Late-Onset Familial Mediterranean Fever: Single-Center Experience And Literature Review

Okan Aydin

Istanbul Universitesi-Cerrahpasa Cerrahpasa Tip Fakultesi

Bugra Han Egeli

Istanbul Universitesi-Cerrahpasa Cerrahpasa Tip Fakultesi

Huri Ozdogan

Istanbul Universitesi-Cerrahpasa Cerrahpasa Tip Fakultesi

Serdal Ugurlu (✉ serdalugurlu@gmail.com)

Istanbul Universitesi Cerrahpasa Tip Fakultesi, Romatoloji Bilim Dalı

Research article

Keywords: Familial Mediterranean Fever, late-onset, early-onset, MEFV mutation, colchicine

Posted Date: February 10th, 2020

DOI: <https://doi.org/10.21203/rs.2.23028/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Introduction: Familial Mediterranean Fever (FMF) is an autoinflammatory disease characterized by recurrent fever and serositis attacks. The disease onset occurs before 20 years of age in 90% of patients. Rarely, the disease onset occurs after 40 years of age.

Aim: We aimed to compare the patients with early and late-onset of disease.

Methods: We did a retrospective analysis of 2020 patients registered in our FMF center in the years 2008-2017. Patients with disease onset after the age of 40 (Group 1) were collected. The control group (Group 2), disease onset before the age of 20, was randomly selected with twice amount of the study group. Demographic, clinical and genetic data were recorded.

Results: Out of 2020 patients, 41 were in group 1 (2.02%). The male to female ratio was 1:1.7 in both groups. The delay of diagnosis was 5.6 ± 5.75 years in group 1, 10.7 ± 12.3 years in group 2. In terms of clinical features, the only significant difference between two groups belonged to fever seen in 26 (63.4%) patients in group 1 and 67 (81.7%) patients in group 2 ($p=0,026$). M694V mutation frequency was higher in group 2 whereas exon 2 mutation frequency was higher in group 1. The mean colchicine dose in the 6 months was 1.38 ± 0.64 mg in group 1, 1.61 ± 0.47 mg in group 2.

Discussion: In patients with late disease onset, the results of decreased mean colchicine dose during the last 6 months, decreased fever ratio, and increased exon 2 mutation frequency might point out to mild disease severity. **Keywords:** Familial Mediterranean Fever, late-onset, early-onset, MEFV mutation, colchicine

Introduction

Familial Mediterranean Fever (FMF) is an autoinflammatory disease characterized by recurrent fever and serositis attacks (1). On average, the attacks last for 1–3 days with the presentation of recurrent fever, abdominal pain, chest pain, joint pain, arthritis and erysipelas like erythema (ELE) and rarely orchitis, pericarditis, and febrile myalgia. The main complication of the disease, causing mortality and morbidity, is AA amyloidosis development (2,3). Colchicine treatment is essential in preventing attacks, chronic subclinical inflammation and secondary amyloidosis (4).

FMF was known to have an autosomal recessive inheritance long before its genetic definition. The disease pathogenesis is associated with a mutation at MEFV gene coding the pyrin protein (5). M694V is the most common and pathogenic mutation. M694V homozygous patients have an earlier onset with more common development of arthritis and amyloidosis and they require a higher colchicine dose treatment (6).

Early disease onset is an important feature of FMF. FMF symptoms develop before the age of 20 in approximately 90% of the patients (7). The mean age of onset is 3–9 years (8). Rarely, the onset can be

later than 40 years. In those cases, FMF prognosis is milder and colchicine dose required is lower (9).

The main aim of this study is to analyze the clinical and genetic features of patients with disease onset at or after the age of 40 and to compare with patients with early (≤ 20 years) disease onset.

Methods

The patient charts and records of 2020 patients who were followed at our tertiary rheumatology center between the years of 2008–2017 were analyzed retrospectively. Fifty-seven patients were found to have a late (> 40 years) disease onset. When these 57 patients were interviewed further, it was understood that even though 16 of them were diagnosed after the age of 40, their attacks developed before the age of 40. Therefore these 16 patients were excluded hence the late-onset group included 41 patients. In order to define a control group, 82 patients were randomly selected from the early onset patient pool so that there was a 1:2 ratio between the study and control groups.

