Internal and Emergency Medicine (2022) 17:1301–1306
https://doi.org/10.1007/s11739-021-02912-8

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Late-onset familial mediterranean fever: single-center experience and literature review

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Received: 14 July 2021 / Accepted: 9 December 2021 / Published online: 21 January 2022

Abstract
Familial Mediterranean fever (FMF) is a hereditary, autoinflammatory disease characterized by recurrent fever and serositis attacks. The disease onset occurs before 20 years of age in 90% of patients and rarely after the 4th decade. The aim of this study is to screen our FMF patient pool for patients with disease onset after age of 40 and to compare them to patients with early onset with regard to clinical and genetic features. The charts of 2020 patients registered in our FMF center in the years 2008–2017 were screened with regard to age of disease onset. Patients with disease onset after the age of 40 were considered as late-onset group (Group 1). The control group (Group 2) consisted of patients with a disease onset before the age of 20 who were randomly selected from the patient pool with twice the number of probands. Demographic, clinical and genetic data were recorded. Out of 2020 patients, the attacks of FMF had started after the fourth decade in 41 patients (2.02%), (Group 1). 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. The only significant difference with regard to clinical features between two groups was the frequency of fever, which was present in 26 (63.4%) patients in group 1 and 67 (81.7%) in group 2 ($p = 0.026$). M694V mutation was more prevalent among early-onset group whereas exon 2 variants were more frequent in patients with late onset. The mean colchicine dose in the last 6 months was 1.38 ± 0.64 mg in group 1, and 1.61 ± 0.47 mg in group 2. FMF may start after 40 years of age in approximately 2% of the patients. Lower frequency of fever, lower daily colchicine dose and lower prevalence of exon 10 mutations point out that FMF patients with a disease onset after 40 years of age experience a milder disease compared to those with an onset before the second decade of life.

Keywords Familial Mediterranean fever · Late onset · Early onset · MEFV mutation · Colchicine

Introduction

Familial Mediterranean fever (FMF), the most common and oldest known of all periodic fever syndromes, is a disorder of the innate immune system and considered a monogenic autoinflammatory disease. MEFV gene, responsible for FMF, is located at chromosome 16 and encodes the pyrin protein. This protein is an integral part of pyrin inflammasome which plays a vital role in the cleavage and release of proinflammatory cytokines IL-1b and IL-18 [1]. However the number of variants reported have exceeded 100 by today, the main mutations that are associated with severe disease are located at exon 10 of pyrin and include p.M694V, p.M680I, p.V726A which are gain-of-function [2]. FMF is considered as an autosomal recessive disease yet over one-third of the patients with clinical FMF either carry one disease associated with MEFV mutation or none. On the other hand, the carrier frequency in high-risk populations such as Armenians, Sephardic Jews, Arabs and Turks is 5–10% [1].

Key points

A group of patients diagnosed with familial Mediterranean fever (FMF) were assessed regarding the impact of age at disease onset on disease phenotype

Mean daily colchicine dose, frequency of fever and Exon 10 mutations are lower among patients with a disease onset over age of 40 years compared to those with an onset before age of 20, probably implicating milder disease severity with late onset

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FMF is characterized by typical attacks of fever and serositis, manifesting as abdominal pain and/or chest pain and/or joint pain and swelling and/or exertional leg pain. Attacks of erythematous rash, which is defined as 'erysipelas-like erythema' (ELE), is another common feature of the disease. These episodes are self-limited and last 1–4 days. Patients are generally symptom-free in between attacks [1]. Attacks of orchitis, pericarditis, protracted febrile myalgia are examples for less frequent attack types. Diversity of the clinical manifestations as well as the frequency, presentation and severity of the attacks cause a significant delay in diagnosis even in high-risk populations [1]. The main complication of the disease is AA amyloidosis which is related with increased mortality and morbidity [2, 3]. Mortality rate has decreased significantly after prophylactic colchicine treatment [4]. However, amyloidosis is still a threat especially to patients who are either non-compliant, and/or who cannot tolerate, or do not respond to therapeutic doses of daily colchicine. Treatment with anti IL-1 agents Anakinra, Canakinumab and Rilonacept has become the treatment of choice in about 10–15% of patients who are considered as intolerant or unresponsive to proper colchicine therapy [5–7].

