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Restless Leg Syndrome in Patients with Multiple Sclerosis and its Effect on Frequency of Daytime Sleepiness and Fatigue of the Patients

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Abstract

Background: Restless leg syndrome (RLS), fatigue and daytime sleepiness are three known co-morbidities in patients with multiple sclerosis (MS). The aim of this study was to evaluate the frequency of RLS in patients with MS and its effect on the frequency of fatigue and daytime sleepiness in these patients. **Material and Methods:** One hundred twenty patients who referred to the Inpatients Neurology Ward of Chamran hospital, affiliated with the Shiraz University of Medical Sciences, from June 2014 to March 2015, were selected as the study participants. The patients with clinically definite MS, according to the 2010 Revised Mc-Donald criteria, and expanded disability status scale (EDSS) ≤ 5.5 were included. RLS, fatigue and daytime sleepiness were assessed by the criteria of the International RLS study group (IRLSSG), fatigue severity scale (FSS) and Epworth sleepiness scale (ESS) respectively and the related statistical analyzes were conducted. **Results:** Seventy eight patients (65%) met all the four IRLSSG criteria, 77 patients (64.1%) suffered from fatigue and only 36 patients (30%) had excessive daytime sleepiness. RLS was not significantly linked to mean age, sex, MS duration, and daytime sleepiness of the studied MS patients, but fatigue was more frequent in MS patients with RLS, which was statistically significant ($P=0.018$). **Conclusion:** The main result of this study is that RLS is a common comorbidity in MS and the patients with MS, who also suffer from RLS. They have frequently experienced higher fatigue symptoms than those without RLS. Therefore, the appropriate diagnosis and management of RLS may improve both RLS and fatigue in these patients. [GMJ. 2016;5(1):7-12]

Keywords: Restless Legs Syndrome; Multiple Sclerosis; Fatigue; Daytime Sleepiness

Introduction

Restless legs syndrome (RLS) is a common neurological movement disorder with a prevalence of 5-15% in different populations [1-3]. This disorder is accompanied by periodic limb movements during sleep (PLMs), in

80% to 90% of cases which in turn contributes to an increase in fatigue and excessive daytime sleepiness which is due to inefficient nocturnal sleep [4, 5]. Age and sex are the two contributing factors in the frequency of RLS as it is about twice more frequent in women and it is more prevalent in the elderly [3, 6, 7].

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The causes of RLS are divided into idiopathic e.g. genetic factors and symptomatic, e.g., secondary to some neurologic and non-neurologic disorders. Iron deficiency anemia [8], chronic renal failure [9], pregnancy [10, 11], antidopaminergic, and antidepressant consumption are the known non-neurologic causes of RLS [12]. Polyneuropathy, Parkinson's disease, and spinocerebellar ataxia are among the neurologic causes [12].

Several studies have suggested a higher prevalence of RLS in the patients with multiple sclerosis (MS). The prevalence range of RLS in MS is from 13.3% reported by Gómez-Choco et al. [13] to 65.1% by Shaygannejad et al. [14]. Some other studies have reported that ALS in patients with MS is five times more frequent than that of the healthy controls [15-17]. Old age, longer duration of the disease, a primary, progressive form of MS, higher severity, and cervical spinal cord involvement increase the possibility of RLS in MS [15, 18]. In addition to more severe symptoms of RLS which is associated with MS [17], the usual co-occurrence of RLS with PLMs, leads to the repeated arousal or microarousal during sleep which can aggravate excessive daytime sleepiness and fatigue in these patients [15]. The aim of the current study is to evaluate the frequency of RLS in the studied MS patients and its effect on the frequency of fatigue and excessive daytime sleepiness in these patients.

Material and Methods

In this study, a cross-sectional study was performed. The population size was calculated based on the result of a previous study [14]:

$$n = \frac{(z_{1-\alpha/2})^2 \times p(1-p)}{d^2}$$

$$\alpha=0.05 \quad p=65.1\% \quad d=9\% \quad n=108$$

From June 2014 to March 2015, by a convenient sampling method, 120 MS patients who referred to the Inpatient Neurology Ward of Chamran hospital, affiliated with the Shiraz University of Medical Sciences, were enrolled in this study. All patients received a routine laboratory test and were visited by a neurologist. After explaining the objectives and methods of the study, a written informed consent form was obtained from all of the participants

and they were assisted throughout the study by the assistant researcher. This study was approved by the Medical Research Ethics Committee of Shiraz University of Medical Sciences (approval number: 92-6358).

