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Original Article RHEUMATOLOGY

Clinical features, functional status, and quality of life in patients with late-onset familial Mediterranean fever

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ABSTRACT

OBJECTIVE: This study aimed to determine the frequency of late-onset familial Mediterranean fever (FMF) and compare the clinical and genetic features, functional status, and health-related quality of life (QoL) of patients with early-onset and late-onset disease.

METHODS: Patients with onset of symptoms ≤20 and >20 years of age were classified as early-onset and late-onset FMF, respectively. The clinical characteristics, MEFV gene mutations, and Pras disease severity scores were recorded. Physical disability and QoL were assessed with the health assessment questionnaire (HAQ) and short form 36 (SF-36), respectively.

RESULTS: The mean age of 138 patients (104 women and 34 men) was 37.7±12.69 years. The percentages of patients with early- and late-onset FMF were 68.1% and 31.9%, respectively. Female sex, mild disease, arthritis, and sacroiliitis were more common in the late-onset group ($p<0.05$). The delay in diagnosis was shorter in the late-onset disease group ($p<0.001$). The percentage of homozygous M694V mutations was lower in late-onset disease ($p=0.015$). There were no differences in HAQ and SF-36 scores between early- and late-onset diseases ($p>0.05$).

CONCLUSION: The patients with late-onset FMF had a female predominance, a shorter delay of diagnosis, more frequent arthritis and sacroiliitis, a less frequent homozygous M694V mutation, and a milder disease severity than those with early-onset disease. Physical function and health-related QoL were similar in early- and late-onset FMF groups.

Keywords: Disease activity; familial Mediterranean fever; functional status; quality of life.

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Familial Mediterranean fever (FMF) is a disease characterized by recurrent, self-limiting episodes of fever, peritonitis, pleuritis, arthritis, and erysipelas-like erythema with autosomal recessive inheritance. Patients are usually asymptomatic between attacks. It predominantly affects people from the Mediterranean region and is the most frequent autoinflammatory disease [1–5].

Another feature of FMF is its predominance in young patients. The first attack occurs in approximately 60% of patients before the age of 10 years, 90% before the age of 20 years, and in the majority of the rest before the age of 40 years. The disease may occur after the age of 40, but it is rare [4]. In 0.5–2% of FMF patients, symptoms occur after the age of 40 years with a milder disease phenotype [6, 7].

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The age of onset may be an important prognostic factor related to the clinical features and course of FMF disease. However, there are conflicting reports regarding the disease activity, attack characteristics, response to colchicine treatment, prognosis, and genetic characteristics of late-onset FMF disease [6–15]. These studies include data from different populations and variable cut-offs used in the definition of early- or late-onset disease. However, to the best of our knowledge, there are currently no data comparing early- and late-onset FMF patients regarding health-related quality of life (QoL) and functional status.

This study aimed to (1) identify the frequency of late-onset FMF disease; (2) evaluate the demographic, clinical, and genetic characteristics of patients with late-onset FMF; and (3) compare the functional status and health-related QoL of patients with early- and late-onset FMF.

Highlight key points

- Late-onset FMF disease may be a distinct subtype with some different clinical features from early-onset FMF disease.
- The patients with late-onset FMF had milder disease severity with less frequent homozygous M694V mutation.
- Physical function and health-related quality of life were similar in patients with early- and late-onset FMF.

MATERIALS AND METHODS

Study Design and Cohort

This cross-sectional study included 138 patients with FMF who were diagnosed according to the Livneh criteria [16]. Patients from the outpatient clinic of the Rheumatology Division were consecutively included in the study between July 2019 and December 2020. The exclusion criteria for the study were being illiterate and being younger than 18 years of age.

The study was approved by the Ethical Committee of the Marmara University Faculty of Medicine (insert number: 09.2019.664; date of approval: 26/07/2019) and conducted in accordance with the Helsinki Declaration. Informed consent was obtained from all the participants.