Approximately in 90% of the patients, first attacks of FMF start before the second, and in about half before the first decade [8]. The mean age of onset is 3–9 years [9]. Early disease onset is characterized by typical FMF phenotype with bouts of fever and serositis and is one of the factors associated with increased risk of amyloidosis among others such as higher daily colchicine dose, attacks of synovitis, male sex, M694V homozygosity and presence of SAA a/a genotype. Since the early papers on FMF, it has been underlined that the risk of FMF onset after age 40 was very low [10–12]. Therefore it has been recommended that one had to re-consider the diagnosis of FMF in a patient with an onset after 4th decade, before making a definite decision. On the other hand, however, rare cases with late onset and that are complicated with amyloidosis have been reported [10–12]. The available information on FMF patients with late onset is not sufficient. Disease presentation, as well as attack characteristics, response to colchicine treatment, prognosis, additional problems related with age, as concomitant medications, issues related with differential diagnosis are some of the topics that need to be looked upon with more depth.

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

Table 1 Clinical features of patients

	Group 1 $n=41$	Group 2 $n=82$	p
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 history, *n* (%)	28(70.0)	50(62.5)	0.417

Methods

The study has a retrospective cohort design. The patient charts and records of 2020 FMF 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 disease onset at or after age of 40 years. When these 57 patients were interviewed further, it was understood that 16 of them were diagnosed after the age of 40, but their attacks had started long before. Therefore after excluding these 16, we ended up with 41 patients (2%). To define a control group with an onset before 20 years of age, 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 fulfilled the Tel-Hashomer criteria [11]. The information on demographics, clinical and genetic data, and treatment responses were recorded.

In addition, a literature review on late-onset FMF was performed on Pubmed and Google Scholar using the key words "familial Mediterranean fever", "late onset" "early onset".

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 ± 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 FMF patients with an onset after 40 years of age (late-onset group -Group 1) and 82 patients with an onset before age 20 (early-onset group–Group 2). The clinical characteristics of both groups are given in Table 1. Female to male ratio was the same in both groups (1.7:1). The mean age of patients in Group 1 was 57.6 ± 6.72 compared to 32.3 ± 9.26 years in group 2. The mean age at onset was 44.7 ± 4.86 to 8.9 ± 4.88 years and mean age at diagnosis was 50.3 ± 6.72 to 19.6 ± 12.05 years in group 1 and 2, respectively. There was a delay in diagnosis of 5.6 ± 5.75 years in group 1 and 10.7 ± 12.39 in group 2, ($p = 0.01$). Disease duration was significantly shorter in group 1 compared to group 2 (12.8 ± 7.07 versus 23.4 ± 11.8 years, $p < 0.001$), as the duration of follow-up (7.32 ± 4.56 years for group 1 and 12.7 ± 8.6 years in group 2, $p < 0.001$).

The most common symptom seen in both groups was abdominal pain. The only significant difference was observed in the frequency of fever. The number of patients who reported febrile attacks was higher in group 2 ($p = 0.026$). Chest pain and myalgia were slightly more common in the early-onset group. Otherwise no significant difference in phenotypes between 2 groups was observed.

FMF-related AA amyloidosis was diagnosed in 2 patients, one from each group. The family history of FMF was present in more than 60% of the patients in both groups.

The distribution of MEFV gene mutations in the study cohort is given in Table 2. In group 2, the number of patients homozygous for M694V mutation were significantly more common compared to the late-onset group ($n = 19$, 23.17% vs. $n = 2$, 4.88%) ($p = 0.008$). The proportion of patients who carry at least one M694V mutation was also significantly higher in group 2 ($p = 0.03$). On the contrary, patients who carry at least one exon 2 mutation were significantly more prevalent in group 1 ($p = 0.03$). Groups were further split into subgroups with regard to presence of M694V, to look for the impact of this mutation on phenotype. In group 2, myalgia was more common among patients without an M694V mutation (26.1–6%) ($p = 0.024$). Furthermore, in group 2, family history of FMF was more prevalent among patients with an M694V mutation (75–43.5%) ($p = 0.009$). No other significant difference was observed.

The data on treatment is summarized in Table 3. The duration of colchicine therapy and the daily 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. Both groups responded to colchicine treatment. Three patients from Group 1 and 5 from Group 2 received anti IL-1 treatment for insufficient response to colchicine.

