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Restless Legs Syndrome in Multiple Sclerosis

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ABSTRACT

Introduction: The co-existence of Restless Legs Syndrome/Willis-Ekbom Disease (RLS/WED/WED) and multiple sclerosis (MS) is a common condition. For this reason, we aimed to evaluate the effects of RLS/WED and its relationship with MS.

Methods: We evaluated the clinical features of 102 patients diagnosed with MS who were in follow-up between 2010 and 2015 in outpatient clinic. All the patients were evaluated for RLS/WED according to the revised International Restless Legs Syndrome Study Group (IRLSSG) diagnostic criteria. The Expanded Disability Status Scale (EDSS), Beck Depression Inventory, Beck Anxiety Inventory and Fatigue Severity Scale scores of all the patients were recorded. The IRLSSG 2003 severity scale was used to determine the degree of RLS/WED.

Results: RLS/WED was detected in 30.4% (n=31) of the patients (MS-RLS/WED+), but not in 69.6% (n=71) (MS-RLS/WED-). The mean EDSS score of the MS-RLS/WED+ patients were 3.2±2.1 while the MS-RLS/WED-patients were 2.0±1.6. The incidences of depression, moderate or severe anxiety, fatigue and intestinal and bladder dysfunction in the MS-RLS/WED+ patients were significantly higher. Regarding to RLS/WED complaints, 32.2% were mild, 35.4% were moderate, 19.3% were severe and 12.9% were very severe. When the MS subgroups were evaluated the highest RLS/WED severity score was found in the secondary progressive MS group. In the patients with pyramidal symptoms and intestinal and bladder dysfunction, the mean RLS/WED severity was significantly higher. The mean RLS/WED severity score was also significantly higher in those with depression and anxiety. The RLS/WED severity was significantly correlated with the number of pyramidal attacks and the EDSS score.

Conclusion: Restless legs syndrome is a cause of depression, anxiety and fatigue and has negative effects on MS patients. Therefore, after the diagnosis of MS, the RLS/WED symptoms and signs should be determined, as soon as possible, in addition to the other MS symptoms. The treatment of this condition should be started early.

Keywords: Restless legs syndrome, multiple sclerosis, fatigue

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INTRODUCTION

Restless legs syndrome, also called Willis-Ekbom disease, (RLS/WED), is a sleep-related movement disorder characterized by irresistible urge to move the legs, often accompanied by unusual or unpleasant sensations. The symptoms occur or worsen at rest, typically during the evening or night, and improve with movement (1). RLS/WED is a common neurological disorder, with an estimated prevalence in the general population ranging between 7% and 9% (2). Iron deficiency, renal insufficiency, rheumatoid arthritis, neuropathy and dopamine antagonist drugs are the most common conditions related to RLS/WED. In addition, neurodegenerative diseases and neuroimmunological diseases such as MS, have been reported frequently in recent studies (3). Depression, anxiety and fatigue symptoms in MS patients may occur during the course of the disease itself, but may also be due to accompanying conditions, such as medications or RLS/WED (4). Increasing RLS/WED symptoms, especially during the evening hours or overnight, can lead to many different conditions, ranging from insomnia to fatigue and even depression (5). In addition, cognitive impairment and a poor quality of life may occur secondary to sleep disturbances (6). Although there have been many studies on the different outcomes regarding to RLS/WED frequency in MS patients in the literature, limited studies have reported on the life effects (7). In this study, we aimed to investigate the conditions of fatigue, depression and anxiety in MS patients with RLS/WED.

METHODS

We evaluated the clinical features of 102 patients [between 18 and 65 years old, with a mini-mental state examination (MMT) score of over 25], who were in follow-up with MS diagnoses between 2010 and 2015 in outpatient clinic. All the patients had definite MS diagnoses according to the 2010 McDonald criteria. All the participants enrolled in terms of age, gender, occupation, place of residence, hand dominance, family history, smoking and alcohol intake, drug use, underlying disease, bladder and bowel problems, duration of MS, age at MS onset, MS type and medications. Those patients with polyneuropathy, lower extremity venous insufficiency, renal failure, iron deficiency anaemia, diabetes, rheumatic disease history, pregnancy, alcohol or narcotic use, dopaminergic-antidopaminergic drug use, psychiatric drug use (selective serotonin reuptake inhibitor, serotonin and norepinephrine reuptake inhibitor), recently diagnosed with MS (6 months earlier) and a new MS episode (3 months earlier) were not included in this study.

