

ORIGINAL RESEARCH

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Frequency of depression, anxiety, and fatigue in fmf patients and their association with disease parameters**Sinem Sag¹, Mustafa Serdar Sag², Ibrahim Tekeoglu¹, Ayhan Kamanli¹, Kemal Nas¹**¹*Sakarya University Faculty of Medicine, Division of Rheumatology, Department of Physical Medicine and Rehabilitation, Sakarya, Turkey*²*Sakarya University Research & Training Hospital, Division of Rheumatology, Department of Physical Medicine and Rehabilitation, Sakarya, Turkey*

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Abstract

The aim of our study was to assess the levels of depression, anxiety, and fatigue in patients diagnosed with FMF (Familial Mediterranean Fever) and to examine their associations with drug compliance, attack, and being employed or not. Patients presenting to our rheumatology outpatient clinic Tel-Hashomer Classification Criteria were included in the study. Fifty-two diagnosed patients followed up in our rheumatology outpatient clinic (35 female, 17 male), and 30 healthy control subjects whose ages and genders match consisting of the accompanists and visitors of the patients (25 female, 5 male) were included. Risk for depression and anxiety was assessed with HADS (Hospital Anxiety and Depression Scale). Depression and anxiety were observed to be significantly more common in the patients with FMF compared to the healthy controls in this study. Also, the frequency of FMF attacks was found to be associated with depression, anxiety, and fatigue and that regular use of colchicine decreased fatigue. In the light of all these results, the mood should definitely be evaluated during the routine practice in case of a chronic disease such as FMF having a younger patient population compared to other rheumatic diseases, and, if needed, psychiatric support should be received. Also, it should be explained to the patients that the regular use of colchicine would be beneficial for both the disease and fatigue. There is a need for follow-up studies with large case series in order to support the results we obtained.

Keywords: Familial mediterranean fever, anxiety, depression**Introduction**

Familial Mediterranean Fever (FMF) is the most common hereditary inflammatory disease characterized by recurrent attacks of fever and serosal inflammation [1].

It is defined by clinical criteria and is associated with mutations of the MEVF gene that are believed to lead to a gain of function in the pyrin protein and thereby to an inappropriate release of Interleukin-1b. [2-5] FMF patients have recurring attacks of fever, pleuritis, peritonitis, arthritis and skin lesions. Colchicine is used for treatment. Colchicine should be used regularly in order to prevent organ injury that may occur during the course of FMF [6].

Anxiety and depression are commonly encountered problems in chronic rheumatologic diseases. They occur in diseases such as rheumatoid arthritis, ankylosing spondylitis [7-9]. However, they are ignored during daily practice. FMF is also a chronic disease characterized by recurrent attacks and, according to a widely accepted view, stress induces FMF attacks [10].

The aim of our study was to assess the levels of depression, anxiety, and fatigue in patients diagnosed with FMF and to examine their associations with drug compliance, attack, and being employed or not.

Material and Method

Patients presenting to our rheumatology outpatient clinic Tel-Hashomer Classification Criteria were included in the study. The patients were selected from FMF patients presenting to the outpatient clinic consecutively. The control group was selected from patient accompanists with no known diseases affecting the musculoskeletal system and from patient visitors and the two groups were matched regarding age and gender. The study was planned as a prospective, cross-sectional study. Patients' age, gender, body mass index (BMI), education status, disease duration, occupation, comorbidities, drugs used, and demographic data were recorded. In accordance with all the principles of Helsinki declaration, consent was obtained from the local ethics committee. Written consent was obtained from all patients.

***Corresponding Author:** Sinem Sag, Sakarya University Faculty of Medicine, Division of Rheumatology, Department of Physical Medicine and Rehabilitation, Sakarya, Turkey
E-mail: drsinemyamac@yahoo.com

Patients younger than 18 and older than 70 years, pregnant and lactating women, patients with orthopedic problems, patients with psychiatric disorders, those with severe systemic diseases

that would prevent working (cardiovascular, respiratory, severe gastroenterological and metabolic pathology), those with another inflammatory disease were excluded from the study.

