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ARTICLE

Restless legs syndrome/Willis-Ekbom disease in multiple sclerosis: a contributing factor for anxiety, disability, sleep disorder, and quality of life

Síndrome de las piernas inquietas/enfermedad de Willis-Ekbom en la esclerosis múltiple: un factor que contribuye a la ansiedad, la discapacidad, los trastornos del sueño y la calidad de vida

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ABSTRACT

Background: Restless legs syndrome (RLS) is one of the most common and burdensome sleep disorders in the course of multiple sclerosis (MS). **Objective:** To evaluate common MS-related symptoms and consequences between groups with and without RLS and further assess the association of quality of life determinants with RLS symptom severity. **Methods:** According to their RLS status, 46 relapsing-remitting MS patients were divided into MS-RLS+ (n=19) and MS-RLS- groups (n=27). Specific questionnaires were administered to assess the patients' health-related quality of life (HRQoL), fatigue levels, sleep quality, daily sleepiness, anxiety, and depression symptoms. Functional capacity was examined using the Expanded Disability Status Scale (EDSS). **Results:** The prevalence of RLS was 41.3%. Compared to the MS-RLS- group, those with RLS had higher EDSS scores, more cranial and spinal lesions, longer disease duration, and were older. In the MS-RLS+ group, symptom severity scores were positively correlated with higher anxiety and poorer sleep quality. The symptom severity score was negatively correlated with mental HRQoL and pain scores. **Conclusion:** In conclusion, the findings of the current study indicate the negative impact of RLS on functional capacity, anxiety, sleep quality, and mental HRQoL of MS patients. Further studies using more accurate diagnostic strategies for identifying RLS and other sleep disorders are necessary to clarify the association of MS with RLS and explore relevant clinical implications.

Keywords: Restless Legs Syndrome; Sleep Disorder; Multiple Sclerosis.

RESUMEN

Antecedentes: El síndrome de piernas inquietas (SPI) es uno de los trastornos del sueño más comunes y onerosos en el curso de la esclerosis múltiple (EM). **Objetivo:** El objetivo de este estudio fue evaluar los síntomas y las consecuencias comunes asociados con la EM entre los grupos con y sin SPI y evaluar aún más la asociación de los determinantes de la calidad de vida con la gravedad de los síntomas del SPI. **Métodos:** De acuerdo con su estado de SPI, 46 pacientes con EM recurrente-remitente se dividieron en los grupos EM-SPI+ (n=19) y EM-SPI- (n=27). Se utilizaron cuestionarios específicos para evaluar la calidad de vida relacionada con la salud (CVRS), los niveles de fatiga, la calidad del sueño, la somnolencia diaria, la ansiedad y los síntomas de depresión de los pacientes. La capacidad funcional se examinó mediante la escala ampliada del estado de discapacidad (*Expanded Disability Status Scale* — EDSS). **Resultados:** La prevalencia de SPI fue del 41,3%. Em comparación com el grupo EM-SPI-, aquellos com SPI tenían púntuaciones más altas em la EDSS, más lesiones craneales y espinales, mayor duración de la enfermedad y eran mayores. Los puntajes de gravedad de los síntomas em el grupo EM-SPI+ se correlacionaron positivamente con una mayor ansiedad y una peor calidad del sueño. Se observaron correlaciones negativas entre la puntuación de gravedad de los síntomas y la CVRS mental y los puntajes de dolor. **Conclusiones:** En conclusión, el estudio actual indica el impacto negativo del SPI en la discapacidad funcional, la ansiedad, la calidad del sueño y la CVRS mental de los pacientes con EM. Se necesitan más estudios que utilicen estrategias de diagnóstico más precisas para identificar el SPI y otros trastornos del sueño para aclarar la asociación de la EM con el SPI y para explorar implicaciones clínicas relevantes.

Palabras clave: Síndrome de Las Piernas Inquietas; Trastornos del Sueño-Vigilia; Esclerosis Múltiple.

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Restless legs syndrome/Willis-Ekbom disease (RLS/WED) is an idiopathic neurological disorder characterized by the distressing urge to move extremities accompanied by uncomfortable sensations[1]. Typically, symptoms occur at rest and during the night and improve with movement[2]. Approximately 15% of the general population has RLS/WED, and the prevalence ranges from 25 to 65% in multiple sclerosis (MS) patients[1,3]. Thus, RLS/WED becomes one of the most common and burdensome sleep disorders in the course of MS[4]. RLS/WED symptoms are linked to demyelination sites among individuals with MS[3]. Its diagnosis and management can be easily overlooked since it occurs at night and has severe accompanying sensory-motor symptoms. These disturbances can result in a poor quality of life[5]. Previous studies of MS patients have shown that RLS/WED contributes to fatigue, impairments on functional capacity, sleep quality, and, therefore, health-related quality of life (HRQoL)[6,7]. In MS patients, some researchers have reported that depression and worse clinical disability are closely related to RLS/WED[8].

