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Restless Legs Syndrome/Willis-Ekbom Disease in Multiple Sclerosis Patients with Spinal Cord Lesions

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ABSTRACT

Introduction: Spinal cord lesions in Multiple Sclerosis (MS) patients are associated with a higher risk of restless legs syndrome (RLS). In this study, we investigated the prevalence of RLS, sleep quality, presence and severity of depression, and the relationship of these parameters with cervical cord lesions in patients with RRMS.

Methods: This study was conducted in the outpatient multiple sclerosis clinic of Marmara University Hospital between October 2013 – February 2014, including 93 patients with the diagnosis of MS. After signing informed consent, demographic data, comorbidities and actual medication of the patients were collected. All patients completed the surveys including Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS) and Beck Depression Inventory (BDI). Prevalence of HBS, sleep quality and depression severity were compared between those with and without cervical cord lesions. Furthermore, the relationship between RLS and sleep quality, depression and expanded disability status scale (EDSS) was assessed.

Results: From overall patients, 72% were women (n=67) and 28% (n=26) were men. From all subjects, 32% (n=30) fulfilled IRLSSG diagnostic criteria. Fifty-seven percent of the patients (n=53) had pathological spinal cord lesions. Patients with RLS had significantly higher prevalence of pathological spinal cord lesions compared to patients without RLS (p=0.04). Sleep quality was found to be poor in both patients with cervical cord lesions and patients with RLS and this was statistically significant (p=0.031, p=0.0001).

Conclusions: In summary, the possibility of RLS development in RRMS patients increases with the presence of lesions in spinal cord. Sleep quality was found to be poor in both patients with cervical cord lesions and patients with RLS. As RLS is a potentially treatable condition, increased awareness of diagnosis of RLS in MS patients may be important for early treatment and improve the comfort of the patient.

Keywords: Restless leg syndrome/Willis-Ekbom disease, multiple sclerosis, spinal cord lesions

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INTRODUCTION

Multiple sclerosis (MS) is an autoimmune disease that affects individuals between 20 and 40 years of age with motor and non-motor symptoms. Four disease types have been described in MS, and relapsing-remitting multiple sclerosis (RRMS) is the most common disease course characterized by attacks and remissions. MS patients may have the poor quality of life (QoL) due to motor symptoms. But even if these patients respond well to treatment and can be free of motor symptoms, they can still have poor QoL due to conditions such as fatigue, depression and restless leg syndrome/Willis-Ekbom disease (RLS/WED).

RLS/WED is a neurological sensorimotor disorder characterized by the urge to move the legs accompanying unpleasant sensation during rest or inactivity. The symptoms only occur or are worse in the evening and night than during the day and partially or relieved by movement, at least as long as the activity continues. The features of the RLS should not be associated with another medical or behavioral disease such as myalgia, venous stasis, leg edema, and positional discomfort (1). The prevalence of clinically significant RLS in the general population ranges from one and five percent and shows regional differences (2). All published data about the prevalence of RLS in MS showed that RLS is more prevalent in MS patients, ranges from 13.3 to 65.1 (3–4).

The pathophysiology of the RLS formation is largely related to impaired dopamine metabolism caused by iron deficiency in the central nervous system. The benefits provided by dopaminergic therapies and various animal models support this hypothesis (5). Diencephalic-spinal (A11) dopaminergic nucleus is a subcortical dopaminergic system that projects into the spinal cord and is involved in antinociception function. It has been previously demonstrated that dopaminergic cell loss in the A11 nucleus in a small number of rats results in increased locomotor activity (6). Same researchers than suggested that dopaminergic neurons located in the A11 region, which are probably the only source of dopaminergic pathways for the spinal cord are involved in the pathology of RLS (7).

In this study, on the bases of these data, we investigated the prevalence of RLS, sleep quality, presence and severity of depression, and the relationship of these parameters with cervical cord lesions in patients with RRMS.

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METHODS

The research was conducted in accordance with the Helsinki Declaration and informed consent was obtained from all subjects.

The study was conducted at outpatient multiple sclerosis clinic of Marmara University Hospital between October 2013-February 2014. Ninety-three patients diagnosed with RRMS were included in the study. Patients must have been at least 18 years old, diagnosed with MS according to McDonald criteria.