Table 2 Distribution of MEFV variants in late (Group1) and early-onset (Group 2) groups

	Group 1 $n = 38$	Group 2 $n = 73$	p
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			
R202Q Homozygous, *n* (%)	2 (2.6)	5 (1.3)	0.744
R202Q Heterozygous, *n* (%)	4 (10.5)	4 (5.4)	0.329
E148Q Heterozigot, *n* (%)	3 (7.9)	3 (4.1)	0.402
Only Exon 2 mutation, *n* (%)	8 (21)	8 (10.9)	0.150
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)	

Table 3 Treatment of the patients

	Group 1 $n = 41$	Group 2 $n = 82$	p
Duration of colchicine treatment, (mean ± SD) (years)	7.37 ± 4.5	12.7 ± 8.6	< 0.001
Initial colchicine dose, (mean-mg/day ± SD) (years)	1.35 ± 0.3	1.36 ± 0.27	0.854
Maximum dose, (mean-mg/day ± SD) (years)	1.7 ± 0.38	1.73 ± 0.31	0.668
Colchicine dose during the last 6 months of treatment, (mean-mg/day ± SD) (years)	1.38 ± 0.64	1.61 ± 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

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Table 4 Results of the literature review including our cohort with regard to early and late-onset FMF patients

	Sayarlioglu et al. (≥20 years vs. <20 years) Turkey (10)	Ureten et al. (>20 years vs. ≤20 years) Turkey (14)	Yasar Bilge et al. (>20 years vs. ≤20 years) Turkey (18)	Tamir et al. (≥40 years vs. <40 years) Israel (15)	Kriegshauser et al. (≥40 years vs. <40 years) Armenia (16)	Endo et al. (≥40 yearsvs. <20 years) Japan (12)	Kishida et al. (≥40 years vs. <20 years) Japan (13)	Present study Aydin et al. (≥40 years vs. <20 years) Turkey
N of patients	401	260	2246	4000	10,370	387	292	2020 total patient pool
N of patients with late onset (%)	57 (14) (≥40 years 5, %1.2)	77 (30%) (≥40 years 0, %0)	613 (27.3%)	20 (%0.5)	354 (3.4)	90 (23.2)	44 (15.1)	41 (2%), 82 early onset**
M:F (late vs early onset)	1.1:1 vs. 1:1.1		1: 1.1 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	1:1.7 vs 1:1.7
Mean delay in diagnosis (yr)	11.2 ± 8.8 vs. 12.1 ± 9	7.25 ± 5.83 vs. 10.3 ± 9.8 $p = 0.003$	3(1–9) vs. 10(3–8) $p = 0.001$	4.9 ± 5.8 vs. 20 ± 13 $p < 0.001$		2(0.5–8) vs. 7(2–15) $p < 0.001$	3(0–28) vs. 12(0.69) $p < 0.001$	5.6 ± 5.7 vs. 10.7 ± 12 $p < 0.01$
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	63.4 vs 81.7 $p < 0.0$
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 $p = 0.002$	87.8 vs. 88.6
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 $p = 0.002$	14.6 vs 29.3
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	24.4 vs. 35.4
Myalgia (%)			13.2 vs. 13			26 vs. 8 $p = 0.005$	15.9 vs. 18	2.4 vs. 12.2
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		7.3 vs. 6.1
Amyloidosis (%)	3.5 vs. 5.8	0 vs. 3.8	8.2 vs. 8.8		0.56 vs. 0.61	3 vs. 1		2.4 vs. 1.2
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 $p = 0.012$	70 vs. 62.5
Colchicine response (%)	98.2 vs. 96.8			100 vs. 82.5		97 vs. 98	95.1 vs. 94.7	87.8 vs. 95.1
M694V homozygous mutation (%)			11.6 vs. 20.9 $p < 0,001$		3.3 vs. 11.4 $p < 0.001$			5.3 vs 26

**To define a control group with an onset before 20 years of age (early-onset 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

Discussion

We compared the clinical and genetic features of FMF with regard to age of onset in our patient population and reviewed the available literature (Table 4). To better highlight the possible differences and similarities, we defined two groups: early onset, if the FMF attacks started before age 20 and late onset, if attacks started after 40 years of age. This approach has been preferred in 2 other studies [12, 13]. However, different age cut-offs for early and late onset have been suggested in other studies, such as onset before and after age 20 or before and after 40 [14–18], (Table 4). Two percent of the patients followed in our FMF clinic between 2008 and 2017 reported onset of disease after their 40th birthday. This ratio is in sound with previous reports (Table 4) except the Japanese case series where it varies between 15 and 23%. This difference among other features may serve as a sign of phenotype diversity between high- and low-risk FMF populations.

In our cohort, there was a preponderance of female patients in both subgroups (63.5%) which was also observed in the total of 2020 FMF patients followed in our clinic between 2008 and 2017 (62%). This similarity prevents a potential gender-based confounding factor. However in the majority of the FMF cohorts reported, a slight male preponderance is more common [19] but there

are other series which report a gender ratio in favor of females.