In this study, we compared common MS-related symptoms, disability status, spinal lesions, sleep quality, daytime sleepiness, fatigue, depression, anxiety, and HRQoL between groups with and without RLS/WED.

METHODS

Participants

After the ethics committee approval (Reference number: 2011-KAEK-25 2016/13-21), the current study enrolled 75 patients diagnosed with relapsing-remitting MS (RRMS), according to the 2010 McDonald criteria, at least 2 years before the evaluation from the neurology clinic of a Training & Research Hospital (Bursa, Turkey). These patients gave their informed consent to participate in this research. Participants aged 18–65 years, with Expanded Disability Status Scale (EDSS) score between 0 and 5.5, and experiencing RLS/WED symptoms at least three times per week were included, while patients with neurological diseases other than MS, any clinical relapse within three months, and any of the secondary RLS/WED symptoms (e.g., iron deficiency, anemia, pregnancy, chronic kidney disease) were excluded. Thus, the final sample consisted of 46 patients.

Updated diagnostic criteria from the International RLS Study Group (IRLSSG) were used to diagnose RLS/WED, and the IRLSSG international RLS (IRLS) rating scale was used to evaluate the severity of RLS/WED symptoms[9,10]. The face-to-face interview was conducted by the same neurologist. Patients were divided into two groups: RLS/WED group (n=19; MS-RLS+) and non-RLS group (n=27; MS-RLS-).

Design and data collection

The participants' demographic and clinical characteristics, including age, gender, body mass index (BMI), and disease duration, were recorded. The same neurologist used the EDSS score to measure physical disability. Biochemical analysis of blood samples was performed at the clinical laboratory of our facility under standard hospital procedures. The MSQoL-54 questionnaire was administered to evaluate HRQoL levels[11]. MSQoL-54 is an MS-specific HRQoL instrument that supplements the SF-36[12]. It has 18 disease-specific questions, measuring social, cognitive, and sexual function, pain, energy, health distress, and overall quality of life. Two summary scores are generated, one for mental HRQoL (mental composite score — MCS-54) and one for physical HRQoL (physical composite score — PCS-54). Standardized scores range from 0 to 100, and higher scores indicate better HRQoL.

Beck Depression Inventory (BDI) was used to assess the patients' depressive symptoms, and the Hamilton Anxiety Rating Scale (HAMA) evaluated anxiety levels. BDI consists of 21 questions and is scored between 0 and 63 points[13]. HAMA is one of the first reliable and valid interviewer-administered instruments assessing the severity of anxiety. It has 14 items rated 0 to 4 with general guidelines for distinguishing the degrees of severity (0=not present, no symptoms; 1=mild; 2=moderate; 3=severe; 4=very severe, incapacitating)[14].

Subjective sleep quality was evaluated by the Pittsburgh Sleep Quality Index (PSQI). PSQI is scored between 0–21 points, and a score >5 points is considered poor sleep quality. The index consists of seven components, including subjective sleep quality, sleep duration, sleep latency, habitual sleep efficiency, use of sleep medication, daytime dysfunction, and sleep disturbances[15].

The Fatigue Severity Scale (FSS) was used for assessing fatigue levels[16], and finally, the Epworth Sleepiness Scale (ESS) was administered to patients to evaluate their daily sleepiness status[17].

We used a 1.5T MRI system to check for any brainstem, hemispheric (especially basal ganglia and deep structures), or spinal (cervical-thoracic) involvement. The site of involvement was classified as the brain and the spinal cord in MS patients. Cranial lesions were considered as <9 or >9. Sagittal T1/T2-weighted and axial T2-weighted sequences were routinely performed in all patients with spinal lesions. The analysis included the extension of the lesion on both sagittal and axial distributions. Two experienced observers conducted the MRI analysis by consensus, unaware to whom the scans belonged.

Statistical analyses

Statistical analyses were carried out using the SPSS software (version 23.0). Independent samples t-test was used to compare quantitative data according to groups. The relationship between the variables in the patient group was examined with Pearson's correlation. Analysis of categorical data, according to groups, was performed with the chi-square test. Analysis results are expressed as mean and standard deviation for quantitative data and frequency and percentage for categorical data. The significance level adopted was $p<0.05$.

RESULTS

In this study, the prevalence of RLS/WED among RRMS patients was 41.3%. Patients were divided into two groups: RLS/WED group (n=19; MS-RLS+) and non-RLS group (n=27; MS-RLS-). Table 1 presents the patients' demographic and clinical characteristics. Six MS-RLS/WED patients had mild symptoms, five had moderate symptoms, six had severe symptoms, and two had very severe symptoms, according to the IRLS rating scale. All patients were receiving MS-immunomodulatory therapy, such as; glatiramer acetate (n=11), interferon (n=9), teriflunomide (n=7) natalizumab (n=1), dimethyl fumarate (n=4), fingolimod (n=12), and ocrelizumab (n=2).

