fever (FMF) is an autosomal recessive disease that is prevalent among eastern Mediterranean populations, mainly non-Ashkenazi Jews, Armenians, Turks, and Arabs. Since a large proportion of all the FMF patients in the world live in Turkey, the Turkish FMF Study Group (FMF-TR) was founded to develop a patient registry database and analyze demographic, clinical, and genetic features.

The cohort was composed of 2838 patients (mean age, 23.0 ± 13.33 yr; range, 2–87 yr), with a male:female ratio of 1.2:1. There was a mean period of 6.9 ± 7.65 years from disease onset to diagnosis; the period was about 2 years shorter for each decade since 1981. Ninety-four percent of patients were living in the central-western parts of the country; however, their familial origins (70% from the central-eastern and Black Sea regions) reflected not only the ongoing east to west migration, but also the historical roots of FMF in Turkey.

Patients' clinical features included peritonitis (93.7%), fever (92.5%), arthritis (47.4%), pleuritis (31.2%), myalgia (39.6%), and erysipelas-like erythema (20.9%). Arthritis, arthralgia, myalgia, and erysipelas-like erythema were significantly more frequent ($p < 0.001$) among patients with disease onset before the age of 18 years.

Genetic analysis of 1090 patients revealed that M694V was the most frequent mutation (51.4%), followed by M680I (14.4%) and V726A (8.6%). Patients with the M694V/M694V genotype were found to have an earlier age of onset and higher frequencies of arthritis and arthralgia compared with the other groups (both $p < 0.001$). In contrast to other reported studies, there was no correlation between amyloidosis and M694V homozygosity in this cohort. However, amyloidosis was still remarkably frequent in our patients (12.9%), and it was prevalent (27.8%) even among the 18 patients with a disease onset after age 40 years. Twenty-two patients (0.8%) had nonamyloid glomerular diseases.

The high prevalence of vasculitides (0.9% for polyarteritis nodosa and 2.7% for Henoch-Schönlein purpura) and high frequency of pericarditis (1.4%) were striking findings in the cohort. Phenotype II cases (those patients with amyloidosis as the presenting or only manifestation of disease) were rare (0.3% or

less). There was a high rate of a past diagnosis of acute rheumatic fever, which suggested a possible misdiagnosis in children with FMF presenting with recurrent arthritis.

To our knowledge, this is the largest series of patients with FMF reported from 1 country. We describe the features of the disease in the Turkish population and show that amyloidosis is still a substantial problem.

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Abbreviations: AA = amyloidosis, secondary amyloidosis; FMF = familial Mediterranean fever.

INTRODUCTION

Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent inflammatory febrile attacks of serosal and synovial membranes³⁶. Although FMF is prevalent mainly among eastern Mediterranean people (non-Ashkenazi Jews, Armenians, Turks, and Arabs), it is observed throughout the world due to extensive population movements of the 20th century^{7,64}.

It is generally accepted that the first case compatible with FMF was reported in 1908^{26,59}, but the disease was not defined as a clinical entity until 1945⁶⁹. A year later the first description of a Turkish patient was published⁴⁰, and thereafter many cases from Turkey have been reported in national and international journals. In the early 1950s the relationship between FMF and its potentially lethal complication, secondary (AA) amyloidosis, was established³⁸. The discovery of colchicine as an effective drug for FMF in the 1970s was a major therapeutic breakthrough^{24,53,95}, and response to this drug can be used to help validate the diagnosis⁵⁶.

The FMF gene, which is located on the short arm of chromosome 16 and symbolized “MEFV” (for MEditerranean FeVer), encodes a protein termed pyrin or marennostin; most of the pathogenic MEFV mutations are located near the C-terminal half, which is an obvious clue to the functional importance of this domain^{20,25}. Phenotype-genotype correlations in FMF have not been resolved definitely, but several investigators have observed more severe disease expression and increased susceptibility to amyloidosis in patients with a specific MEFV mutation that changes amino

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acid 694 of the pyrin protein from methionine to valine (M694V)^{3,10,12,14,22,30,35,37,39,45,64,68}. It is noteworthy that the N-terminal half has been discovered to have structural similarities with several proteins related to apoptosis pathway⁶⁰. While the function of pyrin is not clearly understood, this protein may be involved in interleukin-1 β processing and secretion, with interleukin-1 β and NF-kappaB subsequently inducing the pro-inflammatory response, or pyrin itself may be induced by antiinflammatory cytokines^{13,42,52}. These processes appear to play an important role in the inflammatory pathways that characterize the innate immune system. Regarding pathogenesis, a heightened sensitivity to endotoxin has been demonstrated in an animal model, a finding that also explains the episodic nature of FMF¹³. These discoveries have formed the basis for a new categorization of illnesses such as FMF as “autoinflammatory diseases”²⁷.

