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Original Article

Comparison of clinical features in FMF patients according to severity scores: An analysis with the ISSF scoring system

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Abstract

Objective: Familial Mediterranean fever (FMF), is an auto-inflammatory disease characterized by attacks of fever and serositis. Some scoring systems have been developed to evaluate the severity of the disease, however, predicting the severity of FMF is not possible with current knowledge. Our aim in this study was to evaluate the factors affecting disease severity in FMF.

Methods: This study included 150 FMF patients. The medical data of the patients were collected retrospectively and the International severity scoring system for Familial Mediterranean fever (ISSF) was used to evaluate disease severity.

Results: Patients were sorted into 3 groups based on the ISSF scores; ≤2=mild (Group 1; n: 61), 3-5=moderate (Group 2; n: 70), and ≥6=severe (Group 3; n: 19). Age at the onset of disease and age at diagnosis was younger in patients with severe disease (p: 0.009 and p: 0.031, respectively). Fever, peritonitis, and vasculitis were similar in all 3 groups. Pleuritis, erysipelas-like erythema (ELE), arthritis, myalgia, amyloidosis, and chronic kidney disease (CKD) were more common in Group 3.

Conclusion: FMF patients with early onset and early diagnosis, having more frequent pleuritis, ELE, arthritis, and myalgia tended to manifest a more severe form of the disease. Close monitoring of such patients may prevent the development of amyloidosis and CKD and improve the long-term prognosis of the disease.

Keywords: Familial Mediterranean fever, severity score, international severity score system

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Introduction

Familial Mediterranean fever (FMF), is an auto-inflammatory disease characterized by attacks of fever and serositis. The frequency and severity of attacks affects the quality of life and the course of the disease changes from patient to patient (1). Severe and frequent inflammatory attacks may be resulted with amyloidosis-associated kidney disease that usually progresses to end-stage renal disease (1). The clinical course of FMF is widely heterogeneous; it may vary from mild to severe pictures (2). Colchicine is the first choice of treatment to prevent the attacks and the subsequent development of amyloidosis. However, some patients with severe disease do not respond adequately to colchicine, in which case there is a need for further treatment options, including the use of monoclonal antibodies.

Several factors, including the homozygous M694V mutation and early-onset arthritis, have been associated with progression to amyloidosis (2, 3). However, there is a lack of agreement on the definition or classification of disease severity of FMF and the prediction of severe disease or risk of developing amyloidosis is uncertain. Therefore, our aim in this study was to evaluate the factors affecting disease severity in FMF.

Methods

The study included 150 FMF patients who were followed-up by the rheumatology department. Patients were diagnosed with FMF according to the Livneh criteria (4). The medical records of the patients were evaluated retrospectively and sex, age at the time of study, age at diagnosis, age at onset of the symptoms, presence of clinical findings such as fever, peritonitis, pleuritis, erysipelas-like erythema (ELE), myalgia and arthritis, complications such as amyloidosis and chronic kidney disease (CKD), and colchicine dosage were recorded.

The disease severity scores were evaluated with the international severity score system for familial Mediterranean fever (ISSF), which was developed by Demirkaya et al. (5).

Written informed consent was obtained from all patients who participated in this study.

ISSF score system

This system includes 10 items (9 main items, the 4th item is divided into two parts: a and b). Presence of item 4b (frequency of attacks > 2 per month) is equal to 2 points and the presence of other items is equal to 1 point. A total score ≥6 indicates severe disease, 3-5 means intermediate disease, and a score ≤2 is interpreted as mild disease (5).

This study was approved by the Clinical Research Ethics Committee of Eskişehir Osmangazi University (decision no. 80558721/G-310, Nov 2017).

Statistical analysis

Continuous data was presented as mean±standard deviation. Categorical data was presented as percentage (%) values. The relevance of data to normal distribution was surveyed with the Shapiro-Wilk test. The Mann-Whitney U test was used to compare two non-normally distributed groups. The Pearson Chi-Square test, Continuity Correction Chi-Square Test, Fisher's Exact Chi-Square Test, and Pearson Exact Chi-Square Test were used for cross table analysis. The IBM Statistical Package for the Social Sciences software version 21.0 (IBM SPSS Corp.; Armonk, NY, USA) was used for analysis. A value $p<0.05$ was considered statistically significant.

Results

The study population consisted of 150 FMF patients, of which 87 (58%) were female and 63 (42%) were male. The mean age of the patients was 35.71±13.22 years. The mean age at onset of disease was 16.88±10.87 years and the mean age at diagnosis was 26.95±13.69 years.

Patients were sorted into 3 groups based on the ISSF scores; ≤2=mild (Group1; n: 61), 3-5=moderate (Group 2; n: 70), and ≥6=severe (Group 3; n: 19). The demographic and clinical features of these 3 groups were compared.

Main Points

- Early onset and early diagnosed FMF, frequent pleuritis, ELE, arthritis, and myalgia attacks predict severe disease.
- ISSF system is a user-friendly tool that may help to identify a high-risk patient group.
- Close monitoring of patients with high ISSF scores may protect them from the development of amyloidosis and CKD.

Table 1. The correlation of ISSF scores and demographic features of the patients.