Demographic and Clinical Variables

Data on age, sex, family history of FMF and amyloidosis, disease duration (months), age at symptom onset, age at diagnosis, delay in diagnosis (years), comorbidities, and medications were recorded. The final colchicine dosage, compliance with the colchicine treatment, and colchicine resistance were recorded. Having at least one attack per month at the maximally tolerated dose for 6 months was accepted as colchicine resistance [17]. The frequency, duration, and characteristics of attacks, the presence of amyloidosis, and elevated attack-free acute phase reactants (APR) were also assessed. An increase in erythrocyte sedimentation rate, C-reactive protein, and serum amyloid A levels between attacks was accepted as an elevated attack-free APR. The MEFV gene mutations were recorded. According to the Pras severity score, ≤5 points were classified as a mild disease, 6–10 points as moderate, and ≥10 points as a severe disease of FMF [18].

Patients with onset of symptoms ≤20 and >20 years of age were classified as early-onset and late-onset FMF, respectively. The cut-off selection for the definition of early- and late-onset FMF was chosen to reflect the current literature on FMF [11, 13].

The short form 36 (SF-36) and health assessment questionnaire (HAQ) were used to assess health-related QoL and physical disability in patients with FMF, respectively [19–22].

Statistical Analysis

Descriptive data are expressed as mean, median, standard deviation, min–max, and frequency. Comparisons of categorical variables were done using Chi-square and Fisher's exact tests. Mann-Whitney the U test was used to assess the difference between continuous variables without normal distribution, and results are presented as median (25–75%) values. Statistical significance was set at $p<0.05$. Statistical Package for the Social Sciences (SPSS) Statistics (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) was used for statistical analysis.

RESULTS

The mean age of 138 patients (104 women and 34 men) with FMF was 37.7±12.69 years. The mean duration of the disease was 192.21±150.44 months. The percentage of patients with onset of symptoms ≤20 years old (early onset FMF) was 68.1% (n=94), and those >20 years old (late-onset FMF) was 31.9% (n=44). In 5.8% of the patients (n=8), symptoms started at age ≥40 years. The features of patients are given in Table 1.

Table 1. Demographic and clinical characteristics of the participants

Gender (n, %)	
Female	104 (75.4)
Male	34 (24.6)
Age (mean±SD)	37.7±12.69
Body mass ındex, kg/m^2, (mean±SD)	26.31±5.32
Family history of FMF (n, %)	94 (68.1)
Family history of amyloidosis (n, %)	10 (7.2)
Pras (disease severity score) (%)	
Mild	52.9
Moderate	39.9
Severe	7.2
Duration of disease, months, (mean±SD)	192.21±150.44
Age at symptom onset, year, (mean±SD)	17.90±12.06
Age at diagnosis, year, (mean±SD)	29.05±13.59
Delay in diagnosis, year (median, min–max)	6 (0–50)
Early onset FMF (symptoms onset ≤20 age) (%)	68.1
Adult onset FMF (%)	31.9
Symptoms onset 20–40 age	26.1
Symptoms onset ≥40 age	5.8

SD: Standard deviation; FMF: Familial Mediterranean fever.

The percentage of women in the early- and late-onset disease groups was 70.2% and 86.4%, respectively (p=0.040). The mean ages of patients with early- and late-onset FMF were 34.94±12.39 and 43.68±11.32, respectively (p<0.001). The median (min–max) delay in diagnosis was 12 years (0–50) and 2 years (0–29) in the early- and late-onset disease groups, respectively (p<0.001). Family history of FMF and amyloidosis was not different between early- and late-onset FMF (p=0.687 and p=0.077, respectively).