The estimated prevalence of FMF in Turkey is 1/1000, and the carrier rate is 1:5^{15,51,80,92}. With a population of more than 67 million inhabitants, therefore, a large proportion of all the FMF cases in the world live in Turkey. The Turkish FMF Study Group (FMF-TR) was founded in May 2000 to delineate better the demographic, clinical, and genetic features of FMF in a large cohort.

PATIENTS AND METHODS

Turkish FMF Study Group

Data used for this analysis were obtained from the Turkish FMF Study Group patient registry database generated after all potential FMF referral centers (28 medical schools, 6 major district hospitals, and 7 related medical associations) were invited to join the group. Thirty-five departments in 19 medical schools and 3 hospitals covering internal medicine and pediatrics participated. The centers were located mainly in western and central Turkey, while most of the patients were referred from Ankara, Istanbul, and Izmir. Although this was essentially a retrospective study, participating centers were all encouraged to review and update their patient files.

Genetic Analysis

DNA analyses were done mainly at 6 centers in Turkey, along with genetic institutions in the United Kingdom, France, Israel, and the United States. DNA was isolated from peripheral blood lymphocytes by standard procedures and amplified with sequence-specific primers using the polymerase chain reaction (PCR) technique. Depending on the laboratory, denaturing gradient gel electrophoresis (DGGE), PCR/RFLP, amplification of refractory mutation system (ARMS), and DNA sequencing methods were used to screen for MEFV gene mutations^{1,9}.

The first 3 mutations, M694V, M680I, and V726A, were available in 1090 patients. The following mutations

had been tested in a small group of patients only: E148Q, M694I, R761H, K695R, E148V, and P369S. Since the data sources were inhomogeneous, they were exempt from further analysis.

Registration of Patients, Inclusion Criteria, and Data Collection

The Turkish FMF Study Group patient registry form (available on request) was transformed into a standardized computer database program and distributed to participating institutions, and data were collected in 1 center by electronic communications. Each individual patient file was reviewed using Tel Hashomer diagnostic criteria for definite diagnosis of FMF⁵⁵. These and other definitions are summarized in the Table of Definitions (Appendix 2).

Data collection was completed in December 2001, and 3047 cases were pooled. Patients not definitely fulfilling the diagnostic criteria (73 cases) and repeated entries (136 cases) were excluded from the registry, with the final analysis performed on 2838 patients.

Statistics

We used SPSS for Windows v. 10.0 (SPSS Inc, Chicago, IL), and results are expressed as mean \pm standard deviation (SD) for continuous variables and ratios for categorical variables. Means of the groups were compared with the Student t-test and 1-way ANOVA test, while categorical variables were evaluated with the chi-square test. To assess the risk of developing amyloidosis, the odds ratio was calculated using a general log-linear model. For comparisons, $p < 0.05$ was accepted as significant.

RESULTS

Demographic features of patients and temporal relations to diagnosis are shown in Table 1 and Figure 1. There was no significant difference in the diagnostic delay among patients with early (before the age of 18 years) versus late

TABLE 1. Demographic Features of the Study Group (SD) (n = 2838)

Mean age (yr)	23 (range, 2–87)
Male:female	1541:1297 (1.2:1)
Mean age at disease onset (yr)	9.6 (8.55)
Mean age at diagnosis (yr)	16.4 (11.57)
Mean delay to diagnosis (yr)	6.9 (7.65)
Mean delay according to year of diagnosis (in years)	
<1981 (n = 73)	10.2 (9.77)*
1981–1991 (n = 422)	7.8 (8.60)**
1992–2001 (n = 2119)	6.3 (7.32)***

*vs **p < 0.05; *vs ***p < 0.005; **vs ***p < 0.005

disease onset (data not shown). When we reassessed this parameter among patients diagnosed before 1981, between 1981 and 1991, and from 1992 onwards, we found an average of 2 years' improvement in each decade analyzed. (The delay to diagnosis was 2 years shorter in each successive decade.) These differences were statistically significant for each of the 3 groups (see Table 1).