All the patients were checked further to fulfill Tel Hashomer Criteria for clinical diagnosis (10). The information on demographics, clinical and genetic data such as age, gender, age of disease onset age, age of diagnosis, symptoms, treatment response, and MEFV gene mutations were recorded.

For statistical analysis, SPSS 23 (IBM) was used. For parametric data with normal distribution Student-T test, for non-normal distribution, Mann-Whitney U was used. Parametric data were presented as mean $\pm$ standard deviation. Analysis of categorical data was done with the chi-square test. P value below 0.05 was determined as significant.

Results

The study included 41 patients from the late-onset group (Group 1) and 82 patients from the early-onset group (Group2). In group 1, 26 patients (63%) were female, 15 (37%) were male. In group 2, 52 patients (63%) were female, 30 (37%) were male. Female to male ratio was the same in both groups (1.7:1). The mean age of patients was 57.6 ± 6.72 years in group 1 and 32.3 ± 9.26 years in group 2. The mean age of symptoms was 44.7 ± 4.86 years in group 1 and 8.9 ± 4.88 years in group 2. The mean age of diagnosis was 50.3 ± 6.72 years in group 1 and 19.6 ± 12.05 years in group 2. Delay in diagnosis on average was 5.6 ± 5.75 years in group 1 and 10.7 ± 12.39 years in group 2. The difference between the delay in diagnosis levels was found significant in statistical analysis ($p = 0.013$). Disease duration was 12.8 ± 7.07 years in group 1 and 23.4 ± 11.8 years in group 2. The difference between the disease duration levels was found significant in statistical analysis ($p < 0.001$).

The clinical features of the patients are summarized in Table 1. The most common symptom seen in both groups was abdominal pain. The frequency of fever was significantly higher in group 2 ($p = 0.026$). No significant difference was found in other symptoms. Orchitis was observed in neither of the groups. FMF related AA-Amyloidosis was observed in only a single patient in each group. The family history of

FMF was present in more than 60% of the patients in both groups and there was no significant difference between the two.

Table 1
Clinical features of patients

	Group 1	Group 2	p
	n = 41	n = 82	
Abdominal pain, n (%)	36 (87.8)	71(86.6)	0.850
Chest pain, n (%)	6(14.6)	24(29.3)	0.075
Fever, n (%)	26(63.4)	67(81.7)	0.026
Arthritis, n (%)	10(24.4)	29(35.4)	0.218
Arthralgia, n (%)	18(43.9)	39(47.6)	0.701
Myalgia, n (%)	1(2.4)	10(12.2)	0.098
Erysipelas-like erythema (ELE), n (%)	3(7.3)	5(6.1)	0.796
Amyloidosis, n (%)	1(2.4)	1(1.2)	0.614
Family FMF history, n (%)	28(70.0)	50(62.5)	0.417

The genetic features of the patients are shown in Table 2. In group 2, more patients had homozygous M694V mutations when compared to group 1 ($p = 0.008$). The proportion of patients who carry at least one M694V mutation was also significantly higher in group 2 ($p = 0.03$). Regarding the exon 2 mutations, the proportion of patients who carry at least one exon 2 mutation was significantly higher in group 1 ($p = 0.03$). Groups were further split into subgroups to check if their symptoms were more common if they have an M694V mutation. No significant difference was observed between the subgroups of Group 1 in terms of clinical and treatment information. In group 2, myalgia was more common in patients without an M694V mutation (26.1–6%) ($p = 0.024$). Furthermore in group 2, the presence of the family history of FMF was more common in patients with an M694V mutation (75%- 43.5%) ($p = 0.009$).

