EVALUATION OF THE SLEEP QUALITY IN PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER

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ABSTRACT

Background*: Familial Mediterranean Fever (FMF) is a hereditary autoimmune disorder characterised by acute attacks of fever and serosal inflammation. This study aimed to investigate sleep quality in patients with familial Mediterranean fever (FMF).*

Methods*: The study involved 86 patients. The patients were enrolled in the study during an attack-free period. The sleep quality of all the patients was evaluated by the Pittsburgh Sleep Quality Index (PSQI).*

Results*: The PSQI total score was 6.5±4 and the prevalence of poor sleepers was 50% (43/86) according the PSQI total score in this study. Women with a higher number of attacks per year and patients resistant to the colchicine treatment had a poorer sleep quality ($p<0.05$).*

Conclusions*: This study underlines the need to assess and manage sleep problems in patients with FMF. Poor sleep quality cause other symptoms of the disease to aggravate. So, the physician must also assess the sleep quality when questioning the routine complaints of the patients with FMF.*

Key words*: familial Mediterranean fever, inflammation, sleep quality.*

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Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disease, common in Mediterranean communities and characterized by recurrent and self-limiting fever as well as abdominal pain, pleuritis, arthritis, and skin lesions similar to erysipelas[(1)]. The disease is caused by mutations in the MEFV (FMF gene) located on chromosome 16 and primarily affects Jewish, Armenian, Turkish, and Arab populations[(2)]. The most frequently seen country is Turkey, the prevalance changes between 1:150 and 1:10,000. The prevalance among Armenians is; 1:500. In Israel, FMF incidence varies according to the ethnic group being studied (Ashkenazi or non-Ashkenazi Jews), but that it is observed at a rate of 1:1000 on average[(3)].

Generally the attacks appear irregularly. Patients are usually asymptomatic between acute episodes and routine laboratory tests are mainly normal. Regardless of the affected site, the general characteristics of attacks are very similar: rapid emergence and brevity (6 hours to 4 days) of symptoms, high fever (>38°C), intolerable pain, spontaneous remission, and complete recovery[(4)]. FMF is a lifelong disorder requiring continuous treatment with colchicine. Although current treatments have greatly improved the health status of patients with

FMF, this condition is associated with significant morbidity in some cases, such as amyloid nephropathy[5].

Sleep problems are frequently observed in chronic disease progression. However, they are generally neglected among other symptoms and signs of the disease and rarely investigated by the physician. If the existing chronic disease is accompanied by pain, insomnia was detected in more than 88% of patients[6]. In a great number of studies, sleep problems are highly observed especially when focused on rheumatic diseases such as rheumatoid arthritis[7, 8], fibromyalgia[7, 8], juvenile idiopathic arthritis[9], juvenile dermatomyositis[9] and systemic lupus erythematosus[10], much less is known about FMF[11]. In patients monitored with the diagnosis of rheumatic disease, a close relationship was observed between symptoms such as disfluency, tiredness and sleep problems associated to the disease[12]. The results of the study conducted in children with FMF suggested that exercise-induced myalgia might contribute to sleep disturbances in FMF as well as ongoing subclinical inflammation[5]. Therefore, detection and treatment of sleep-related complaints of a patient is of great importance for the treatment of the disease.

Given the lack of data regarding the nature of sleep problems in FMF patients, the objective of this study was to determine the sleep quality and their frequency in patients monitored with the diagnosis of FMF.

Materials and methods

Subjects

This study was conducted at the Rheumatology Department in Meram Medical School of Necmettin Erbakan University from January 2012 to December 2013. The study included 86 patients who used colchicine regularly and fulfilled the clinical criteria for the diagnosis of FMF[13] (Table 1). The patients were enrolled in the study during an attack-free period.

The patients younger than 18 and older than 65 years, the patients who had an attack during the last 2 weeks, those with inflammatory rheumatic diseases other than FMF, those on the non-regular use of colchicine, those on the use of drugs which affect sleep quality, those suffering from hypothyroidism or anaemia, those with morbid obesity, and those with pregnancy or with diminished cognitive function were excluded out of the study.

Local ethics committee approved the study. All the participants were informed about the study, and written consent was obtained from all of them.