All the participants were questioned about their RLS/WED symptoms using the 2012 revised International Restless Legs Syndrome Study Group (IRLSSG) diagnostic criteria by the investigator clinician in May-August 2015. The 2003 IRLSSG severity scale was used to determine the degree of RLS/WED symptoms. According to the RLS/WED severity scale, 31–

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40 points was very severe, 21–30 points was severe, 11–20 points was moderate and 1–10 points was mild. The Beck Depression Index (BDI), Beck Anxiety Index (BAI) and Fatigue Severity Scale (FSS) were applied to all patients. According to the BDI, scores over 18 were considered to be significant. For the BAI scores, 8–15 points was mild, 16–25 points was moderate and 26–63 points was severe. A FSS score of 45 and above was considered to be significant. The disability level of each patient was calculated according to the Expanded Disability Status Scale (EDSS).

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 15.0 for Windows was used for the statistical analysis. The Mann-Whitney U test was used to compare two independent groups of numerical variables, and the Kruskal-Wallis test was used to compare multiple groups of numerical variables. The rates in the independent groups were compared with a chi-squared analysis. Linear regression analysis was used to compare binary and ordered linear regression analysis for categorical binary variables. The statistical significance level of alpha was accepted as $p<0.05$.

RESULTS

The mean age of the patients was 36.0±11.2 years old, the mean MS onset age was 29.1±9.9 years old, and the mean MS duration was 6.9±5.8 years. Of the patients, 67.6% (n=69) were females and 32.4% (n=33) were males. When the MS types were analyzed, it was found that 72.5% (n=74) had relapsing-remitting (RR), 13.7% (n=14) had secondary progressive (SP), 6.9% (n=7) had clinically isolated syndrome (CIS), 3.9% (n=4) had primary progressive (PP) and 2.9% (n=3) had progressive-relapsing (PR). RLS/WED was detected in 30.4% of the patients (n=31) (MS-RLS/WED+), with 69.6% (n=71) undetected (MS-RLS/WED-). The majority of MS-RLS/WED+ patients were in the RR group, with a total of 17 patients; but the incidence of RLS/WED was highest in the SP MS subgroup (9 patients). In the other MS subgroups had 2 PR, 2 CIS and 1 PP (Figure 1).

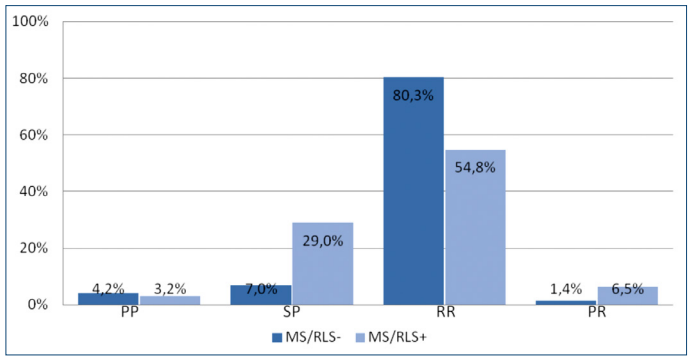

Figure 1. Relationship between restless legs syndrome (RLS) and the multiple sclerosis (MS) subtypes.

MS/RLS+: MS patients with RLS, MS/RLS-: MS patients without RLS, PP: primary progressive, SP: secondary progressive, RR: relapsing remitting, PR: progressive relapsing

The demographic and clinical characteristics of the patients are shown in Table 1. There was no statistically significant difference between the MS-RLS/WED+ and MS-RLS/WED-groups in terms of the age, sex, MS onset age, MS symptoms onset, MS episodes, MS duration and MS attack type ($p>0.05$). In the MS-RLS/WED+ patients, the pyramidal attack episodes, shortening of lower and upper limb vibration sensory examinations, and incidence of bowel and bladder dysfunction were statistically significant. In parallel with these, the average EDSS (3.2±2.1) of the MS-RLS/WED+ group was significantly higher than in the MS-RLS/WED-(2.0±1.6) ($p=0.007$) (Figure 2). Depressive complaints were detected in 36.3% of the patients according to the BDI scores for investigating the effects of RLS/WED. When the patients were evaluated according to the BAI, 33.3% had mild, 24.5% had moderate and 12.7% had severe anxiety disorders. The incidence of depressive complaints and moderate anxiety were significantly higher in the MS-RLS/WED+ than in the MS-RLS/WED- ($p<0.001$). The BDI and BAI results were significantly related RLS (OR: 4.10