Table 2
Genetic features of the patients

	Group 1	Group 2	p
	n = 38	n = 73	
Exon 10 Mutation			
M694V Homozygous, n (%)	2(5.3)	19(26.0)	0.008
M680I Homozygous, n (%)	1(2.6)	6(8.2)	0.250
V726A Homozygous, n (%)	1(2.6)	1(1.3)	0.635
M694V Heterozygous, n (%)	9(23.6)	12(16.4)	0.355
M680I Heterozygous, n (%)	2(5.3)	2(2.7)	0.498
V726A Heterozygous, n (%)	4(10.5)	1(1.3)	0.027
At least one Exon 10 mutation, n (%)	28(73.7)	63(86.3)	0.101
At least one M694V mutation, n (%)	18(47.4)	50(68.5)	0.030
Exon 2 Mutation			
At least one Exon 2 mutation, n (%)	20(52.6)	23(31.5)	0.030
No mutation, n (%)	2 (5.3)	1 (1.4)	0.230
Unknown, n (%)	3/41(%7.3)	9/82 (10.9)	

The treatment information of the patients was summarized in Table 3. The duration of colchicine treatment and the colchicine dose during the last 6 months of treatment were significantly higher in group 2 ($p < 0.001$ and $p = 0.04$). Colchicine response was determined as at least a 50% decrease in attack severity and frequency. Colchicine response was high in both groups without a statistical difference between each other ($p = 0.162$). In cases of low colchicine response, anti IL-1 treatment was given to 7.3% of group 1, and 6.1% of group 2 ($p = 0.796$).

Table 3
Treatment information of the patients

	Group 1	Group 2	p
	n = 41	n = 82	
Duration of colchicine treatment, (mean $\pm$ SD) (years)	7.37 $\pm$ 4.5	12.7 $\pm$ 8.6	< 0.001
Initial colchicine dose, (mean-mg/day $\pm$ SD) (years)	1.35 $\pm$ 0.3	1.36 $\pm$ 0.27	0.854
Maximum dose, (mean-mg/day $\pm$ SD) (years)	1.7 $\pm$ 0.38	1.73 $\pm$ 0.31	0.668
Colchicine dose during the last 6 months of treatment, (mean-mg/day $\pm$ SD) (years)	1.38 $\pm$ 0.64	1.61 $\pm$ 0.47	0.04
Colchicine response, n (%)	36(87.8)	77(95.1)	0.162
Anti IL-1 treatment, n (%)	3(7.3)	5(6.1)	0.796

Discussion

We compared the clinical and genetic features of FMF with the main parameter of the age of onset. We found that in patients with late-onset of disease, the disease presentation is milder and more atypical. Similar studies are summarized in Table 4.

Table 4

Previous studies comparing the clinical and genetic features of early and late-onset FMF patients

	Sayarlioglu et al. (≥ 20 y vs. <20 y) Turkey (54)	Ureten et al. (> 20 y vs. ≤ 20 y) Turkey (104)	Yasar Bilge et al. (> 20 y vs. ≤ 20 y) Turkey (109)	Tamir et al. (≥ 40 y vs. <40 y) Israel (105)	Kriegshauser et al. (≥ 40 y vs. <40 y) Armenia (106)	Endo et al. (≥ 40 y vs. <20 y) Japan (107)	Kishida et al. (≥ 40 y vs. <20 y) Japan (108)
Patient count	401	260	2246	4000	10370	387	292
Late onset patient count and percentage	57, 14% (≥ 40 y: 5, %1,2)	77, 30% (≥ 40 y: 0, %0)	613, 27.3%	20, %0,5	354, %3,4	90, %23,2	44, %15,1
Gender (M:F)	1.1:1 vs. 1:1.1		1: 11 vs. 1:1.1	4:1 vs. 1.5:1	1:1.2 vs. 1.1:1	1:1.4 vs. 1:1.7	1:1.3 vs. 1:2.1
Mean delay in diagnosis	11.2 $\pm$ 8.8 vs. 12.1 $\pm$ 9	7.25 $\pm$ 5.83 vs. 10.3 $\pm$ 9.8 P = 0.003	3(1–9) vs. 10(3–8) P = 0.001	4.9 $\pm$ 5.8 vs. 20 $\pm$ 13 P < 0.001		2(0.5–8) vs. 7(2–15) P < 0.001	3(0–28) vs. 12(0.69) P < 0.001
Fever %	94.7 vs. 96.2	89.6 vs. 90.7	86.8 vs. 93.8 P < 0.001	5 vs. 30 P < 0.001	89.5 vs. 92.5 P = 0.04		97.7 vs. 99.2
Abdominal Pain %	94.7 vs. 92.4	92.2 vs. 91.8	91 vs. 96 P < 0.001	100 vs. 92.5	90.4 vs. 86.3 P = 0.03	30 vs. 64 P < 0.001	40.9 vs. 67.2 P = 0.002
Chest Pain %	43.9 vs. 54.7	25.8 vs. 36..6	38.3 vs. 51.4 P < 0.001	5 vs. 45 P < 0.001	43.2 vs. 48.6 P = 0.04	24 vs. 45 P = 0.002	25 vs. 52.3 P = 0.002
Arthritis %	42.1 vs. 64.5 P = 0.001	33.8 vs. 48.6 P = 0.02	30.2 vs. 43.5 P < 0.001	10 vs. 78 P < 0.001	17.5 vs. 16.8	62 vs. 32 P < 0.001	45.5 vs. 41.4
Myalgia %			13.2 vs. 13			26 vs. 8 P = 0.005	15.9 vs. 18