	ISSF Scores				
	≤2 (1)	3-5 (2)	≥6 (3)	p	Multi-correlation
Age (years)	35.09±13.75	37.61±13.51	30.68±8.68	0.160	-
Age at onset of disease (years)	16.88±9.07	18.48±12.25	10.94±9.06	0.009	1-3: 0.048 2-3: 0.028
Age at diagnosis (years)	26.62±12.83	29.31±14.40	19.34±11.13	0.031	1-2: 0.038 1-3: 0.033

Table 2. Comparison of clinical features of 3 patient groups.

	ISSF Scores			
	≤2 (1)	3-5 (2)	≥6 (3)	p
Fever	49 (80.3%)	63 (90.0%)	17 (89.5%)	0.253
Peritonitis	54 (88.5%)	65 (92.9%)	18 (94.7%)	0.579
Pleuritis	20 (32.8%)	33 (47.15%)	14 (73.7%)	0.006
Vasculitis	3 (4.9%)	7 (10.0%)	3 (15.8%)	0.293
ELE	11 (18.0%)	40 (57.1%)	13 (68.4%)	<0.001
Arthritis	7 (11.5%)	19 (27.1%)	9 (47.4%)	0.003
Myalgia	20 (32.8%)	19 (27.1%)	11 (57.9%)	0.041
Amyloidosis	3 (4.9%)	10 (14.3%)	9 (47.4%)	<0.001
CKD	2 (3.3%)	1 (1.4%)	4 (21.1%)	0.001

ELE: erysipelas-like erythema; CKD: chronic kidney disease.

Table 3. Comparison of dosage and duration of colchicine treatment between the groups.

	ISSF Scores				
	<2 (1)	3-5 (2)	>6 (3)	p	Multi-correlation p
Dosage of colchicine	1.29±0.34	1.41±0.60	1.34±0.55	0.517	-
Duration of colchicine usage	8.20±6.73	7.19±5.48	11.28±5.91	0.019	1-2: 0.024 1-3: 0.021

Patients with severe disease were found to be younger than patients with mild and moderate disease at onset and at diagnosis (16.88±9.07 years vs. 18.48±12.25 years vs. 10.94±9.06 years, p: 0.009 and 26.62±12.83 years vs. 29.31±14.40 years vs. 19.34±11.13 years, p: 0.031, respectively) (Table 1).

Fever, peritonitis, and vasculitis occurred similarly across the 3 groups. Pleuritis, ELE, arthritis, myalgia, amyloidosis, and CKD were more common in the severe disease group. The detailed comparison of all 3 groups is listed in Table 2.

Of the 150 FMF patients, 135 had available genetic test records. The M694V mutation was the most common MEFV mutation found from this data.

Although the dosage of colchicine was similar in all groups, the treatment duration was longer in the severe disease group (8.20±6.73 years vs. 7.19±5.48 years vs. 11.28±5.91 years, p: 0.019) (Table 3).

Discussion

In the current study, FMF patients were classified into 3 different groups according to their ISSF scores; group 1; mild, group 2; moderate, group 3; severe. Age at onset of disease and age at diagnosis were younger in Group 3. Pleuritis, ELE, arthritis, myalgia, amyloidosis, and CKD were more common in the severe

disease group. Gender distribution was not significantly different among groups. Fever and peritonitis, the most common features of FMF and mostly always the most common complaints on the first admission, were similar in all groups without any difference. Also, vasculitis did not show any difference among the groups, but it is one of the rarest clinical findings among all groups.

Disease severity correlates with early-onset disease, causing early admission. This finding is inconsistent with the results of a recent study (6).

Amyloidosis is the most feared complication of FMF and both arthritis and pleuritis were found to be related to the development of amyloidosis in a previous study by Kasifoglu et al. (7). In the current study, pleuritis, ELE, arthritis, and myalgia are more common in severe disease. These features may lead to increased inflammatory response, resulting in amyloidosis. Amyloidosis is also more frequent in the severe disease group.

Certain MEFV mutations, especially M694V, is suggested to be responsible for the development of amyloidosis (7). Also, Mor et al. (2) found a correlation between the M694V mutation and the severity of disease. However, we did not observe such a correlation and the frequency of M694V mutation was the same in all groups in our study. Factors in additional to genetic mutations, such as country of residence and early onset, may have a combined effect on disease severity.

Colchicine dosage did not show any difference between the groups, but the duration of colchicine treatment was longer in Group 3. Early onset and early diagnosis are some of the features of severe disease that lead to long-term colchicine treatment. However, the colchicine dosage may not be correlated with disease severity because individual differences in pharmacogenetics may be related to the net effective dosage of colchicine (8).

The small sample size was the most important limitation of our study. New prospective studies with a larger number of patients may present additional factors affecting the severity of disease in FMF. The ISSF system is a suitable tool for use in daily practice and may help to identify a high-risk patient group.

In conclusion, FMF patients with early onset and early diagnosis of the disease, having more frequent pleuritis, ELE, arthritis, and myalgia, tend to experience a more severe disease form. Management of this subgroup of patient and being attentive to the onset of new symptoms in the follow-up may be meaningful. Close monitoring of patients with severe disease may prevent the development of amyloidosis and CKD and improve their long-term prognosis.

Ethics Committee Approval: Ethics committee approval was received for this study from the Clinical Research Ethics Committee of Eskişehir Osmangazi University (Decision Number: 80558721/G-310; Decision Date: November 2017).

Informed consent: Written informed consent was obtained from the patients who participated in this study.

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