Ninety-four percent of patients were recruited from centers within central-western parts of the country. When the data were analyzed with regard to patients' paternal and maternal origins, however, a different pattern of distribution was obtained: 70% had originated from central-eastern and Black Sea regions. The consanguinity rate was 24%, highest in central Anatolia (26%) and lowest in the Aegean region (15%). This rate is similar to the overall consanguinity rate in Turkey⁸².

Clinical Characteristics

The frequencies of the main characteristics of the disease are shown in Table 2. The only finding with significant gender difference was erysipelas-like erythema (Figure 2): 318 of 1378 male patients (23.1%) and 212 of 1154 female patients (18.4%) had documented erysipelas-like erythema ($p < 0.01$). Appendectomy was the leading abdominal operation (504 of 2647 patients, 19%), followed by cholecystectomy (1.6%). The main clinical features are presented along with data from 3 other major ethnic groups in Table 3.

We compared clinical and genetic characteristics of patients with early versus late onset of disease (before or after 18 yr). Arthritis, arthralgia, myalgia, and erysipelas-like erythema were significantly more frequent ($p < 0.001$) among the early-onset subgroup (Table 4). Eighteen patients had disease onset after the age of 40 years.

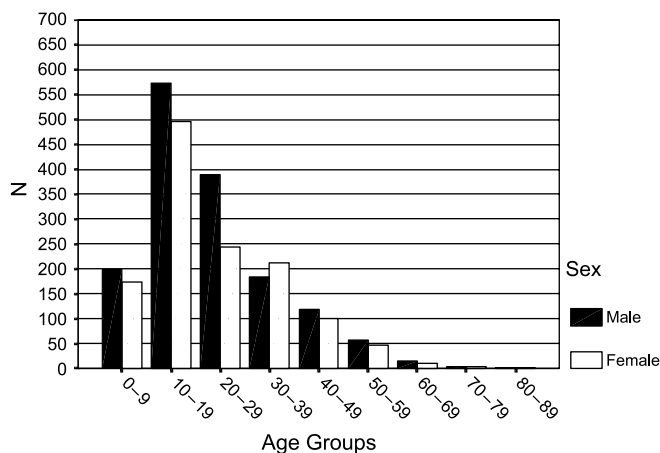


FIGURE 1. Age distribution of patients in the study group (n = 2838).



FIGURE 2. Erysipelas-like erythema in a patient with familial Mediterranean fever.

Arthritis and Other Musculoskeletal Features

Overall, 2002 (72.1%) of patients had musculoskeletal features (see Table 4). The male:female ratio of these patients was 1083:917 (1.2:1). The mean age of disease onset was 8.8 (± 7.79) yr, which was younger than patients without these features ($p < 0.05$). Musculoskeletal findings were increased among patients who had more frequent attacks, amyloidosis, and poor response to colchicine ($p < 0.05$). When patients with arthritis were analyzed separately, they had younger age of onset, more erysipelas-like erythema and more myalgia, and were more frequently associated with vasculitis than those without arthritis ($p < 0.05$). Sixty-four patients had spondylarthritis.

Pericarditis

Of the 2468 patients with sufficient data in the registry, 60 (2.4%) patients had at least 1 attack of pericarditis during their disease course: 34 had definite (positive clinical and laboratory findings) and 26 had probable pericarditis (diagnosis based on clinical findings only). Recurrent pericarditis was the initial and only manifestation of FMF in 2 patients in whom the diagnosis was supported by genetic analysis. In all patients except 2, the pericardial attacks resolved spontaneously. Urgent pericardiocentesis due to pericardial tamponade in 1 patient and pericardiectomy for the treatment of constrictive pericarditis in the other were required.

Amyloidosis and Renal Involvement

Data were available from 2436 cases to evaluate the frequency and characteristics of renal involvement. Among these patients, 316 (12.9%) had biopsy-proven amyloidosis. Demographic and clinical details of patients with and with-

TABLE 2. Clinical Features of Patients in the Study Group (n = 2838)

