



Severity and frequency of restless legs syndrome in patients with familial Mediterranean fever

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Abstract

Objective: Restless legs syndrome (RLS) is a common sensory motor disorder. RLS an urge to move the extremities that may be accompanied by dysesthesias, and significantly affects quality of life of affected patients. The frequency of RLS is higher in different systemic inflammatory diseases. Familial Mediterranean fever (FMF) is an inherited inflammatory disease characterized by attacks of polyserositis, arthritis, and fever. The prevalence of RLS in patients with FMF is unknown. This study aimed to evaluate the prevalence rate of RLS in a sample of patients with FMF and compare this prevalence with that of a matched normal population.

Method: A total of 60 patients with FMF and 60 healthy controls were studied. All participants underwent a neurological examination. Diagnostic criteria as proposed by the International Restless Legs Syndrome Study Group (IRLSSG) were used to define RLS. The IRLSSG rating scale for the severity of RLS was applied to determine the severity of symptoms.

Results: The prevalence of RLS was not significantly different between patients and controls. Although the mean International Restless Legs Syndrome Rating Scale (IRLSRS) scores tended to be higher in patients compared with controls, this difference was not significant. When each item of the severity scale was compared between the two groups, significantly higher scores were found in some items of the IRLSRS in patients with FMF compared with controls.

Conclusion: According to this result, RLS symptoms in patients with FMF were more frequent and lasted longer than those in controls.

Keywords

Familial Mediterranean fever, restless legs syndrome, association

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Introduction

Restless legs syndrome (RLS) is a common neurological disorder that significantly affects quality of life of affected patients.^{1,2} This disease is a sensory motor disorder. RLS is described as an urge to move the extremities that may be accompanied by dysesthesias, which is referred to as an unpleasant, abnormal sensation while at rest. Uncomfortable sensations are relieved by movement and commonly worsen at night.² Epidemiological studies show that RLS occurs in 3%–15% of the population in adults.²⁻⁴

The majority of cases of RLS appear to be idiopathic in origin (primary RLS). Secondary cases are encountered in patients with various neurological and systemic diseases². RLS occurs with increased frequency during the course of several systemic inflammatory diseases.⁵⁻¹¹

Inflammatory diseases of the body are a group of systemic disorders, which are characterized by enhanced systemic inflammation and oxidative stress due to a defect in the innate immune system.¹² Familial Mediterranean fever (FMF) is an inherited disease that is characterized by attacks of polyserositis, arthritis, and fever. Recurrent non-specific inflammation in different joints, the peritoneum, and pleura causes clinical symptoms. The prevalence of FMF is high along the eastern Mediterranean coast and among the Turkish population.^{13,14}

Although an increased frequency of RLS in different systemic inflammatory diseases has

been reported, an association between FMF and RLS has not been investigated. Therefore, this study aimed to evaluate the prevalence rate of RLS in a sample of patients with FMF and compare this prevalence with that of a matched normal population

Materials and Methods

We studied 60 patients with FMF at Cumhuriyet Medical University Hospital from January 2014 to September 2014. Diagnosis of FMF was made according the Tel-Hashomer criteria and MEFV gene analysis (Table 1).¹⁵ Healthy age- and sex-matched control volunteers were recruited from the general population.

All patients and control subjects underwent a structured interview on concurrent similar diseases that cause RLS symptoms. Subjects with diabetes mellitus, chronic kidney disease, malignancies, rheumatoid arthritis (RA), systemic lupus erythamotosis (SLE), inflammatory gastrointestinal diseases, malignancies, and neurological diseases, including multiple sclerosis, polyneuropathy, and Parkinson’s disease, were excluded from the study. Patients and controls subjects who were taking medications that could potentially interfere with RLS and subjects with alcohol dependency were not included.

The study was approved by the local ethics committee. All of the subjects gave written informed consent according to the Declaration of Helsinki.

Table 1. Diagnostic Criteria for Familial Mediterranean Fever.

Tel-Hashomer diagnostic criteria (15)	
<i>Major criteria</i>	<i>Minor criteria</i>
Recurrent febrile episodes with serositis (peritonitis, synovitis, or pleuritis)	Recurrent febrile episodes
Amyloidosis of AA type without a predisposing disease	Erysipelas-like erythema
Favourable response to regular colchicine treatment	FMF in a first-degree relative

Definitive diagnosis: two major or one major and two minor criteria. Probable diagnosis: one major and one minor criteria.