After signing informed consent, patients filled out special inquiry forms. Demographic data, comorbidities and actual medication of the patients were collected. The diagnosis of RLS was confirmed with the International Restless Legs Syndrome Study Group (IRLSSG) diagnostic criteria. Patients, who responded positively to all five questions, were assessed as positive for RLS. Patients with negative or positive family history who developed RLS symptoms after MS onset were included in the study. The patients also completed other surveys including Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS) and Beck Depression Inventory (BDI) with the assistance of trained personnel. A global PSQI score >5 is shown to have a diagnostic sensitivity of 89.6% and a specificity of 86.5% and was used to separate good sleepers (<5) from poor sleepers (>5). The patients were divided into two groups as poor sleepers and good sleepers and investigated whether they were associated with RLS and cervical cord lesions. ESS was developed to evaluate the 'daytime sleepiness' of the patients. Eight different conditions were scored by the patient between the number of 0 and 3, as the total score can range from 0 to 24. Higher EDSS scores suggest patients 'daytime sleepiness' or patients 'average sleep propensity' . BDI is the self-administered scale involving 21 questions. Each questions are scored between the number of 0 and 3. The evaluation of the severity of the depression varies depending on the total score.

Blood samples were examined for blood count and biochemistry. Levels of B and D vitamins and iron metabolism parameters were also collected. We collected the results of cervical and cranial magnetic resonance imaging (MRI) of all patients.

Depression severity, sleep quality and prevalence of RLS were compared between those with and without cervical cord lesions. Furthermore, the relationship between RLS and sleep quality, depression and expanded disability status scale (EDSS) was assessed.

Statistical Analysis

Statistical Package for Social Sciences (SPSS, ver. 20.0, IBM computers, New York, USA) was used for all statistical analysis. A $p<0.05$ was considered significant. Student's test for parametric data and Mann-Whitney U-test for nonparametric data were used to compare between groups. Kolmogorov-Smirnov and Kruskal-Wallis test were used to evaluate the association between the groups in case of nonparametric data.

RESULTS

We evaluated 93 patients diagnosed with RRMS according to McDonald criteria. From overall patients, 72% were women (n=67) and 28% (n=26) were men. Mean age was 34.6±8.61 years, with MS duration 4.7±3.7 years. From all subjects, 32% (n=30) fulfilled IRLSSG diagnostic criteria. Comparing RLS + and RLS-patients, there was no difference in gender, disease duration, and upper motor neuron signs.

Although the level of B12 vitamin are in normal range in both RLS + and RLS-patients, the level of B12 vitamin was higher in RLS + patients. The other results of the blood tests are shown in Table 1.

Table 1. Differences in blood tests between RLS (+) and RLS (-) subgroups

	RLS (+)	RLS (-)	p-value
Ferritin (ng/ml)	25.29±19.85	20.56±10.41	0.134
Vitamin B12 (pg/ml)	286.26±123.29	225.07±71.81	0.003
Vitamin D (ng/ml)	21.42±5.18	20.23±4.27	0.246

Table 2. Differences between RLS (+) and RLS (-) subgroup

	RLS (+)	RLS (-)	p value
Male gender	9	17	0.807
	% 30	% 27	
Spinal cord lesion	22	31	0.043
	% 73	% 49	

RLS=Restless Leg Syndrome

Table 3. Sleep quality in MS patients with and without spinal cord lesions

	Spinal cord lesion (+)	Spinal cord lesion (-)	p value
Poor sleep	n=33	n=15	
Good sleep	n=20	n=25	p=0.031

Table 4. Sleep quality in MS patients with and without RLS

	RLS (+)	RLS (-)	p value
Poor sleep	n=24	n=24	
Good sleep	n=6	n=39	p=0.0001

RLS=Restless Leg Syndrome

Fifty-seven percent of the patients (n=53) had pathological spinal cord lesions. Patients with RLS had the significantly higher prevalence of pathological spinal cord lesions compared to patients without RLS (p=0.04) (Table 2). While the mean EDSS of the patients with RLS was 3.30±1.09, the patient without RLS was 1.9±1.4 (p=0.0001).

Even the patients with multiple sclerosis with cervical cord lesions tend to have higher beck depression scores, no statistical significance was found. Patients with cervical cord lesions have a lower quality sleep index when assessed according to the Pittsburgh sleep quality index, and this was statistically significant (p=0.031) (Table 3). Patients with RLS had higher BDI, and this was statistically significant (p=0.0001). Patients with RLS have a lower quality sleep index when assessed according to the PSQI, and this was statistically significant (p=0.0001) (Table 4). When we evaluate the subdivisions of the PSQI, there was a statistically significant difference in subjective sleep quality (p=0.0001), sleep latency (p=0.0001), sleep duration (p=0.001), habitual sleep efficiency (p=0.003), sleep disturbances (p=0.007) and daytime dysfunction (p=0.001). There was no difference in ESS when comparing between patients with or without RLS.