Table 1. Demographic and clinical characteristics of the patients

	MS-RLS/WED-(N=71)	MS-RLS/WED+ (N=31)	
Age	34.8±10.6	38.7±12.4	0.161
Gender (F/M)	45/26	24/7	0.163
Age at MS onset	28.5±9.3	30.5±11.3	0.485
Duration of MS	6.2±5.0	8.3±7.1	0.299
MS clinical subtypes (%)			
Primary progressive	3 (4.2)	1 (3.2)	0.014
Secondary progressive	5 (7)	9 (29)	
Relapsing-remitting	57 (80.3)	17 (54.8)	
Progressive-relapsing	1 (1.4)	2 (6.5)	
Clinically isolated syndrome	5 (7)	2 (6.5)	
Total number of attacks	3.6±3.2	4.5±4.9	0.442
Number of pyramidal attacks	1.1±1.3	1.6±1.5	0.042
Number of cerebellar attacks	0.3±0.6	0.7±1.2	0.148
Number of sensory attacks	1.5±4.9	1.2±2.0	0.837
Number of brainstem attacks	0.6±0.7	0.5±0.8	0.447
Number of visual attacks	0.5±0.8	0.5±0.8	0.608
Number of mental attacks	0.0±0.1	0.0±0.2	0.552
Number of intestinal-bladder dysfunction	0.0±0.1	0.1±0.4	0.164
Duration of sense of vibration-upper	15.1±2.9	13.0±4.5	0.010
Duration of sense of vibration-lower	10.7±2.8	8.8±4.6	0.039
EDSS	2.0±1.6	3.2±2.1	0.007

MS, multiple sclerosis; EDSS, expanded disability status scale; MS-RLS/WED+, MS patients with restless legs syndrome; MS-RLS/WED-, MS patients without restless legs syndrome.

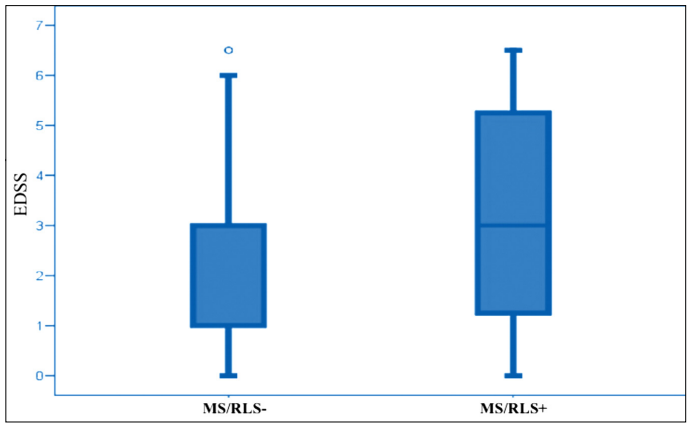

Figure 2. Relationship between restless legs syndrome (RLS) and the Expanded Disability Status Scale (EDSS).
MS/RLS+: multiple sclerosis patients with RLS, MS/RLS-: multiple sclerosis patients without RLS

Table 2a. Relationship between the EDSS with BDI and BAI complaints

		N	EDSS		p
			Mean	SD	
BDI	No	65	1.66	1.84	<0.01
	Yes	37	2.54	2.06	
BAI	No	30	2.30	1.93	<0.01
	Mild	34	2.57	1.83	
	Moderate	25	2.12	1.86	
	Severe	13	2.69	1.72	

The BDI and BAI results clearly showed that after controlling for EDSS, RLS has significant effect (p<0.001) than EDSS (p<0.01).

p<0.001; OR: 7.8 p<0.001 respectively for BDI and BAI) than EDSS (OR: 1.47 p<0.01; OR: 1.14 p<0.01 respectively for BDI and BAI)) (Table 2a).