	Sayarlioglu et al. (≥ 20 y vs. <20 y) Turkey (54)	Ureten et al. (> 20 y vs. ≤ 20 y) Turkey (104)	Yasar Bilge et al. (> 20 y vs. ≤ 20 y) Turkey (109)	Tamir et al. (≥ 40 y vs. <40 y) Israel (105)	Kriegshauser et al. (≥ 40 y vs. <40 y) Armenia (106)	Endo et al. (≥ 40 y vs. <20 y) Japan (107)	Kishida et al. (≥ 40 y vs. <20 y) Japan (108)
ELE %	7 vs. 17.4 P = 0.004	19.5 vs. 32.4 P = 0.03	15.2 vs. 26.9 P < 0.001	15 vs. 20	9.9 vs. 15 P = 0.009	19 vs. 10	
Amyloidosis %	3.5 vs. 5.8	0 vs. 3.8	8.2 vs. 8.8		0.56 vs. 0.61	3 vs. 1	
Family history %	57.9 vs. 55.5		53 vs. 59 P = 0.003	65 vs. 72.5	29.9 vs. 34	12 vs. 28 P = 0.018	6.8 vs. 28.9 P = 0.012
Colchicine response	98.2 vs. 96.8			100 vs. 82.5		97 vs. 98	95.1 vs. 94.7
M694V homozygous mutation %			11.6 vs. 20.9 P < 0,001		3.3 vs. 11.4 P < 0.001		

In our study, both in the above 40-year group and below 20-year group included 63,4% of female patients. This ratio is similar to the 2020 patients followed in our clinic in 2008–2017 in which 62.1% of the patients are female. This similarity prevents a potential gender-based confounding factor. The gender ratio of our study is similar to previous studies (11, 12).

Delay in diagnosis is common in FMF. In our study delay in Group 1 was 5.6 ± 5.75 and in Group 2 was 10.7 ± 12.39 , this difference was found significant ($p = 0.013$). Furthermore, in the studies of Tamir et al. and Sayarlioglu et al. the delay was found significantly lower in late-onset patients (9, 13). This can be due to increased self-awareness among more aged patients. In addition, this means that there will be patients presenting to the clinic with non-specific FMF symptoms such as abdominal pain, fever, and joint pain. This study is valuable since it suggests the inclusion of FMF to the differential diagnosis of these complaints even if the patient is above 40 years old. Furthermore, as FMF is a disease diagnosed with history taking and physical exam only, it saves the institutions from expensive imaging techniques and blood tests to explain undiagnosed abdominal pain, fever or any symptom of FMF.

Regarding the clinical features, the only symptom with a significant difference was fever when comparing two groups. Fever was observed in 63.4% of the patients in group 1, and 81.7% of the patients in group 2 ($p = 0.026$). This difference hints at an atypical presentation at the late onset of the disease. Fever was also found to be more frequent in patients with disease onset before 40 years when compared to after

40 years in the study of Tamir et al (13). In an Armenian cohort with 10370 patients, fever was also found to be more frequent with earlier onset (14). Nevertheless, fever was also found to be the most common second symptom in group 1.