Major criteria	Minor criteria	Supportive criteria
Typical attack	1-3. Incomplete attacks 1 or more of the	1. Family history of FMF
1. Peritonitis (generalized)	1. Abdomen	2. Appropriate ethnic origin
2. Pleuritis (unilateral) or pericarditis	2. Chest	3. Age<20 years at disease onset
3. Monoarthritis (hip, knee, ankle)	3. Joint	4-7. Features of attacks
4. Fever alone	4. Exertional leg pain	4. Severe, requiring bed rest
	5. Favorable response to colchicine	5. Spontaneous remission
		6. Symptom-free interval
		7. Transient inflammatory response, with 1 or more abnormal test result for white blood cell count, erythrocyte sedimentation rate, serum amyloid A, and/or fibrinogen
		8. Episodic proteinuria/hematuria
		9. Unproductive laparotomy or removal of white appendix
		10. Consanguinity of parents
The diagnosis of FMF is suggested by the presence of at least 1 of 4 major criteria, 2 of 5 minor criteria, 1 minor criterion plus 5 of all 10 supportive criteria, or 4 of 5 specific supportive criteria		

Table 1: Criteria for the diagnosis of familial Mediterranean fever (FMF)[12].

Data collection

All the patients completed a questionnaire, which gathered age, gender, duration of disease, dosage and duration of colchicine use, compliance with the medication, family history, frequency and types of attacks. The participants were requested not to exercise 24 hours before the second visit, so as not to influence the Pittsburgh Sleep Quality Index (PSQI) scores.

During the second visit, the sleep quality of all the patients was evaluated by the PSQI. This instrument was recorded by a researcher.

Assessment of sleep quality

PSQI was created by Buyse et al. in 1989 to assess sleep quality[14]. Validity and reliability studies were performed by Agargun et al[15]. The PSQI consists of 24 questions, 19 of which are self-rated by the individual and the other 5 are answered by the partner or roommate of the individual. The total score ranges between 0 and 21 points. A higher total score indicates worse sleep quality. Based on the total score, sleep quality is rated as good (0-5 points) or poor (6-21 points).

Statistical analysis

Conformance of the variables to a normal distribution was investigated using visual and analytical methods. Mean (± standard deviation) values were used in the presentation of data. Clinical data conforming to a normal distribution were compared using a Student's t test, and those not conforming to a normal distribution were compared using a Mann-Whitney U test. A Chi-square test was used for comparison of frequencies. The statistical significance level was set at $p<0.05$.

Results

Of 103 study participants, 12 were excluded due to unwillingness to respond to the questionnaire and 5 due to time constraints, which resulted in incomplete responses to the questionnaire. Thus, the study was completed with a total of 86 patients. 32 patients were male (37.2%) and 56 were female (62.8%) with an average age of 33.4±12.0. Demographic data and clinical features of the patients in this study are shown in Table 2.

Parameter	Statistic
Gender (M/F)	32/54
Age (years) (mean±SD)	33.4 ± 12.0
Age of diagnosis (months) (mean±SD)	28.3 ± 11.9
Renal failure of the patients (n (%))	2 (2.3%)
Amyloidosis of the patients (n (%))	1 (1.1%)
FMF history in the family (n (%))	49 (56.3%)
Renal failure in the family (n (%))	11 (12.6%)
Amyloidosis in the family (n (%))	7 (8%)
Duration of colchicine use (years) (mean±SD)	5.18 ± 4.8
Dosage of colchicine	
0.5 mg/day (n (%))	4 (4.6%)
1 mg/day (n (%))	30 (34.9%)
1.5 mg/day (n (%))	47 (54.7%)
2 mg/day (n (%))	5 (5.7%)
Attacks while using colchicine (n (%))	49 (56.3%)
Attacks types	
Fever (n (%))	67 (77%)
Peritonitis (n (%))	74 (85.1%)
Pleuritis (n (%))	52 (59.8%)
Arthritis (n (%))	43 (50%)
Frequency of attacks	
More than 3 times for a month	53 (61.6%)
3 to 6 times for a month	12 (13.9%)
More than 6 times for a month	21 (24.4%)
FMF: Familial Mediterranean Fever, M: Male, F: Female, SD: Standard deviation	

Table 2: Demographic data and clinical characteristics of the patients with FMF (n=86).

The mean PSQI total score was 6.5±4 and the prevalence of poor sleepers was 50%(43/86) by PSQI total score in this study. PSQI total score was detected to increase (p=0.008) as the number of attacks per year increases. PSQI total score indicated that women have a poorer sleep quality than men (p=0.032). A poorer sleep quality was detected in patients who were resistant to the colchicine treatment (p=0.003), who had peritonitis attacks in the follow-up period (p=0.047). Demographic data and clinical features of the good sleepers compared with the poor sleepers are shown in Table 3.