Clinical Feature	Present	Absent	“Unknown”/ Data Missing	No. of Patients with Data Available	Percentage Present (of Patients with Data Available)
Fever	2603	157	53/25	2813	92.5
Peritonitis	2635	143	33/27	2811	93.7
Pleuritis	816	1710	89/223	2615	31.2
Arthritis	1264	1342	62/170	2668	47.4
Arthralgia	1190	1102	104/241	2597	49.7
Erysipelas-like erythema	530	1952	50/306	2532	20.9
Myalgia	1028	1449	120/241	2597	39.6
Protracted febrile myalgia	57	2415	60/306	2532	2.3
Protracted arthritis	71	2591	43/133	2705	2.6

out amyloidosis are shown in Table 5. Delay in diagnosis of FMF (9.4 ± 8.60 yr vs. 6.3 ± 7.14 yr) and positive family history of amyloidosis (78/203, 38%, vs. 142/1679, 8%) significantly increased the risk of development of amyloidosis (odds ratio, 4.54; $p < 0.001$). Five of the 18 patients who had experienced their first attack after 40 years of age developed amyloidosis. Presentation of the patients with amyloidosis at diagnosis included asymptomatic proteinuria (n = 99), nephrotic syndrome (n = 123), and renal failure (n = 88). Seventy-five patients were on dialysis: 58 on hemodialysis and 17 on peritoneal dialysis. Renal transplantation was performed on 14 patients, 3 of whom had posttransplant recurrences. Twenty-two patients (0.8%) had nonamyloid glomerular diseases (Table 6), 4 of whom also had renal amyloidosis.

Phenotype II

Nine patients presented with amyloidosis before the onset of clinical symptoms of FMF (“phenotype II”). Five of these had family members with FMF, 2 others were positive for M694V, and in the remaining 2, classical attacks started after the diagnosis of amyloidosis. One of the patients, who was found to be M694V homozygous, also

had HLA-B27-negative ankylosing spondylitis. Genetic analysis was performed in 4 of these 9 patients: 2 were found to be M694V homozygotes, 1 was a carrier of M694V, and no mutation was detected in the fourth.

“FMF-Associated” Diseases

Patient files were reviewed for previous diagnoses of certain diseases that may be associated with FMF^{36,49}. Overall, 377 of 2716 patients had such notations; the frequencies of these diseases are shown in Table 7. There were 235 males and 142 females for a ratio of 1.65:1, and the mean age of onset of FMF was 10.2 ± 8.18 years. The clinical and genetic features of this subgroup were compatible with the main study population.

Response to Colchicine

All but 2.4% of patients had been prescribed colchicine, with 80% reporting regular use of the drug, 17% irregular use, and 0.6% during attacks only. Among the 2258 patients with available data, 51.2% had complete response, 46% had occasional attacks despite colchicine, and 2.8% were nonresponsive. The response rates (frequency and duration of FMF attacks before and after colchicine treatment) of patients using the drug regularly are demonstrated in Figure 3. Both the frequency and duration of attacks were significantly reduced after colchicine ($p = 0.000$).

Distribution of MEFV Mutations

Mutation analysis was available in 1090 patients. The leading mutation was M694V, seen in 51.4% (1121/2180), followed by M680I in 14.4% (313/2180), and V726A in 8.6% (188/2180). These 3 major mutations were searched for in every genotyped patient. For the evaluation of phenotype-genotype correlation, the patients were divided into 4 groups: patients homozygous for M694V (n = 306), homozygous for M680I (n = 42), simple and compound heterozygous for

TABLE 3. Clinical Features of Study Group Patients in Percentages Compared with Other Ethnic Groups

	Turks (PR)	Jews (ref. 71)	Arabs (ref. 58)	Armenians (ref. 66)
No. of patients	2838	470	192	100
Fever	92.5	100	100	100
Peritonitis	93.7	95	82	96
Pleuritis	31.2	40	43	87
Arthritis	47.4	77	37	37
Erysipelas-like erythema	20.9	46	3	8

Abbreviations: PR, present report.