The attack frequency was not different in the early- and late-onset disease groups (p=0.896). The most common symptoms during the attack were fever and abdominal pain in both groups. The percentages of arthritis and sacroiliitis were significantly higher in patients with late-onset FMF (p=0.026 and p=0.037, respectively). Other FMF-related manifestations were similar between early- and late-onset FMF (p>0.05). Henoch-Schönlein purpura was detected in only one patient with late-onset FMF. According to the Pras disease severity score, the percentage of patients with mild disease was higher in the late-onset disease group (77.3%, p<0.001). The final colchicine dosage, compliance with colchicine treatment, presence of colchicine resistance, and elevated attack-free APR were similar in the early- and late-onset disease groups (p>0.05). FMF-related amyloidosis was present only in three patients with early-onset FMF. Comparisons of the clinical and demographic features of the patients between early- and late-onset FMF are given in Table 2. The percentage of M694V gene mutations was significantly lower in the late-onset disease group (p=0.040). The distribution of MEFV gene mutations is given in Table 3.

There were no significant differences in HAQ and SF-36 scores between early- and late-onset FMF groups (p>0.05) (Table 4).

DISCUSSION

Although some evidence suggests that late-onset FMF is a distinct subtype with a milder disease course, the results of these studies are conflicting. The present study identified the frequency of late-onset FMF disease and its demographic, clinical, and genetic features, as well as the functional status and health-related QoL of early-onset versus late-onset FMF patients.

We found that the percentage of patients with onset of symptoms >20 years of age (late-onset FMF) was 31.9%. Similarly, previous studies reported that disease started before the age of 20 in approximately 70% of FMF patients [11, 13]. In 5.8% of patients in our study, the age at onset of symptoms was ≥40 years of age, which was higher than expected. The rate of patients with FMF symptoms starting after the age of 40 was between 0.5% and 3.40% in previous studies, which is lower than the results of our study [6–8, 12, 15].

In the current study, there was a predominance of women in both subgroups, and the percentage of women was higher in the late-onset disease group. However, in previous studies, no difference has been reported in gender distribution between early- and late-onset disease groups [8–10, 13]. In another study, patients with the first attack after the age of 40 were more often female [12]. On the other hand, the different studies on FMF from Turkiye found the female-male ratio to be 1.9:1 and 1:1.2 [15, 23]. The present study's finding of female predominance in late-onset FMF needs to be confirmed in larger epidemiologic studies.

In the present study, the delay in diagnosis and duration of disease were significantly shorter in the late-onset disease group. The previous studies also re-

Table 2. Comparison of demographic and clinical features in early and late-onset FMF patients

	Early-onset disease (n=94)	Late-onset disease (n=44)	p
Age, median (range)	36 (23–45)	41 (35–53.5)	<**0.001**
Gender, (%)			**0.040**
Female	70.2	86.4	
Male	29.8	13.6	
Family history of FMF, (%)	67.0	70.5	0.687
Family history of amyloidosis, (%)	10.6	0.0	0.077
Disease duration (months), median (range)	204 (96–324)	73.5 (48–180)	<**0.001**
Age at diagnosis, median (range)	23 (14–38.2)	34.5 (26.5–43.5)	<**0.001**
Age at symptom onset, median (range)	11 (7–15)	30 (24.2–36.7)	<**0.001**
Delay in diagnosis (years), median (range)	12 (2–23.2)	2 (0–5)	<**0.001**
Attack frequency in last 6 months, median (range)	2 (0–4)	1.5 (0–4)	0.896
Attack duration (days), median (range)	2 (1–3)	2 (1–3)	0.254
Clinical findings, (%)			
Fever	84.0	70.5	0.064
Abdominal pain	90.4	90.9	0.928
Chest pain	34.0	36.4	0.790
Arthralgia	31.9	38.6	0.437
Myalgia	30.9	20.5	0.203
Arthritis	7.4	20.5	**0.026**
ELE	1.1	4.5	0.238
Headache	11.6	20.5	0.182
Leg pain	20.2	13.6	0.350
PFM	4.1	6.9	0.621
PA	0	0	–
Sacroiliitis, (%)	4.3	15.9	**0.037**
Final colchicine dosage (mg/day), median (range)	1.5 (1–1.5)	1.5 (1–1.5)	0.587
Compliance with colchicine treatment, (%)	83.0	90.9	0.217
Colchicine resistance, (%)	15.2	11.6	0.576
Elevated attack free AFRs, (%)	31.2	23.3	0.342
Amyloidosis, (%)	4.1	0	0.551
Pras severity score, (%)			<**0.001**
Mild	41.5	77.3	
Moderate	47.9	22.7	
Severe	10.6	0.0	