A detailed neurological examination was performed by a neurologist in all subjects. This examination included deep tendon reflexes, pathological reflexes, muscle power, perception of a pinprick, touch, joint position, and vibration, and extrapyramidal signs.

Diagnosis of RLS was assessed in patients and controls according to the four essential diagnostic criteria established by the international RLS Study Group. These criteria were as follows: (1) an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; (2) the urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity, such as lying or sitting; (3) the urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues, and (4) the urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night.¹⁶ All of the subjects who received a positive diagnosis of RLS were asked to complete the 10-item International Restless Legs Syndrome Rating Scale (IRLSRS) to assess the severity of symptoms¹⁷. This rating scale was developed based on questions proposed by the members of the International RLS Study Group. Each question had a set of five response options that were graded from no RLS or impact (score = 0) to very severe RLS (score = 4). This produced a total score that ranged from 0 to 40.

In all of the participants, blood chemistry parameters, including a full blood count,

measurement of iron, ferritin, glucose, urea, creatinine, aspartate transaminase, alanine transaminase, calcium, potassium, magnesium, vitamin B 12, and folate levels, and thyroid hormone profiles were investigated.

Statistical analyses

Data are presented as mean \pm SD. Statistical analysis was performed with the Statistical Package for the Social Sciences for Windows (SPSS version 15.0, Chicago, IL, USA). Comparison of variables between the groups was performed with the Student's *t* test and the Mann–Whitney U test for numerical variables, and the chi-square test was used for categorical data. For all comparisons, *P* values less than 0.05 were considered significant.

Results

In the study group, there were 60 patients with FMF (47 females and 13 males) and the mean age was 35.00 ± 10.50 years. The control group was composed of 60 healthy individuals (47 females and 13 males) and the mean age was 34.81 ± 7.71 years. The distribution of age and sex was not different between the groups.

The diagnosis of RLS was established in 13 (21.7%) patients with FMF and in 10 (16.7%) controls using the RLS questionnaire (Table 2). The prevalence of RLS was not significantly different between patients with FMF and control subjects. The mean IRLSRS score was 24.15 ± 5.66 in patients

Table 2. Restless Legs Syndrome Frequency and Rating Scale Scores of the groups.

Groups	RLS+	RLS–	RLS (%)	IRLSRS	t/p value
Patients with FMF	13	47	21.7	24.15	t: 1.58
Controls	10	50	16.7	24.15	P: 0.127

RLS: Restless legs syndrome, RLS+: diagnosis of Restless legs syndrome, RLS–: no diagnosis of Restless legs syndrome, FMF: familial Mediterranean fever, IRLSRS: International Restless Legs Syndrome Rating Scale.

Table 3. Each Items Differences of the IRLSRS Between the Groups.

Groups	IRLSRS items									
	1	2	3	4	5	6	7	8	9	10
FMF/RLS	2.46	2.46	1.61	2.0	2.23	2.38	3.23	2.84	2.38	2.53
Control/RLS	2.20	2.40	1.70	1.90	2.40	2.30	2.30	2.0	1.80	2.00
P value	0.303	0.833	0.713	0.761	0.734	0.619	0.011	0.004	0.07	0.196

IRLSRS: International Restless Legs Syndrome Rating Scale, FMF/RLS: familial Mediterranean fever and restless legs syndrome, control/RLS: Control subjects and restless legs syndrome.

with FMF and RLS and 21.00 ± 5.66 in controls with RLS (Table 2). Although the prevalence of RLS and the mean IRLSRS scores tended to be higher in patients compared with controls, these differences were not significant. Each item of the severity scale was then compared between the two groups. Significantly higher scores were found in items seven and eight of the IRLSRS in patients with FMF compared with controls. Item seven rates the frequency of RLS symptoms and item eight rates the duration of symptoms. According to this result, RLS symptoms of patients with FMF were more frequent and lasted longer than controls (Table 3).

Blood levels of iron, ferritin, and haemoglobin, hormone profiles, and blood chemistry parameters were not significantly different between the groups.