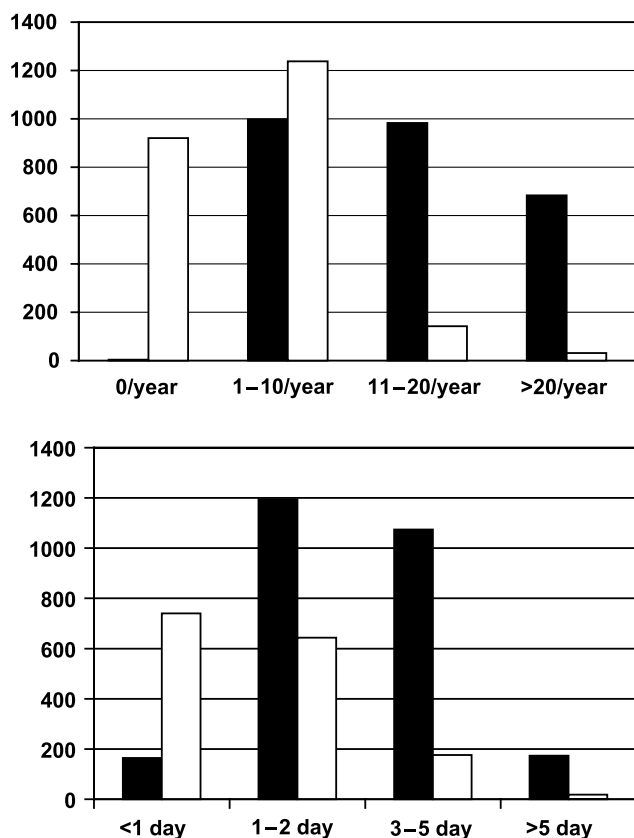


FIGURE 3. Frequency (per year) and duration (in days) of FMF attacks before and after colchicine. Black bar = precolchicine; white bar = postcolchicine; Y axis = number of patients.

M694V (n = 509), and patients without M694V mutation plus those in whom none of the investigated mutations could be found (n = 233). Patients with the M694V/M694V genotype were found to have an earlier age of onset and higher frequency of arthritis and arthralgia compared with the other groups (p < 0.001 and p < 0.001, respectively). There were no statistically significant differences between the groups for other clinical features including fever, abdominal pain, erysipelas-like erythema, and the development of amyloidosis.

DISCUSSION

To our knowledge, this multicenter study is the largest series of FMF patients reported from 1 country. Since the estimated prevalence of the disease in Turkey is 0.1%^{15,51}, this cohort is about 5% of the total number of FMF cases in the country. Most of the medical schools and referral hospitals of the country were part of the study group, hence this low rate may indicate that many patients remain undiagnosed and that mild forms of the disease may exist without being identified.

The relatively large number of patients recruited from various geographic regions and a wide range of subspecialty clinics may have helped to minimize referral bias. The large number of cases facilitated our ability to disclose more rare forms, and presentations of the disease such as pericarditis, nonamyloid renal involvement, and amyloidosis complicating late-onset FMF were magnified.

The results of the current analysis are in agreement with our preliminary observations that patients with FMF originate mainly from the non-Mediterranean regions of Turkey^{48,79,90}. Eighty-six percent of the patients were born in 1 of the 3 major provinces located in the central and western parts of the country. However, when the parental origins were considered, over 70% of the cases originated from central and eastern Anatolia and inner Black Sea regions. The intense migration of people from east to west Turkey, and the scarcity of centers from eastern and southeastern regions among the Turkish FMF Study Group participants might help to explain these discrepancies. No such patient-parent discrepancies were observed with respect to their origins among other control groups^{79,90}. Likewise, the Black Sea region was underrepresented with only 1 participating center, but a quarter of the parents originated from this region.

Not unlike results found in other ethnic groups, M694V was the leading mutation in the Turkish FMF Study Group patients. The M680I mutation, which is notably rare among Jews and relatively more prevalent in Armenians and Arabs, was the second most common mutation in our patients. Several investigators have observed an earlier age of onset, higher frequency of arthritis, and higher prevalence of amyloidosis in M694V homozygous patients^{3,10,12,14,21,30,35,39,45,64,68}. Although our data to this

TABLE 4. Clinical Features Relative to Age at Disease Onset*

Clinical Feature	Age at Disease Onset <18 yr (%)	Age at Disease Onset >18 yr (%)	p Value	X ²
Arthritis	1120/2165 (51.7)	105/388 (27.1)	<0.001	0.000
Arthralgia	987/1908 (51.7)	149/373 (39.9)	<0.001	0.000
Myalgia	879/2115 (41.6)	112/368 (30.4)	<0.001	0.000
Erysipelas-like erythema	478/2044 (23.4)	39/376 (10.4)	<0.001	0.000

*Denominators are number of patients with data available.