Risk for depression and anxiety was assessed with Hospital anxiety and depression scale (HADS). It has been developed for determining the risk of anxiety and depression in the patient and for measuring its level and change in severity. Validity and reliability of the scale was studied by Aydemir et al. The lowest score that the patients could obtain from both subscales is 0 and the highest score is 21. Cut-off points of the Turkish version of HADS were 10 for the anxiety subscale (HAD-A) and 7 for the depression subscale (HAD-D) [11].

Fatigue severity scale was used to assess fatigue level [12].

Statistical analysis

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analyses. For evaluating study data, in addition to descriptive statistical methods (mean, standard deviation, median, frequency, rate, minimum, maximum), in the comparison of quantitative data, student's t test was used for comparing two groups with variables showing normal distribution and Mann Whitney U test for comparing two groups with variables not showing normal distribution. For comparing three or more groups not showing normal distribution, Kruskal Wallis test was used and Mann Whitney U test was used

for identifying the group causing the difference. Pearson's chi-square test, Fisher Freeman Halton Test, Fisher's exact test and Yates' continuity correction test (Yates corrected Chi-square) were used for comparing qualitative data. Spearman's correlation analysis was used in the analysis of inter-variable correlations. Significance was evaluated at levels of $p < 0.01$ and $p < 0.05$.

Results

Fifty-two diagnosed patients followed up in our rheumatology outpatient clinic (35 female, 17 male), and 30 healthy control subjects whose ages and genders match consisting of the accompanists and visitors of the patients (25 female, 5 male) were included.

All of the patients were taking colchicine medication. As an additional rheumatologic disease, three patients had spondiloartropathy. Of the patients, 47 (94%) used colchicine regularly. Thirty-four of them (68%) had a positive family history. The comparison of the demographic characteristics of the groups was summarized in Table-1.

The depression, anxiety, and fatigue severity scales (FSS) of the groups were summarized in Table-2.

Depression and anxiety levels of FMF patients, working and non-working, are summarized in Table-3.

Table 1. Evaluation of demographic characteristics according to groups

		Patient group (n=52)	Healthy group (n=30)	p
Age	Mean±SD	38,13±12,08	41,50±6,15	0,078
BMI	Mean±SD	25,24±6,07	25,54±8,75	0,099
		n (%)	n (%)	
Sex	Female	35 (67,3)	25 (83,3)	0,092
	Male	17(32,7)	5 (16,7)	
Smoking	No	39 (75,6)	25 (82,9)	0,247
	Yes	13(24,4)	5 (17,1)	
Duration of diagnosis (year)	Mean±SD	7,04±8,29		
Time between complaint and diagnosis	Mean±SD	14,38±10,76		
Student-t Test		Pearson Chi-Square Test		*p<0,05

Table 2. Assessment of Hospital Depression Scale (anxiety and withdrawal subscale) and Fatigue Severity Scale scores by groups

		Patient (n=52)	Healthy (n=30)	p
HDO Anxiety	Mean±SD	8,19±4,16	5,42±2,39	a0,008
HDO Depression	Mean±SD	6,93±3,88	4,76±2,44	a0,047
FSS	Mean±SD	38,57±16,34	13,13±7,48	a0,004
Time between complaint and diagnosis	Mean±SD	14,38±10,76		

aStudent-t Test

Table 2. Assessment of Hospital Depression Scale (anxiety and withdrawal subscale) and Fatigue Severity Scale scores by groups

		Working	Healthy (n=30)	p
(n=20)	Non-working (n=32)	p	5,42±2,39	a0,008
HDO Anxiety	Mean±SD	8,54±3,97	8,41±3,80	a0,758
HDO Depression	Mean±SD	5,42±2,26	7,04± 3,95	a0,149
FSS	Mean±SD	32,83±14,91	39,12±16,50	a0,421

aStudent-t Test

In Table-4, the frequency of attacks was found to be significant with anxiety and depression in the positive direction, while the negative correlation between fatigue and regular drug use was shown.