Homozygous M694V mutation in FMF is known to be associated with increased severity of the disease and amyloidosis development (12, 15). In our study, in group 1, 2 (5.3%) patients had a homozygous M694V mutation whereas 19 (26%) patients had it in group 2 ($p = 0.008$). In addition, the proportion of patients carrying at least a single copy of M694V mutation was also found significantly higher (0.03). However, group 1 had a higher exon 2 mutation ratio of 52.6% when compared to group 2 with a ratio of 31.5% ($p = 0.03$). In a study by Ureten et al. comparing M694V homozygous, heterozygous and other mutations, disease onset was found to be lower in relative order (12). Similar findings were presented in other studies (13, 14, 16). Our results are consistent with previous studies. Currently, mutations such as E148Q and R202Q are defined to be clinically unknown, even benign polymorphisms by some authors yet our findings on the frequency of these mutations in late-onset patients suggest its importance. Even though these patients are clinically milder, amyloidosis prevalence and hospital visit count were not found lower than early-onset patients. Therefore, further analysis of exon 2 mutations with larger cohorts is required.

Referring to colchicine treatment, the beginning dose, maximum colchicine dose, and colchicine response was similar in both groups. Our results are similar to two studies from Japan (17, 18). However, colchicine dose in the last 6 months was found significantly higher in early-onset patients ($p = 0.04$). Sayarlioglu et al. also found similar colchicine responses in both groups (9). Whereas, Tamir et al. found that despite low colchicine dose, late-onset patients had a better treatment response (13). The low colchicine dose in the last 6 months can be interpreted as mild disease severity. FMF is the disease of the innate immune system where an autoinflammation is the main explanation of the pathogenesis (1). The milder clinical presentation in patients with late-onset of FMF can be explained as the activity of the innate immune system declines with age (19).

The major limitation of our study was its retrospective design. In the meantime, due to its cohort including over 2000 patients, case-based missing data at chart reviews did not affect the overall results. Another limitation was the lack of patient numerical disease assessment. This challenged our evaluation of the disease severity nevertheless information on colchicine dose enhanced our understanding objectively. The lack of acute phase reactants might seem like a limitation, but FMF is a disease with a clinical diagnosis hence the laboratory values like acute phase reactants are not required. Our primary focus was on the age of diagnosis. Acute phase reactants are more valid during follow-ups to prevent amyloidosis development. The amyloidosis rate in our study was 1.6% which was already low when compared to previous studies where it was found to be approximately 10% (11, 15). The last limitation of our study was related to genetic analysis. We could not find the genetic information of 9.7% of the patients, yet the statistical analysis of the remaining data was still significant.

Conclusion

We found 41 (2.02 %) patients with disease onset of 40 years and after among 2020 FMF patients. When compared to early-onset patients, fever was less common and the colchicine dose in the last 6 months was lower. In addition, M694V mutation was less common and Exon 2 mutations were more common among late-onset patients. These findings conclude that late-onset patients can have an atypical presentation and regardless of age when there are clinical findings present, FMF should be in the differential diagnosis.

Declarations

Ethics approval and consent to participate

Verbal consent was received from the participants of the study. The study was approved by Cerrahpasa Medical School Ethics Committee. (#83045809)

Consent for publication

Consent for publication was received from every author.

Availability of data and material

The data is available to be shared if necessary.

Competing interests

There are no competing interests

Funding

No funds were required for the study.

Authors' contributions

All of the authors worked on data gathering, analysis and writing of the manuscript.

References

1. Lidar M, Livneh A. Familial Mediterranean fever: clinical, molecular and management advancements. The Netherlands journal of medicine. 2007 Oct;65(9):318–24.
2. Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and review of the literature. The American journal of medicine. 1967.
3. Sönmez HE, Batu ED, Özen S. Familial Mediterranean fever: current perspectives. Journal of inflammation research. 2016;9:13–20.