Parameter	Good sleepers (PSQI≤5) (n=43)	Poor sleepers (PSQI>5) (n=43)	p value
Gender (M/F)	19/24	13/30	0.03
Age (years) (mean±SD)	32,5 ± 10,7	34,3 ± 13,2	0.48
Age of diagnosis (months) (mean±SD)	26.9 ± 10.5	29.8 ± 13.1	0.26
Renal failure of the patients (n (%))	0	2 (4.6%)	0.24
Amyloidosis of the patients (n (%))	1 (2.3%)	0	0.5
FMF history in the family (n (%))	26 (60.4%)	23 (53.4%)	0.33
Renal failure in the family (n (%))	6 (14%)	5 (11.6%)	0.5
Amyloidosis in the family (n (%))	3 (7%)	4 (9.3%)	0.5
Duration of colchicine use (years) (mean±SD)	5.8 ± 4.9	4.5 ± 4.7	0.21
Attacks while using colchicine (n (%))	16 (18.6%)	33 (38.3%)	<0.001
Attacks types			
Fever (n (%))	30 (34.8%)	37 (43%)	0.059
Peritonitis (n (%))	34 (39.5%)	40 (46.5%)	0.059
Pleuritis (n (%))	26 (30.2%)	26 (30.2%)	0.58
Arthritis (n (%))	20 (23.2%)	23 (26.7%)	0.33
Frequency of attacks (mean±SD)	1.41±0.79	1.83±0.87	0.022
≤3 times for a month (n (%))	33 (76.7%)	20 (46.5%)	0.074
>3 times for a month (n (%))	2 (4.6%)	10 (23.3%)	0.021
PSQI: Pittsburgh Sleep Quality Index, M: Male, F: Female, SD: Standard deviation			

Table 3:Demographic data and clinical characteristics of good versus poor sleepers .

Discussion

Sleep problems are common in chronic rheumatic diseases. In this study aiming to determine the sleep quality, we detected a poor sleep quality in the majority of patients with FMF. Women with a higher number of attacks per year and patients resistant to the colchicine treatment had a poorer sleep quality.

Sleep problems were detected in various rheumatic and musculoskeletal diseases, including

systemic lupus erythematosus, primary Sjögren's syndrome, osteoarthritis, lumbago, benign joint hypermobility syndrome and ankylosing spondylitis[10, 16]. So, in FMF, the sleep quality is expected to be affected. In a previous study by Ozcakar et al.[2] investigating the influence of subclinical inflammation on daily life of FMF patients, the authors asked questions about four items concerning weakness, lack of appetite, unwillingness to do daily activities, and sleep problems before and at least 6 months after colchicine therapy. They defined sleep problems as 'a decrease in the duration and quality of sleep'. Although they did not use a validated tool to assess sleep habits, they reported a significant decrease in the rate of sleep problems after colchicine therapy. Similarly, we detected a poor sleep quality in the majority of patients with FMF and patients resistant to the colchicine treatment had a poorer sleep quality in this study.

FMF is a disease that might often cause debilitating physical effects such as arthritis and chronic renal insufficiency, which would definitely cause sleep disturbances[9, 17]. In present study 2.3% of the patients had renal failure and 50% of patients had arthritis attacks.

Previous studies demonstrated that the number of attacks negatively affects sleep quality of FMF patients. Higher numbers of FMF attacks were associated with difficulty in falling asleep, more night waking and sleep disordered-breathing[5]. Similarly, this study detected that sleep quality is much more affected in patients with a higher number of attacks per year. We believe that the positive correlation between the number of FMF attacks and sleep disturbances may point out underlying inflammation. Because previous studies showed that inflammatory mediators effect the regulation of sleep in the central nervous system[19-20]. Interleukin-6 (IL-6), a proinflammatory cytokine, elevation was shown to affect the organism, with a focus on sleep-related symptoms and fatigue[21]. It is demonstrated that IL-6 was increased either during or between attacks in FMF patients[22].

The present study has some limitations. First, because the study was conducted in a single center, it cannot be generalized to the whole population, and so the situation has decreased the strength of the study. Second, there is no control group in our study. Third, disease severity score, MEFV mutation and serum C-reactive protein levels were not recorded for each patient. Finally, the present study was designed as cross-sectional, not longitudinal. Therefore, further and longitudinal studies are needed to support the results.

In conclusion, this study underlines the need to assess and manage sleep problems in patients with FMF. Poor sleep quality cause other symptoms of the disease to aggravate. So, the physician must also assess the sleep quality when questioning the routine complaints of the patients with FMF.

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