Discussion

This study is the first to evaluate the frequency of RLS in patients with FMF. Many studies have reported an increase in RLS in several inflammatory diseases, including RA, SLE, Sjogren syndrome, Behçet’s disease, and Crohn’s disease.^{8–11,18–20} Reynolds et al.¹⁸ found an increased prevalence of RLS in patients with RA. Similar findings were reported by Salih et al., Taylor-Gjevrev et al., and Ishaq et al.^{19–21} No studies have reported an interaction between an increased frequency of RLS and serum ferritin levels. Hassan et al.⁹ found that the

prevalence of RLS in patients with SLE was 37.5% compared with 12.5% in control subjects. An association between RLS and SLE disease has been reported in a recent study¹⁰. Ediz et al.¹¹ recently reported that 29.4% of patients with Behçet’s disease had RLS compared with 4.8% of control subjects. These authors evaluated serum iron, ferritin, and haemoglobin levels, and mean corpuscular volume in the RLS group. They did not find any difference in these parameters between Behçet’s disease and RLS with those without RLS.

The exact pathophysiology of RLS remains unclear. The majority of RLS cases appear to be idiopathic in origin. Secondary cases are encountered in various underlying medical conditions, such as iron deficiency anaemia, renal failure, and pregnancy.² Approximately 40% of cases of RLS have a positive family history with dominant inheritance and several gene loci related to RLS have been identified.^{2,22} Although the pathophysiological mechanism underlying this disease is not completely understood, defective brain iron metabolism contributes to the pathogenesis of RLS. The descending diencephalospinal dopaminergic neurons, which are considered to originate in the A11 neurons of the hypothalamus, are proposed to play an important role in the pathophysiology of RLS.²³

The role of inflammation in RLS has been suggested by several studies that showed an increased ratio of small intestinal

bacterial overgrowth.²⁴ Additionally, there have been several case reports of RLS during the course of infections, such as human immunodeficiency virus, Streptococcus, mycoplasma, hepatitis C, Borrelia, and systemic inflammatory disease, including SLE, Sjogren's syndrome, and RA.²⁴⁻²⁶ Previous studies have shown that hepcidin is a protein in humans and is an important regulator of entry of iron into the circulation.²⁴ Expression of hepcidin is increased in the systemic inflammatory state. Upregulation of hepcidin leads to decreased absorption of iron and may decrease availability of iron in the central nervous system.²⁴

Forms of neurological involvement that may be encountered in FMF or are related to FMF-related diseases or treatment complications are as follows. Common neurological manifestations related to FMF are headaches and muscle pain.²⁷ Creatine kinase and electromyography results of patients with FMF are normal in those with myalgia. However, myopathy has also been reported in amyloidotic kidney transplant recipients with FMF.²⁸

Central nervous system involvement is relatively uncommon in FMF compared with that of the peripheral nervous system. Various types of seizures, cerebral venous sinus thrombosis, pseudotumour cerebri, optic neuritis, central nervous system vasculitis associated with systemic vasculitis, demyelinating lesions, ischaemic stroke, and recurrent aseptic meningitis have been reported.^{27,29-31}

The present study showed that the prevalence of RLS in patients with FMF was higher compared with that in controls, but this difference was not significant. Our study might have been underpowered regarding the number of subjects. The IRLSSG severity scale total score tended to be higher in patients compared with controls. However, significantly higher scores were obtained in some items of the scale in patients with FMF compared with controls. According to this

result, RLS symptoms were more frequent and lasted longer in patients with FMF than in controls.

RLS has a broad worldwide prevalence between 0.01% and 18.3%.³² The prevalence of RLS was reported as 3.2% and 9.7% in different prevalence studies in Turkey, with a relatively high prevalence in the centre of Turkey.³³⁻³⁷ The frequency of RLS in our control group appears to be higher than that reported previously in prevalence studies in Turkey.^{34,35} One reason for this discrepancy among studies may be the geographical location of Sivas City. All of the cities in these previous prevalence studies of RLS were at a lower altitude than Sivas (altitude of Sivas is 1285 m). The prevalence of RLS is greater among individuals who live in areas with a higher altitude.³⁸

The circadian rhythm of motor restlessness and sensory symptoms in RLS and the association of symptoms with endogenous melatonin levels suggest that ultraviolet radiation may be related to RLS expression³². Our study was conducted in a region with long-lasting winters, and people traditionally wear concealing clothing. These factors likely reduced sunlight exposure and this could affect the frequency of RLS.

To the best of our knowledge, this is the first study to investigate the prevalence of RLS in patients with FMF. We did not find an increased frequency of RLS in patients with FMF. However, results of this pilot study show that RLS symptoms in patients with FMF are more frequent and last longer than those in controls. Further investigations are needed to examine the potential effect of severity of symptoms on sleep and quality of life, and to assess the prevalence of RLS in a larger number of patients with FMF.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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