Patient Selection

The inclusion criteria were: the patients who were between 16–65 years old with a definite diagnosis of MS according to the 2010 revised McDonald criteria for the diagnosis of MS [19] regarding their clinical course and treatment and those with expanded severity status scale (EDSS) ≤ 5.5 .

The Exclusion criteria were: the concurrent history of anaemia (Hb $<14\text{mg/dl}$ and Hb $<12\text{mg/dl}$ for men and women respectively), renal failure (serum creatinine >1.4 and >1.2 mg/dl for men and women respectively), hypothyroidism (serum TSH $>5\text{mIu/dl}$), pregnancy, diabetes (serum FBS $>120\text{mg/dl}$), the current history of depression and taking antidepressant, alcohol consumption, and the concomitant taking of sedatives (e.g. clonazepam), and antidopaminergic drugs and high dose steroid therapy during the past three months prior to the study.

RLS Assessment

The signs and symptoms of RLS were diagnosed in each patient using the International RLS Study Group (IRLSSG) criteria [1]. IRLSSG criteria comprise of four items: 1) unpleasant sensations in their legs; 2) worsening of the symptoms during rest; 3) the relief of symptoms of movement, and 4) exacerbation of the symptoms in the evening or at night. Due to more frequent sensory symptoms in patients with MS, to exclude RLS misdiagnosis, only patients who had all these four criteria were considered having RLS.

Daytime Sleepiness Assessment

The Epworth sleepiness scale (ESS) [20] questionnaire was used to evaluate daytime sleepiness. We used the validated Persian version of ESS [21] in our study. This scale comprises of eight items, in which each item is rated on a 4-point rating scale. The total ESS score ranges between 0 and 24, and the score ≥ 10 is accepted as having excessive daytime sleepiness.

Fatigue Assessment

All patients completed the validated Persian version of fatigue severity scale (FSS) [22] to evaluate the impact of fatigue. The FSS is a 9-item questionnaire that assesses the general effect of fatigue on some personal and social aspects of life. Each item is rated on a 7-point scale from 1 (strongly disagree) to 7 (strongly agree). After totaling scores of all the items the cut-off ≥ 36 was considered as exhaustibility.

Statistical Analysis

SPSS software version 17 (SPSS Inc, Chicago, IL) was used for the statistical analysis of the data. The frequency (%), mean and standard deviation (SD) were used for the description of the variables. The Chi-square test was used to compare qualitative variables. A T-test and Mann-Whitney tests were also used to compare quantitative variables. A P value less than 0.05 was considered as statistically significant.

Results

For the 120 patients who enrolled in this study with the age range of 18 to 55 years, the mean age was 33.1 ± 7.4 and the disease duration of 6.39 ± 5.16 years. 91 cases (75.5%) were female, and 29 (24.2%) were male. In this study, 78 MS patients (65%) with the mean age of 33.6 ± 7.26 met all the four criteria for RLS diagnosis. Fatigue was observed in 77

(64.2%) of the MS patients who achieved the score of >36 by FSS assessment. The mean age and disease duration of MS patients with fatigue were 34.5 ± 7.12 and the disease duration of 7.23 ± 5.03 years, respectively. Also the frequency of 36 (30%), for daytime sleepiness results which were assessed by ESS was included. The mean age and the disease duration of the MS patients with daytime sleepiness were 33.86 ± 7.37 and 6.6 ± 5.53 years, respectively. Table 1, represents the frequency of RLS and its relation to some demographic and clinical characteristics, fatigue, and daytime sleepiness. As indicated in Table 1, the MS patients with RLS experienced more fatigue symptoms and signs ($P = 0.018$), but there was no statistically significant difference in the age, gender, durations of MS and the evidence of daytime sleepiness between MS patients with or without RLS.

Discussion

The prevalence of RLS in the general population is reported to be between 1% to 12% in different studies [15, 23]. Some studies have indicated the lower frequency of RLS in Asian countries [24], with a prevalence of 7.5% in South Korea [25] and 1.06 % in a non-institutionalized Japanese elderly population [26]. Also, in a population-based study of 2,099 Iranian healthy people, Najafi, et al. [24] reported a prevalence of 8% and a female to male ratio of 1.75 for RLS.

Table 1. Frequency of RLS in the Studied MS Patients and its Relations with Some Demographic Data, Fatigue, and Excessive Daytime Sleepiness.