FMF: Familial Mediterranean fever; ELE: Erysipelas-like erythema; PFM: Protracted febrile myalgia; PA: Protracted arthritis; AFR: Acute phase reactant. Continuous variables were given as median (25–75%) values. Significant p-values were presented in bold.

ported similar results [9–11, 13]. The shorter delay in diagnosis in the late-onset FMF group may be because adult patients notice new symptoms more easily, and differential diagnosis is easier in these patients.

We found that there were no differences in family histories of FMF and amyloidosis between early- and late-onset diseases. Similarly, Sayarlıoğlu et al. [8] reported that the presence of a positive family history was not different between early- and late-onset FMF. However, Yaşar Bilge et al. [13] and Endo et al. [9] found that patients with early-onset FMF more often had a positive family history. On the other hand, no differences were reported in the frequency of amyloidosis between the early- and late-onset FMF groups

Table 3. Comparison of MEFV gene mutation distribution in early and late-onset FMF patients

	Early-onset disease, % (n=75)	Late-onset disease, % (n=33%)	p
M694V homozygous	32.0	9.1	**0.015**
M694V heterozygous	30.7	42.4	0.214
M680I homozygous	0.0	0.0	–
M680I heterozygous	4.0	6.1	0.640
V726A homozygous	0.0	6.1	0.091
V726A heterozygous	4.0	0.0	0.551
E148Q homozygous	0.0	0.0	–
E148Q heterozygous	10.7	18.2	0.353

FMF: Familial Mediterranean fever. Significant p-values were presented in bold. These mutations were not separately listed in the table (n): P369S Homozygous (1), P369S Heterozygous (2), E148Q Heterozygous/R202Q Heterozygous (2), M680I Heterozygous/R202Q Heterozygous (1), M694V Heterozygous/E148Q Heterozygous (1), M694V Heterozygous/E148Q Heterozygous/R202Q Heterozygous (1), M694V Heterozygous/M680I Heterozygous/R202Q Heterozygous (1), M694V Heterozygous/R202Q Heterozygous (4), V726A Heterozygous/E148Q Heterozygous (1).

Table 4. Comparison of function and quality of life in early and late-onset FMF groups

	Early-onset disease (n=94) Median (range)	Late-onset disease (n=44) Median (range)	p
HAQ	0.15 (0–0.39)	0.15 (0–0.57)	0.349
SF-36			
Physical function	75 (50–90)	67.5 (55–80)	0.264
Physical role	50 (25–100)	50 (0–100)	0.430
Role emotional	66.7 (0–100)	50 (0–100)	0.334
Vitality	40 (30–60)	45 (35–55)	0.923
Mental health	52 (36–68)	56 (40–64)	0.564
Social function	62.5 (50–75)	62.5 (50–75)	0.576
Bodily pain	57.5 (31.8–75.6)	51.2 (35–67.5)	0.570
General health	40 (25–55)	40 (30–55)	0.452

FMF: Familial Mediterranean fever; HAQ: Health assessment questionnaire; SF-36: Short form 36.

[9, 11, 13, 15, 24]. In our study, biopsy-proven amyloidosis was detected in three patients (2.17% of the FMF patients) and in those with early-onset FMF. The factors associated with amyloidosis may be family history, genetic features, male sex, environmental factors, and country of residence [24–27]. The rate of FMF patients with amyloidosis in Turkiye has been reported to be 8.6% [24]. The relatively low rate of amyloidosis found in our study can be explained by several factors, such as early diagnosis, early initiation of treatment, and good compliance to therapy, especially in the late-onset group.