Table 1. Correlation of duration of depression, anxiety and fatigue with regular drug use and other parameters

	Depression	Anxiety	FSS
	r	r	r
Duration illness	0,220	0,056	0,116
Frequency of attacks	0,592	0,401	0,328
Regular use of medication	-0,100	0,082	-0,301

r=Spearman'ın Korelasyon Katsayısı $p < 0,05$

Discussion

Depression and anxiety were observed to be significantly more common in the patients with FMF compared to the healthy controls in this study. Also, the frequency of FMF attacks was found to be associated with depression, anxiety, and fatigue and that regular use of colchicine decreased fatigue.

The studies conducted today revealed that some cytokines as well as IL-1, IL-6 and TNF alpha were associated with anxiety [13,14].

Even during the attack-free periods of the FMF patients, it was suggested that the levels of some cytokines such as IL-18, IL-2, IL-6, IL-12, IL-17 were high and that these elevated levels indicated subclinical inflammation [14-18]. The frequency of anxiety and depression were shown to be increased in some inflammatory diseases with chronic inflammation [19].

A study demonstrated that serotonin was also effective in the pathophysiology of FMF and that SSRI therapy could be useful [20-22].

All these changes brought on by chronic inflammation and their reflections on the clinical picture can lead to the mood changes of patients. Whether there are mood changes and fatigue or not in patients with FMF have also been an issue of concern.

In a study conducted recently by Duruoğlu et al [19], depression, anxiety, and fatigue were investigated in FMF patients. Depression and anxiety scores were found to be higher in FMF patients compared to the control group. The other two studies conducted determined the prevalence of anxiety higher in FMF patients compared to the control subjects, however, no difference was detected among their depression scores [23-26].

Higher frequency of anxiety and depression was noted in FMF patients compared to healthy control subjects in the study conducted by Kucuksahin et al [27].

In a study including adolescents and children with FMF, depression scores were determined to be higher than healthy control subjects. The present study indicated an association between the frequency of FMF-attacks and levels of anxiety and depression.

We also found the levels of anxiety and depression significantly higher in FMF patients than in healthy control subjects. There was a positive correlation between attack frequency and fatigue, anxiety, and depression. In contradistinction to our study, a

negative correlation was detected between the number of attacks and fatigue in the study by Duruoğlu et al [19].

The changes in the patients' gender, education status, disease severity, medication doses and variations in genetic mutations may have caused this result. The regular use of colchicine was not associated with anxiety and depression whereas we found a negative correlation between regular use of colchicine and fatigue. Unlike other studies, we divided the FMF patients into two groups, namely employed and unemployed. No difference was found between two groups in terms of depression, anxiety, and fatigue.

The limitations of our study included not involving a very high number of patients into the study, not using an overall quality of life scale, not designing the study as a cross-sectional study, not including any patients during an attack. Cross-sectional planning of our work also has its limitations.

Conclusion

The frequency of depression, anxiety, and fatigue was found to be more common in FMF patients compared to the healthy control subjects in our study. The regular use of colchicine had a negative correlation with fatigue. In the light of all these results, the mood should definitely be evaluated during the routine practice in case of a chronic disease such as FMF having a younger patient population compared to other rheumatic diseases, and, if needed, psychiatric support should be received. Also, it should be explained to the patients that the regular use of colchicine would be beneficial for both the disease and fatigue. There is a need for follow-up studies with large case series in order to support the results we obtained.

Competing interests

The authors declare that they have no competing interest.

Financial Disclosure

The financial support for this study was provided by the investigators themselves.

Ethical approval

Ethical approval was obtained from the hospital administration to use the patients' data.

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