TABLE 5. Demographic Features of Patients With and Without Amyloidosis (n = 2436)

	Patients With Amyloidosis (n = 316)	Patients Without Amyloidosis (n = 2120)	p Value
Male:female	178:138 (1.28)	1152:968 (1.19)	NS
Mean age at onset of symptoms, yr (SD)	9.6 (8.07)	8.9 (8.28)	NS
Mean age at diagnosis, yr (SD)	19.2 (11.84)	15.2 (11.05)	<0.001
Delay in diagnosis of FMF, yr (SD)	9.4 (8.60)	6.3 (7.14)	<0.001
Family history of FMF	102/316 (32%)	716/2120 (34%)	NS
Family history of amyloidosis	78/203 (38%)	142/1679 (8%)	<0.001

Abbreviations: NS, not significant.

point are consistent with previous findings, the results regarding amyloidosis were contradictory to those of several other studies. Historically, the risk for amyloidosis has been considered to be unequally dispersed among various ethnic groups; even people with similar ethnic backgrounds living in different environments were found to harbor different risk rates⁵⁴. Although most previous genetic studies showed that M694V was the leading locus of risk for developing amyloidosis, patients with mutations other than M694V would still be prone to this complication^{8,64,86}. Besides, 2 major studies from Turkey had not demonstrated an association between the development of amyloidosis and M694V homozygosity^{76,88}. More recently, an increased risk of amyloidosis among M694V homozygotes has been reported by 2 different Turkish groups^{65,91}. The development of amyloidosis secondary to FMF seems not to be explained only by the presence of any particular known genotype. Some other determinants such as environmental factors and modifier genes may have additional effects^{2,11,62,78}. When a sufficient number of FMF patients with different ethnic backgrounds have been evaluated, the genetic basis of the relationship between FMF and amyloidosis will be better understood.

It is generally accepted that late-onset FMF has a milder clinical picture, which implies less inflammatory burden, and hence a lower risk of amyloidosis^{61,72}. However, 5 of our 18 patients with a disease onset after age 40 years had amyloidosis. Mild clinical presentation may be misleading, as FMF patients may have “subclinical” inflammation during the attack-free intervals^{32,46,81}. Another possible explanation for this rather unexpected finding may be that in several patients who had purely arthritic attacks during childhood, the disease may have remained undiagnosed (or been misdiagnosed as juvenile chronic arthritis or acute rheumatic fever), and thus the patients were deprived of colchicine treatment. An even more important clinical implication of this observation would be that the severity of the disease course and development of amyloidosis may not be uniformly concordant.

This peculiarity may also be another difficulty of defining “phenotype II” cases. The classical description of phenotype II is a patient with a positive family history of FMF, who has developed AA-type amyloidosis without experiencing clinical features of the disease¹⁷. Genetic

TABLE 6. Renal Pathology of 22 Patients With Nonamyloid Glomerular Diseases

	No. of Patients (n = 22)
Mesangiocapillary glomerulonephritis	6 (2 with amyloidosis)
Mesangial proliferative glomerulonephritis	6 (1 with amyloidosis)
Diffuse endocapillary proliferative glomerulonephritis	5
Focal glomerular sclerosis	1
Membranous glomerulonephritis	1
IgA nephropathy	1
Polyarteritis nodosa	2 (1 with amyloidosis)

TABLE 7. Frequency of Diseases That May Be Associated With FMF

	No. of Patients (%)*	M:F
Henoch-Schönlein purpura	75 (2.7)	53:22
Polyarteritis nodosa	24 (0.9)	12:12
Behçet syndrome	14 (0.5)	7:7
Chronic inflammatory arthritis	37 (1.3)	16:21
Systemic lupus erythematosus	4 (0.1)	0:4
Acute rheumatic fever	139 (5)	100:39
Seronegative spondylarthritis	64 (2.3)	36:28
APSGN	10 (0.4)	5:5
Uveitis	6 (0.2)	3:3
Inflammatory bowel disease	4 (0.1)	3:1

Abbreviations: APSGN, acute poststreptococcal glomerulonephritis.
*Percentage of 2716 patients with data available.

analysis would strengthen the clinical diagnosis of phenotype II to a certain extent, but would still be inconclusive, as there are a substantial number of FMF patients with no demonstrable mutations, while some of the asymptomatic relatives may be homozygous or compound heterozygous (so-called phenotype III cases)^{4,29,80}. Among our patients, 9 patients had a probable diagnosis of phenotype II (0.3%), and 4 of them were genotyped. Besides the 2 patients with 2 mutations, 1 was a carrier, and none of the 3 common mutations was detected in the other. We propose that patients with AA amyloidosis without a predisposing disease can be classed as phenotype II if they have other family members with FMF, and/or 2 MEFV mutations, and/or develop classical FMF attacks after the diagnosis of amyloidosis. A final note regarding its prevalence is that phenotype II seems to be quite rare^{31,34,35,43}.