DISCUSSION

In our study, we found that 32% of patients fulfilled IRLSSG diagnostic criteria. According to published data, the prevalence of RLS ranges from 13.3 to 65.1 in MS patients. The wide variability between the prevalence of the RLS in MS patients is due to the difference of the diagnostic methods used for RLS diagnosis. Some authors used patient-filled questionnaires and the highest RLS prevalence were found in these studies. In our study, an interview and neurological examination were conducted by a neurologist. Some authors used a threshold of two days with RLS symptoms per week, reported a prevalence of 19% and in another study without applying the threshold prevalence of RLS was reported 32% (8). We didn't use the frequency threshold for RLS symptoms.

As we mentioned before, patients with and without family history and developed RLS symptoms after MS onset were included in the study. In a study performed by Vavrova et al., 6.4% of MS patients had RLS symptoms before the onset of MS and that 2.4% of MS patients had a positive family history and experienced RLS before the diagnosis of MS (8). The prevalence of idiopathic RLS in MS patients is 2.4–13.5%, which is similar to the general population. In our cohort, the prevalence of RLS may be found higher because patients with and without the family history were included in the study.

According to the results of Turkish Adult Profile and Epidemiology of Sleep Study (TAPES), the prevalence for RLS was reported as 5.2% in general population (9). Apart from MS some other chronic diseases such as end-stage renal disease, rheumatoid arthritis, epilepsia, myelopathy, hypothyroidism or hyperthyroidism, iron deficiency and pregnancy may cause secondary RLS. In a study evaluating the frequency of RLS in adults with epilepsy, the prevalence of RLS was found 5.2% similar to that observed in the general Turkish population (10). When we evaluate the RLS in patients with end-stage renal disease, the prevalence of RLS seems to be more common than in the general population, ranges from %7 to %45 (11).

Spinal cord lesions in MS patients were associated with a higher risk of RLS (12). Similarly, we found that the prevalence of cervical MR lesion was higher in patients with RLS than patients without RLS. The hypothalamic A11 region has been identified in several species as the primary source of descending dopamine (DA) to the spinal cord. Projections from the A11 region may reach the relevant regions in the spinal cord via diencephalospinal tract. Projections from the A11 region may contribute to locomotion, pain control and restless leg syndrome (5). In animal models, damage to the A11 site has resulted in increased locomotor activity. Therefore, any demyelinating lesion that occurs in this pathway in the spinal cord may lead to increased locomotor activity including RLS (7).

In general, women are more frequently affected by RLS than men. Age and sex in MS/RLS+ patients have been reported to be similar in those with MS/RLS-patients in most studies (13–15). We did not reveal gender difference comparing RLS + and RLS-patients. In a great majority of studies, the EDSS score, which is indicative of the severity of MS, is shown to be higher in RLS + patients (15–16). We found higher EDSS scores in patients with RLS. On the other hand, some conflicting data is showing that the EDSS score RLS+ patients was similar to that in RLS-patients (17).

Poor sleep and depression are common complaints in patients with MS. (18–19). The causes of sleep disturbances may pertain to MS-related symptoms such as fatigue and pain (20). In the present study, we report a higher frequency of poor sleep in MS patients (% 80). Separate analyses of each PSQI component showed that increased sleep latency and subjective sleep quality were the most frequent complaint among MS patients, followed by sleep duration, habitual sleep efficiency, sleep disturbances and daytime dysfunction. In a previous study investigating daytime sleepiness in MS patients, the researchers found no evidence for overall increased daytime sleepiness compared to healthy controls (21). In this study, the prevalence of daytime sleepiness in MS patients was 5.8%.

There are several limitations in our study. First, patients with and without the family history of RLS were included in the study and subgroup analysis of these patients was not evaluated. MS-related factors such as fatigue and pain were not evaluated, and their association with sleep disturbance has not been assessed. As this is a cross-sectional study, we cannot determine the relationship between the time of RLS onset and the occurrence of cervical cord lesion. Therefore, there is still a need for prospective studies to elucidate the relationship between RLS and cervical cord lesions.

In conclusion, multiple sclerosis patients with RLS had significantly higher prevalence of pathological spinal cord lesions compared to patients without RLS. The diagnosis of RLS in MS patients was related to the higher EDSS scores. Sleep quality was found to be poor in both patients with cervical cord lesions and patients with RLS. As RLS is a potentially treatable condition, increased awareness of diagnosis of RLS in MS patients may be important for early treatment and improve the comfort of the patient.

Ethics Committee Approval: The research was conducted in accordance with the Helsinki Declaration.

Informed Consent: Informed consent was obtained from all subjects.

Peer-review: Externally peer-reviewed.

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