4. Ozen S, Demirkaya E, Erer B, Livneh A, Ben-Chetrit E, Giancane G, et al. EULAR recommendations for the management of familial Mediterranean fever. *Annals of the Rheumatic Diseases*. 2016.
5. Touitou I. The spectrum of Familial Mediterranean Fever (FMF) mutations. *European journal of human genetics: EJHG*. 2001 Jul;9(7):473–83.
6. Ben-Chetrit E, Levy M. Familial Mediterranean fever. *Lancet (London, England)*. 1998 Feb 28;351(9103):659–64.
7. Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and review of the literature. *The American journal of medicine*. 1967.
8. Federici S, Sormani MP, Ozen S, Lachmann HJ, Amarian G, Woo P, et al. Evidence-based provisional clinical classification criteria for autoinflammatory periodic fevers. *Annals of the rheumatic diseases*. 2015 May;74(5):799–805.
9. Sayarlioglu M, Cefle A, Inanc M, Kamali S, Dalkilic E, Gul A, et al. Characteristics of patients with adult-onset familial Mediterranean fever in Turkey: analysis of 401 cases. *International journal of clinical practice*. 2005 Feb;59(2):202–5.
10. Sohar E, Gafni G, Pras M. Tel Hashomer criteria for the diagnosis of FMF. In: *Proceedings of the First International Conference on FMF London, UK: Freund Publishing House, Tel Aviv*. 1997.
11. Tunca M, Ozdogan H, Kasapcopur O, Yalcinkaya F, Ozen S, Topaloglu R, et al. Familial Mediterranean Fever (FMF) in Turkey: Results of a nationwide multicenter study. *Medicine*. 2005.
12. Ureten K, Gönülalan G, Akbal E, Güneş F, Akyürek O, Ozbek M, et al. Demographic, clinical and mutational characteristics of Turkish familial Mediterranean fever patients: results of a single center in Central Anatolia. *Rheumatology international* 2010 May;30(7):911–5.
13. Tamir N, Langevitz P, Zemer D, Pras E, Shinar Y, Padeh S, et al. Late-onset familial Mediterranean fever (FMF): a subset with distinct clinical, demographic, and molecular genetic characteristics. *American journal of medical genetics*. 1999 Nov 5;87(1):30–5.
14. Kriegshäuser G, Enko D, Hayrapetyan H, Atoyan S, Oberkanins C, Sarkisian T. Clinical and genetic heterogeneity in a large cohort of Armenian patients with late-onset familial Mediterranean fever. *Genetics in medicine: official journal of the American College of Medical Genetics*. 2018;20(12):1583–8.
15. Kasifoglu T, Bilge SY, Sari I, Solmaz D, Senel S, Emmungil H, et al. Amyloidosis and its related factors in Turkish patients with familial Mediterranean fever: a multicentre study. *Rheumatology (Oxford, England)*. 2014 Apr;53(4):741–5.
16. Yasar Bilge NS, Sari I, Solmaz D, Senel S, Emmungil H, Kilic L, et al. Comparison of early versus late onset familial mediterranean fever. *International Journal of Rheumatic Diseases*. 2018;21(4):880–4.
17. Endo Y, Koga T, Ishida M, Fujita Y, Tsuji S, Takatani A, et al. Musculoskeletal manifestations occur predominantly in patients with later-onset familial Mediterranean fever: Data from a multicenter, prospective national cohort study in Japan. *Arthritis research & therapy*. 2018 Nov 20;20(1):257.
18. Kishida D, Yazaki M, Nakamura A, Tsuchiya-Suzuki A, Shimojima Y, Sekijima Y. Late-onset familial Mediterranean fever in Japan. *Modern rheumatology*. 2019 Jun 25;1–4.

19. Shaw AC, Goldstein DR, Montgomery RR. Age-dependent dysregulation of innate immunity. Vol. 13, Nature Reviews Immunology. 2013. p. 875–87.

Key Points

- We aimed to compare the patients diagnosed with Familial Mediterranean Fever (FMF) with early and late-onset of disease.
- In patients with late disease onset, the results of decreased mean colchicine dose during the last 6 months, decreased fever ratio, and increased exon 2 mutation frequency might point out to mild disease severity.