MS Patients	Female n (%)	Male n (%)	MS Duration Mean years \pm SD	Age Mean \pm SD	FSS+ n (%)	FSS- n (%)	ESS+ n (%)	ESS- n (%)
RLS+	62 (79.5)	16 (20.5)	6.8 ± 5.1	33.6 ± 7.26	56 (71.8)	22 (28.2)	26 (33.3)	52 (66.7)
RLS-	29 (69)	13 (31)	5.91 ± 5.23	32.2 ± 7.67	21 (50)	21 (50)	19 (23.8)	23 (76.2)
P value	NS*		NS §	NS ‡	0.018*		NS*	

*chi-square; § Mann-Whitney; ‡ t-test

The association between MS and RLS has been investigated in several studies. In a case-control study of 202 patients with MS and 212 healthy controls, Deriue *et al.* [17] reported a frequency of 45% for RLS in the MS patients in comparison with the frequency of 14.4% in the healthy controls. Moreover, they did not find any relationship between age, gender, MS course and durations, EDSS scores and developing RLS. The high prevalence of RLS in MS had no relation to age, sex, and MS duration and the frequency of RLS in this study [17] was similar to that of our findings.

In another study conducted by Manconi *et al.* [16], they reported that RLS in the patients with MS was 5.4 times more prevalent than that of the controls. This study also documented that the risk factors for developing RLS in MS patients were old age, primary progressive type, longer duration and more severe course of MS, which was measured by EDSS score [16]. Moreover, the involvement of the spinal cord by demyelinating lesions of MS is also a risk factor for RLS [18].

In a Brazilian multicenter study with a meta-analysis of the literature [27], the authors showed that the patients with MS had four times higher chance of getting RLS. Also, some case-control studies have reported that RLS was 2.25 to 5.4 times more frequent in patients with MS than that of the general population [16, 28].

Similar to our findings, in a case-control study of 126 Iranian patients with MS and 126 healthy controls, Shaygannejad *et al.* [14] found that the prevalence of RLS in their patients and controls were respectively 65.1% and 12.7%, but the frequency of RLS was not related to the age, gender and durations of MS. However, in this study [14], they found that RLS was more frequent in patients with MS, who had disabilities like higher EDSS score. Based on our exclusion criteria, the patients with EDSS > 5.5 were not evaluated. Hence, we did not evaluate the effect of the disability status of MS on the frequency of RLS. In another study of 205 Iranian patients with MS, Miri, *et al.* [29] found RLS in 27.8% of patients which was similar to that of our findings. They reported there was no difference between MS with or without RLS regarding

age, gender, MS durations and course.

The other findings of the present study revealed that the frequency of fatigue and excessive daytime sleepiness in MS patients was 64.1% and 30%, respectively. These results also showed that MS patients with RLS, complain of fatigue more than those without RLS ($P=0.018$), but there was no difference between MS patients with or without RLS regarding excessive daytime sleepiness. It seems that fatigue is the most common symptom in MS patients, which has multifactorial causes such as central, peripheral, immunological, hormonal, psychosomatic and pharmacological [15]. Moreira *et al.* [30], in an evaluation of 44 patients with MS to find the evidence of RLS, fatigue and sleep quality, reported the frequency of 73% and 6.8% for fatigue and excessive daytime sleepiness, respectively. Nevertheless, they did not find any relation between RLS and fatigue and excessive daytime sleepiness in their study. In another study which was conducted on 100 Iranian MS patients [31], the frequency of fatigue and excessive daytime sleepiness was 64% and 4%, respectively. They also found that depression had a negative effect on fatigue of the studied subjects [31]. Recently, Sieminski *et al.* [32] studied RLS in the patients with MS and found the negative effect of RLS on fatigue and sleep quality of patients and postulated that iron deficiency and chronic inflammation may have contributed to the development of RLS in patients with MS.

The limitations of our study are the lack of normal healthy controls, and we did not consider the effect of clinical course, treatment and disability status of MS on the studied variables.

Conclusion

RLS, as a common co-morbidity of multiple sclerosis, was established by the results of this study. At the same time, the patients with MS who suffered from RLS have experienced significantly higher fatigue symptoms than those without RLS. The appropriate diagnosis and management of RLS may improve both RLS and fatigue in these patients. Hence, we believe that further studies are required to scrutinize this issue in more depth.

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Conflict of Interests

The authors report that there is no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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