Delay in diagnosis is a common problem in FMF, even in high-risk populations [5]. In our study cohort, mean diagnostic delay in late-onset group was significantly shorter than that observed in early-onset group,(5.6 ± 5.75 years to 10.7 ± 12.39 years, $p = 0.013$). This observation has been shared by almost all the previous papers and the difference was found to be significant in papers by Tamir et al. and Sayarlioglu et al. [10, 15]. This can be due to increased self-awareness among more aged population. Besides, the differential diagnosis list for recurrent fever and abdominal or chest pain with increased acute phase response in a patient aged 40 years or over compared to a young patient below the age of 20 with same complaints will include different disease entities. As fever and abdominal pain are more common complaints in childhood, thus, maybe overlooked, whereas these can be signs of serious pathologies in an elder person, therefore, necessitates early close work-up. This approach may explain the shorter delay in diagnosis in the elder FMF population. This study as well as the others on the subject suggest to include FMF, especially in populations at risk, to the differential diagnosis process of patients above 40 years of age with various signs and symptoms included in the spectrum of FMF manifestations. Furthermore, as FMF is a disease diagnosed mainly by history taking and physical examination, this approach may prevent expensive imaging techniques and laboratory examinations.

Regarding the clinical features, the only symptom with a significant difference was the frequency of fever between 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 observation has been also shared by Tamir et al. [15]. In an Armenian cohort with 10,370 patients, fever was also associated with early-onset FMF [16]. Nevertheless, fever was the second most common symptom in group 1. Attacks without fever generally cause delay in diagnosis and are a sign of mild disease activity.

Homozygous M694V mutation in FMF is known to be associated with severe disease and amyloidosis [4, 5]. In our study population, the number of patients with homozygous M694V mutation was significantly low in Group 1 compared to Group 2 ($n = 2$, 5.3% vs $n = 19$, 26%, respectively), ($p = 0.008$). The proportion of patients carrying at least a single copy of M694V mutation was also significantly high in the early-onset group. On the other hand, exon 2 variants were more common in the late-onset group (Group 1, 52.6%; Group 2, 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 [14]. Similar findings were presented in other studies [15–18]. In the interpretation of the genetic testing of MEFV gene by a panel of specialists, 9 of the suggested variants (M680I, M694V, M694I, V726A, A744S, R761H, I692del, E167D, T267I) have been accepted as definitely pathogenic, however, 5 variants (E148Q, P369S, F479L, K695R, I591T) were considered as variants of uncertain significance (VUS) [9]. Another common variant R202Q was defined as a polymorphism and decided not to be reported because of no diagnostic impact [9]. Still there are numerous studies on the significance of VUS as well as on the role of R202Q [6]. A recent comprehensive paper from Israel suggests that a single heterozygous E148Q variant is unlikely to aggravate the FMF phenotype [19]. However another recent paper from Armenia suggest that the country of origin may influence the pathogenicity of E148Q, also pointing out the probable influence of environmental factors and modifier genes on the expression of a phenotype [20].

Late-onset FMF in high-risk populations such as Turks, may also resemble that of the Japanese FMF cohort, with mild disease severity, late disease onset, good response to moderate dose of colchicine, low risk of amyloidosis and increased E148Q prevalence [12, 13].

Regarding treatment, the initial daily colchicine dose, maximum received colchicine dose, and colchicine response were similar in both groups. Our results resemble two other studies from Japan [12, 13], however, colchicine dose in the last 6 months was found significantly higher in early-onset patients. Sayarlioglu et al. also reported similar findings [10]. Whereas, Tamir et al. observed that despite low colchicine dose, late-onset patients had a better treatment response [15]. The low colchicine dose in the last 6 months can be interpreted as a clue to mild disease severity in late-onset FMF patients [1].

The major limitation of our study was its retrospective design, however, due to the FMF patient- pool including over 2000 patients, case-based missing data at chart reviews did not affect the overall results. Major limitations, also related with retrospective design, were the lack of standardized patient and physician global assessments and status of acute phase response. The primary aim of this study was to assess clinical and genetic characteristics of our cohort with respect to age of onset, we did not include the above parameters due to the problems in reliability of retrospective, and non-standardized data. The final limitation is the missing genetic information in 12 patients.

Conclusion

Approximately in 2% of the patients with FMF, the disease starts after the age of 40. Patients with late-onset FMF seem to have less severe disease. Fever is less common, daily colchicine dose is lower and exon 10 variants are less prevalent among late-onset patient population. On the other hand, the number of patients who carry one or two copies of M694V

is significantly more in patients whose disease starts before the age of 20 years. These results suggest that especially in high-risk populations, FMF should be considered in differential diagnosis regardless of age of onset.

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

Funding The authors do not have any financial support or other benefits from commercial sources for the work reported on in the manuscript. This article is archived in the preprint server. (https://doi.org/10.21203/rs.2.23028/v1).