Although amyloidosis was less prevalent than expected among Turkish M694V homozygotes, its prevalence was alarmingly high in the whole group (12.9%). This rate may be a reflection of the delay in diagnosis and/or inadequate colchicine therapy. On the other hand, many mild cases may have remained undiagnosed, and thus severe cases carrying a higher risk of amyloidosis may have been over-represented. If the above ratio was applicable to all the FMF patients in the country, several thousand cases of AA amyloidosis would be expected to exist; therefore, a referral bias cannot be excluded. Together with a delayed diagnosis of FMF, positive family history of amyloidosis was an important risk factor for the development of amyloidosis in our patients (odds ratio, 4.54). This was originally observed by 2 different Turkish groups, 1 of which showed that a family history of amyloidosis was associated with an odds ratio of 2.4 for the development of amyloidosis in the proband^{62,89}.

Twenty-two patients had nonamyloid glomerular disease in the current series. Indeed, it was reported that patients with FMF are prone to exhibit a variety of glomerular lesions other than amyloidosis. An important source of confusion is the interpretation of persistent albuminuria as a sign of amyloidosis without any histologic proof. The actual frequency of nonamyloid glomerular lesions depends largely on the number of kidney biopsies performed in patients with abnormal urinary findings^{63,74,87}.

Another important observation is that some patients experience occasional attacks of FMF despite colchicine treatment. Although colchicine is a very effective drug in treating FMF and is unique in preventing the development of amyloidosis, novel therapeutic supplements are needed to alleviate these unpredictable and incapacitating attacks.

The association of Henoch-Schönlein purpura and polyarteritis nodosa with FMF is well established; early reports date back to the 1950s^{6,19,49,50}. The prevalence of Henoch-Schönlein purpura is estimated as 2.7/100 and of

polyarteritis nodosa as 9/1000 among this study group. These figures are significantly higher than the prevalence reported in the general population, which is 8/1000 for Henoch-Schönlein purpura and 6/100,000 for polyarteritis nodosa⁴⁴. No male predilection but a younger age of onset was observed in this FMF-related vasculitis group when compared with patients with classical polyarteritis nodosa, which is a disease of the fifth decade and older. We propose that FMF should be included in the list of etiologic factors described for these vasculitides, especially in populations at high risk for FMF. Indeed, it was also shown that most children with FMF-associated vasculitis have identifiable mutations in the MEFV gene^{23,75}. Fourteen FMF patients were reported to have coexisting Behçet syndrome among the current study population (5/1000), which was not different from the overall prevalence in Turkey⁹². No case of Behçet syndrome was detected in children aged younger than 16 years in another epidemiologic study from Turkey, but 3 of the 14 patients in the current study were aged younger than 16 years⁵¹. Authors have reported that the concomitant occurrence of Behçet syndrome and FMF was much higher than expected in the general Israeli population, and have suggested that MEFV mutations may serve as susceptibility factors in this syndrome^{67,77}. The possible association between FMF and Behçet syndrome, however, is not as clear as the association with Henoch-Schönlein purpura and polyarteritis nodosa. The reported concurrence may be related simply to the ethnic origin of the patients or may reflect a true disease association⁵. Without properly designed studies, it is difficult to draw a definite conclusion.

The frequency of acute rheumatic fever was high in our FMF population (4.9%). We believe most of these retrospective data on acute rheumatic fever reflect true FMF arthritis attacks. This is implied by the high rate of amyloidosis among these patients. Many of these patients may have been diagnosed erroneously as having acute rheumatic fever, and thus received only penicillin prophylaxis while the initiation of colchicine was delayed. Although the predisposition to have acute rheumatic fever is more likely multifactorial or may be polygenic, a 2002 study⁸⁴ revealed that the frequency of an MEFV mutation in patients with rheumatic carditis or rheumatic heart disease was 4 times greater than in the estimated frequency of normal population. This noteworthy finding deserves attention because of the possible relationship between acute rheumatic fever and FMF. Pediatricians practicing in the eastern Mediterranean should be aware that FMF may present solely with attacks of arthritis, and they should consider FMF in the differential diagnosis of acute rheumatic fever. To elucidate the true incidence of acute rheumatic fever in patients with FMF, a future genetic study addressing this question should enroll patients with rheumatic carditis.