In addition, 38.7% (n=12) of the MS-RLS/WED+ patients fulfilled the fatigue criteria, and this ratio was significantly higher than in the MS-RLS/WED-group (p=0.001). Moreover, the incidence of intestinal and bladder dysfunction in the MS-RLS/WED+ group was significantly higher (p=0.001) (Table 2b). The RLS/WED complaints were 32.2% mild, 35.4%

Table 2b. Effects of restless legs syndrome (RLS/WED) on the quality of life of the multiple sclerosis (MS) patients

		MS-RLS/WED-		MS-RLS/WED+		
		N	%	N	%	p
Intestinal dysfunction	No	65	91.5	20	64.5	0.001
	Yes	6	8.5	11	35.5	
Bladder dysfunction	No	50	70.4	11	35.5	0.001
	Yes	21	29.6	20	64.5	
BDI	No	54	76.1	11	35.5	<0.001
	Yes	17	23.9	20	64.5	
BAI	No	29	40.8	1	3.2	<0.001
	Mild	28	39.4	6	19.4	
	Moderate	8	11.3	17	54.8	
	Severe	6	8.5	7	22.6	
Fatigue	No	64	90.1	19	61.3	0.001
	Yes	7	9.9	12	38.7	

MS-RLS/WED+, MS patients with RLS/WED; MS-RLS/WED-, MS patients without RLS/WED; BDI, Beck depression inventory; BAI, Beck anxiety inventory.

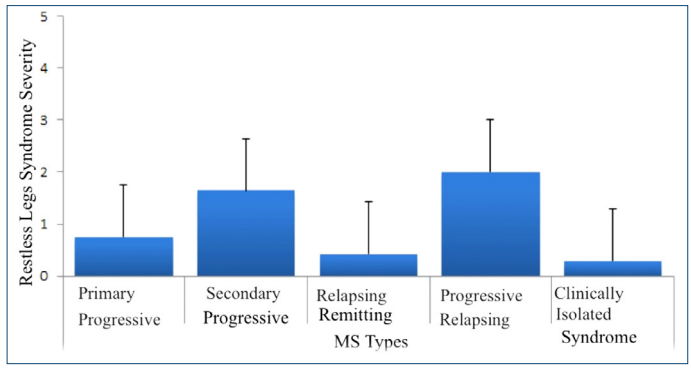

Figure 3. Relationship between the restless legs syndrome severity and the multiple sclerosis (MS) subtypes.

moderate, 19.3% severe and 12.9% very severe. When the relationship between the RLS/WED severity and the parameters was examined, there was a statistically significant difference among the MS clinical subtypes (The RLS/WED severity in the SP group was significantly higher than that in the RR group (p<0.001)) (Figure 3). The mean RLS/WED severity score in the patients with pyramidal symptoms and intestinal and bladder dysfunction was statistically higher than in those without RLS/WED. The mean RLS/WED severity score was significantly higher in those patients with depressive complaints, when compared to those patients without depressive complaints (p<0.001). In addition, there was a statistically significant difference between the anxiety grades and the RLS/WED severity (p<0.001). Moreover, the mean RLS/WED severity was significantly higher in those patients who had moderate to severe anxiety than in those who had no anxiety and those who had moderate to mild anxiety (p<0.001 for all). RLS/WED was positively correlated with the severity of the pyramidal episodes and the EDSS score, and it was negatively correlated with the loss of the sense of vibration, which was statistically significant (Table 3).

Table 3. Relationship between the restless legs syndrome (RLS/WED) severity and the clinical features of multiple sclerosis (MS)

	RLS/WED severity	
	rho	p
Age at onset of MS	0.081	0.419
Duration of MS	0.161	0.105
Number of attacks	0.128	0.201
Number of pyramidal attacks	0.254	0.010
Number of sensorial attacks	0.003	0.975
Bladder and intestinal dysfunction	0.132	0.187
Duration of sense of vibration-upper	-0.304	0.002
Duration of sense of vibration-lower	-0.277	0.005
EDSS	0.341	<0.001

EDSS, expanded disability status.

DISCUSSION

In previous studies, RLS/WED has been reported as a common condition in MS patients (7), with a prevalence ranging from 13.3% to 65.1%. In their study, Gomez-Choco et al. did not find a significant difference in the RLS/WED incidence between the MS group and the control group, with rates of 13.3% and 9.3%, respectively (8). The highest rate was found in a study conducted by Shaygannejad et al., who reported an incidence of 65.1% (n=126 MS patients) (9). The wide range of RLS/WED prevalence may be