Availability of data and materials The data are available to be shared if necessary.

Declarations

Conflict of interest There are no competing interests.

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.

References

1. Lidar M, Livneh A (2007) Familial Mediterranean fever: clinical, molecular and management advancements. Neth J Med 65(9):318–324
2. Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever A survey of 470 cases and review of the literature. Am J Med. 1967;43(2):227–53.
3. Sönmez HE, Batu ED, Özen S (2016) Familial Mediterranean fever: current perspectives. J Inflamm Res 9:13–20
4. Ozen S, Demirkaya E, Erer B, Livneh A, Ben-Chetrit E, Giancane G et al (2016) EULAR recommendations for the management of familial Mediterranean fever. Ann Rheum Dis 75(4):644–651
5. Egeli BH, Ugurlu S. Familial Mediterranean Fever: Clinical State Of The Art. QJM. 2020 Oct 20:hcaa291.
6. Wilson SP, Cassel SL (2010) Inflammasome-mediated autoinflammatory disorders. Postgrad Med 122(5):125–133
7. Touitou I (2001) The spectrum of Familial Mediterranean Fever (FMF) mutations. Eur J Hum Genet 9(7):473–483
8. Ben-Chetrit E, Levy M (1998) Familial Mediterranean fever. Lancet (London, England) 351(9103):659–664
9. Federici S, Sormani MP, Ozen S, Lachmann HJ, Amaryan G, Woo P, et al. Paediatric Rheumatology International Trials Organisation (PRINTO) and Eurofever Project. Evidence-based provisional clinical classification criteria for autoinflammatory periodic fevers. Ann Rheum Dis. 2015;74(5):799–805.
10. Sayarlioglu M, Cefle A, Inanc M, Kamali S, Dalkilic E, Gul A et al (2005) Characteristics of patients with adult-onset familial Mediterranean fever in Turkey: analysis of 401 cases. Int J Clin Pract 59(2):202–205
11. Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T et al (1997) Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum 40(10):1879–1885
12. Endo Y, Koga T, Ishida M, Fujita Y, Tsuji S, Takatani A et al (2018) Musculoskeletal manifestations occur predominantly in patients with later-onset familial Mediterranean fever: data from a multicenter, prospective national cohort study in Japan. Arthritis Res Ther 20(1):257
13. Kishida D, Yazaki M, Nakamura A, Tsuchiya-Suzuki A, Shimojima Y, Sekijima Y. Late-onset familial Mediterranean fever in Japan. Mod Rheumatol. 2019:1–4
14. Ureten K, Gönülalan G, Akbal E, Güneş F, Akyürek O, Ozbek M, Oztürk MA (2010) Demographic, clinical and mutational characteristics of Turkish familial Mediterranean fever patients: results of a single center in Central Anatolia. Rheumatol Int 30(7):911–915
15. Tamir N, Langevitz P, Zemer D, Pras E, Shinar Y, Padeh S et al (1999) Late-onset familial Mediterranean fever (FMF): a subset with distinct clinical, demographic, and molecular genetic characteristics. Am J Med Genet 87(1):30–35
16. Kriegshäuser G, Enko D, Hayrapetyan H, Atoyan S, Oberkanins C, Sarkisian T (2018) Clinical and genetic heterogeneity in a large cohort of Armenian patients with late-onset familial Mediterranean fever. Genet Med 20(12):1583–1588
17. Kasifoglu T, Bilge SY, Sari I, Solmaz D, Senel S, Emmungil H et al (2014) Amyloidosis and its related factors in Turkish patients with familial Mediterranean fever: a multicentre study. Rheumatology (Oxford) 53(4):741–745
18. Yasar Bilge NS, Sari I, Solmaz D, Senel S, Emmungil H, Kilic L et al (2018) Comparison of early versus late onset familial Mediterranean fever. Int J Rheum Dis 21(4):880–884
19. Tirosh I, Yacobi Y, Vivante A, Barel O, Ben-Moshe Y, Erez Granat O, et al. Clinical significance of E148Q heterozygous variant in paediatric Familial Mediterranean Fever. Rheumatology (Oxford). 2021 Feb 9:keab128.
20. Atoyan S, Hayrapetyan H, Yeghiazaryan A, Ben-Chetrit E, Sarkisian T (2020) Is the country of living important in the phenotypic expression of E148Q mutation? The Armenian experience. Clin Exp Rheumatol 38(Suppl 127):124–125
21. Tunca M, Akar S, Onen F, Ozdogan H, Kasapcopur O, Yalcinkaya F, et al. Turkish FMF Study Group. Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. Medicine (Baltimore). 2005;84(1):1–11.