In the present study, the frequency and duration of attacks did not differ between patients with early- and late-onset FMF. Although similar results have been reported in previous studies [9, 10], other studies have reported a higher frequency of attacks in patients with early-onset FMF [11, 15].

We also found that FMF-related manifestations did not differ between the groups, except that arthritis and sacroiliitis were more common in patients with late-onset FMF. In contrast, other studies reported that patients with late-onset FMF had less frequent fever, peritonitis, pleuritis, erysipelas-like erythema,

and arthritis [13, 15]. However, other studies found that adult-onset FMF patients had less frequent arthritis and erysipelas-like erythema [8, 11]. In contrast, Endo et al. [9] found that the percentages of arthralgia and myalgia were higher in patients with late-onset FMF. Additionally, this study found overlapping autoimmune diseases, including rheumatoid arthritis, more frequently in patients with later-onset FMF [9]. In contrast, the percentage of arthritis and myalgia were not different between the groups in another study [10]. Moreover, Bodur et al. [15] have found that overlapping autoimmune diseases, including sacroiliitis, were not different between early- and late-onset diseases.

We found no differences in colchicine dosage, compliance, resistance, and elevated attack-free APR between early- and late-onset disease groups. Similarly, the response to colchicine treatment and colchicine dosage did not differ between early- and late-onset FMF in previous studies [8–10]. Exceptionally, one study reported that the percentage of colchicine-resistant patients was higher in early-onset FMF. However, the definition of colchicine-resistance used in this study was different from ours [15]. Additionally, we found that disease severity was lower in the late-onset disease group. This result is in line with those of previous studies that found early-onset FMF to be associated with more severe disease [11, 15].

We found that the homozygous M694V mutation is less frequent in late-onset disease. Previous studies showed that the homozygous genetic pattern and mutation of M694V were more common in patients with early-onset FMF [11, 13, 15]. In another study, the M694I mutation was less frequent in patients with late-onset disease [10]. Although one study found that heterozygous E148Q mutations were more prevalent in adult-onset FMF patients [13], in another study, E148Q was not significantly different among the groups [10]. The homozygous M694V mutation (24%) has been shown to be the most common mutation in Turkiye [28] and associated with earlier disease onset [29].

In the current study, we compared the patients with early- and late-onset disease groups regarding HAQ and SF-36 scores. Although Bodur et al. [30] reported a relationship between FMF-QoL score and late-onset FMF (>20 years), other studies found no correlations between age of disease onset and FMF-QoL and SF-36 [31, 32]. On the other hand, previous studies found that QoL was impaired in patients with FMF [33, 34], and it was not associated with disease activity [33, 35]. However, another study reported that FMF-QoL was significantly associated with severe disease activity and HAQ score in patients with FMF [30]. In the present study, although patients with late-onset disease had milder disease severity, the SF-36 and HAQ scores were not different between the groups.

The main limitation of this study is the small sample size at a single center. In addition, since amyloidosis is an important complication of FMF, its evaluation is important. However, due to the low rate of patients with amyloidosis in our study, we could not compare the frequency of amyloidosis between the early-onset and late-onset groups. In addition, data available on FMF patients in whom symptoms started over the age of 40 years reported that they may have distinct clinical features. Since the proportion of patients over the age of 40 was low in our study, we could not divide the patients into three groups according to the age at disease onset as: ≤20, 20–40, and >40 years.

Conclusion

In conclusion, late-onset FMF disease had a female predominance, a shorter delay of diagnosis, more frequent arthritis and sacroiliitis, a less frequent homozygous M694V mutation, and a milder disease severity than early-onset FMF disease. We did not find any differences in physical function or health-related QoL between early- and late-onset FMF. Further studies in larger populations are needed to eliminate the heterogeneity of data on late-onset FMF disease, standardize its definition, and determine its effects on clinical course and prognosis.

Ethics Committee Approval: The Marmara University Clinical Research Ethics Committee granted approval for this study (date: 26.07.2019, number: 09.2019.664).

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