due to the difficulty in diagnosing RLS/WED in MS patients, and the fact that the sensorimotor symptoms seen in MS can mimic RLS/WED (10, 11). In our study, the prevalence of RLS/WED in MS patients was 31.3%, which was consistent with literature. The REMS study performed by Manconi et al., the RLS/WED incidence was 5.4 times higher in the MS patients than in the control group. Moreover, advanced age, a long MS duration, high pyramidal and sensory impairment, and the PP MS subtype were identified as the reasons for the increased risk (1). In their study with Czech individuals, Vavrova et al. found that RLS/WED was most common in the SP MS subtype (12). When we evaluated the subgroups of MS, RLS was found to be more frequent in patients with RRMS, but its association with SPMS group was significantly higher. In contrast with the REMS trial, there was no statistically significant difference between the groups in terms of the MS duration, age at MS onset and type of MS attack. Some previous studies have reported that patients with RLS/WED have higher EDSS scores. This may be related to the onset of RLS/WED in the later years, which is associated with the increased degree of disability over time and the progression of the clinic of MS. However, a patient with a higher EDSS score may develop RLS/WED more easily, and the pathological process leading to RLS/WED may simultaneously worsen over the course of MS (7). There was no statistically significant relationship between the two groups in terms of the average age in our study, but the EDSS scores of the patients with RLS/WED were statistically higher than in those without RLS/WED. Fatigue was recently recognized as the most common symptom of MS. It adversely affects daily activities and causes an increase in disability. In their study, Aydar et al. detected fatigue in 61.2% of their MS patients (13). Moreira et al. confirmed that RLS/WED is common in MS patients, and that it is associated with poor sleep quality and fatigue (14). Moreover, Manconi et al. and Miri et al. showed that insomnia is very common in MS patients with RLS/WED (15, 16). In our study, fatigue was found in 18.6% of the MS patients, and it increased to 38.7% in the MS-RLS/WED+ group, which was statistically significant (p=0.001). There are a number of studies describing the prevalence of RLS/WED in MS, but there are limited studies evaluating the relationships between fatigue and sleep disturbances (17). Only Ayder et al. drew attention to depression, and they found depression in 49.2% of the MS patients and 13.2% of the control group in their study. However, the reasons for the differences in the depression rates between the MS-RLS/WED+ and MS-RLS/WED-patient groups have not been evaluated (13, 17). In order to evaluate the effects of RLS/WED on MS patients we applied the BDI, BAI and FSS. Based on the results of the BDI scores, depressive complaints was detected in 36.3% of the MS patients. The MS-RLS/WED+ patients exhibited 33.3% mild, 24.5% moderate and 12.7% severe anxiety disorders when assessed by the BAI. The incidence of depressive complaints and moderate to severe anxiety in the MS-RLS/WED+ patients was statistically higher than in the MS-RLS/WED-patients (p<0.001). In the REMS study, Manconi et al. used the IRLS/WEDSG scale, and they found that the RLS/WED severity was very advanced in the MS patients (1). Aydar et al. and Fragoso et al. obtained similar results using the same scale (13, 18). The IRLSSG scale was also used to determine the RLS/WED severity in our study. The presence of RLS/WED and the severity of RLS/WED were significantly higher in patients with pyramidal symptoms or bowel-bladder dysfunction.

In addition, the mean RLS/WED severity score was statistically higher than in those without depression and anxiety (p<0.001). There was a significant positive correlation between the severity of the RLS/WED, the number of pyramidal attacks and the EDSS score. The BDI and BAI results clearly showed strong correlation with RLS than EDSS. The BDI and BAI results were significantly related RLS (OR: 4.10 p<0.001; OR: 7.8-p<0.001 respectively for BDI and BAI) than EDSS (OR: 1.47 p<0.01; OR: 1.14 p<0.01 respectively for BDI and BAI))

In conclusion, the presence of pyramidal involvement and high EDSS scores in MS patients were found to be related to the presence and severity of RLS/WED. In the MS-RLS/WED+ patients, depression, anxiety, fatigue and intestinal and bladder dysfunction were more common than MS-RLS/WED-group, and RLS/WED seems to the reason. And these symptoms are increased by the RLS/WED severity. For this reason, RLS/WED complaints should be identified as soon as possible after the diagnosis of MS, in addition to the other symptoms, and the treatment of this condition, which has a detrimental effects on the quality of life, should be regulated.

Ethics Committee Approval: The study was approved by the Institutional Ethics Committee of T.C. Sağlık Bakanlığı Istanbul Training and Research Hospital (date: 06.02.2015, no: 568).

Informed Consent: Informed consent was obtained from all patients or their legal guardians, following provision of detailed information on the study examinations and tests.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - UE; Design - TG; Supervision - UE; Resource - TG; Material: TG; Data Collection and/ or Processing - TG; Analysis and/or Interpretation - TG; Literature Search - YE; Writing - YE; Critical Reviews - OÖY.

Conflict of Interest: No conflict of interest was declared by the authors.

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