The incidence of acute appendicitis is about 0.1% and probably declining^{33,47,85}. The positive history of appendectomy (19%) in the young population of the current study is relatively high, suggesting that many of these patients may have been operated on unnecessarily. At least 2% of patients with acute abdomen seen in the emergency ward of a major hospital in Istanbul were found to be definite FMF cases⁴¹.

Pericardial involvement is a rare manifestation of FMF. It is usually accompanied by other features of the disease. Pericardial attacks subside spontaneously in almost all patients without sequelae. Although the occurrence of pericarditis in FMF has been the subject of several case reports, pericardial involvement has not been reported in large FMF series in the past^{16,18,21,57,70,71,73,83,94,96}. In the largest study to date²⁸, authors reevaluated pericardial involvement in 1553 thoracic attacks of 3976 FMF patients and clearly showed that pericarditis did occur as a manifestation of FMF, with a prevalence of 0.7%. The prevalence of definite pericardial involvement in the current study was 1.4%. Although this is 2 times greater than that of the aforementioned study, pericarditis is still a relatively uncommon manifestation in our patients, compared to other forms of serositis.

The current study inevitably bears the drawbacks of retrospective data collection. Although the participating centers were encouraged to update their patient files, and 2119/2838 (74.7%) of the patients were diagnosed during the last decade (see Table 1), these measures probably are not sufficient to overcome the negative impact of retrospectively obtained data. Moreover, there are still some general problems of describing certain characteristics and aspects of FMF, such as disease severity, response to colchicine, and "phenotype II." These problems are further accentuated in a study such as this, when numerous centers pool their data. Likewise, the data on the presence of other diseases may have several sources of bias, and should be considered with caution. Centers may be prone to recruit and report patients with more than 1 pathology. In addition, some of the other diseases may have been diagnosed elsewhere, raising the question of the relevance of the available data. This shortcoming was particularly evident in cases with a previous diagnosis of acute rheumatic fever. The overlapping features of diseases, especially arthritis, may cause diagnostic inaccuracy.

Almost 60 years after being fully recognized as a disease, FMF is explored mainly at the molecular level now. Nevertheless, several clinical topics require in-depth clarification. In addition to the above-mentioned shortcomings, the follow-up of pregnant patients on colchicine, the relevance of "subclinical" inflammation as an accelerator of atherosclerosis in FMF, and the assessment of elderly FMF patients who use other drugs along with colchicine are a few of the issues demanding well-controlled prospective studies.

Conclusion

To our knowledge, this is the largest FMF population reported from 1 country so far. With this study population, we can provide a general description of the disease in the Turkish population, and we have a sufficient number of patients displaying rare clinical characteristics to study in detail. The data reveal some interesting characteristics of FMF and show us that amyloidosis is still a considerable problem among our patients; even those with a disease onset after age 40 years are not free from this risk. While exciting knowledge is emerging from laboratory investigations of the pathogenetic mechanisms of FMF, prospective clinical studies with sufficiently large numbers of patients and different ethnic groups will help us understand better this noteworthy disease.

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APPENDIX 2: LIST OF DEFINITIONS

Tel-Hashomer Criteria for Diagnosis of FMF⁵⁵

Major Criteria:

1. Recurrent febrile episodes accompanied by peritonitis, pleuritis, or synovitis
2. Amyloidosis of AA-type without predisposing disease
3. Favorable response to continuous colchicine treatment

Minor Criteria:

1. Recurrent febrile episodes
2. Erysipelas-like erythema
3. Positive history of FMF in a first-degree relative

Definite Diagnosis: 2 major criteria or 1 major and 2 minor criteria

Probable Diagnosis: 1 major and 1 minor criterion

Pericarditis

Probable Diagnosis: Presence of retrosternal typical pericardial chest pain and/or pericardial friction rub observed and documented by a physician

Definite Diagnosis: Chest radiographic and/or electrocardiographic and/or echocardiographic documentation in addition to clinical signs

Protracted Arthritis

Arthritis with duration longer than 4 weeks

Protracted Febrile Myalgia

Severe muscle pains with duration up to 6 weeks accompanied by high fever

Phenotype II

A patient fulfilling any one of the following definitions:

1. Biopsy-proven AA amyloidosis without prior symptoms of FMF, or a predisposing disease, in a patient with a positive family history of FMF
2. Classical FMF attacks appearing after biopsy-proven AA amyloidosis
3. Biopsy-proven AA amyloidosis plus presence of 2 mutations

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