Compared with the MS-RLS/WED- group, those with RLS/WED were older and had higher EDSS scores, longer disease duration, and more cranial and spinal lesions. Serum iron and ferritin levels did not differ between the two groups (p=0.567; p=0.757).

No significant differences were detected between the groups regarding BDI, HAMA, PSQI, FSS, ESS, and mental and physical HRQoL scores (p>0.05) (Table 2).

Moreover, in the MS-RLS/WED+ group, the IRLS score was positively correlated with HAMA (r=0.540; p=0.017) and PSQI (r=0.625; p=0.004) scores. The IRLS score was negatively correlated with mental HRQoL (r=-0.477; p=0.039) and pain scores (r=-0.482; p=0.037, Table 3).

RLS/WED symptom severity showed no correlation with the number of spinal lesions, EDSS, iron, and ferritin levels (p<0.005).

Table 1. Demographic and clinical characteristics of the groups according to restless legs syndrome diagnosis.

	MS-RLS+ (n=19) mean±SD	MS-RLS- (n=27) mean±SD	p-value*
Age (years)	45.32±10.61	38.07±7.74	**0.010**
Weight (kg)	70.42±12.36	70.96±13.11	0.888
Height (cm)	164.47±6.53	165.04±7.85	0.799
BMI	26.22±5.36	25.88±3.19	0.807
EDSS	1.87±1.03	1.22±0.58	**0.020**
Number of spinal lesions	2.74±1.76	1.33±1.3	**0.003**
Disease duration (years)	11.11±5.82	8.26±6.89	0.149
	n (%)	n (%)	
Gender(m/f)	5/14	5/22	0.719
Number of cranial lesions			
<9	1 (5.3)	9 (33.3)	**0.031**
>9	18 (94.7)	18 (66.7)	
Use of antidepressants (Yes/No)	8/11	7/20	0.405

MS-RLS: multiple sclerosis-restless legs syndrome; SD: standard deviation; *with Student's t-test; RLS: restless legs syndrome; BMI: body mass index; EDSS: Expanded Disability Status Scale. Bold text indicates a statistically significant difference with a p-value<0.05.

Table 2. Questionnaire results of the groups.

	MS-RLS- mean±SD	MS-RLS+ mean±SD	p-value*
BDI	13.04±11.08	15.53±9.12	0.428
HAMA	12.37±9.3	14.89±9.04	0.364
PSQI	6.07±4.57	7.74±4.57	0.231
FSS	33.7±17.71	37.42±16.38	0.474
ESS	2.63±2.99	3.95±3.67	0.187
Mental HRQoL (MCS-54)	54.73±18.48	58.3±17.25	0.512
Physical HRQoL (PCS-54)	56.06±20.93	60.29±25.11	0.538
Social function	68.33±25.3	76.31±32.66	0.355
Cognitive function	52.04±32.32	65.24±27.47	0.155
Pain	57.28±26.58	67.37±33.87	0.264
Energy	38.37±22.22	44±27.19	0.445
Health distress	60.79±23.51	70.26±28.65	0.225
Sexual function	57.71±36.91	30.7±40.45	**0.023**
Overall quality of life	55.81±20.46	57.92±18.59	0.722

MS-RLS: multiple sclerosis-restless legs syndrome; SD: standard deviation; *with Student's t-test; RLS: restless legs syndrome; BDI: Beck Depression Inventory; HAMA: Hamilton Anxiety Rating Scale; PSQI: Pittsburgh Sleep Quality Index; FSS: Fatigue Severity Scale; ESS: Epworth Sleepiness Scale; HRQoL: health-related quality of life. MCS: mental composite score; PCS: physical composite score. Bold text indicates a statistically significant difference with a p-value<0.05.

Table 3. Correlation analysis of restless legs syndrome symptom severity and quality of life determinants in the multiple sclerosis-restless legs syndrome+ group.

		RLS symptom severity (IRLS)
BDI	r	0.423
	p-value	0.071
HAMA	r	**0.540**
	p-value	**0.017**
PSQI	r	**0.625**
	p-value	**0.004**
FSS	r	0.054
	p-value	0.826
ESS	r	0.221
	p-value	0.362
Mental HRQoL (MCS-54)	r	**-0.477**
	p-value	**0.039**
Physical HRQoL (PCS-54)	r	-0.334
	p-value	0.162
Social function	r	-0.315
	p-value	0.189
Cognitive function	r	-0.072
	p-value	0.770
Pain	r	**-0.482**
	p-value	**0.037**
Energy	r	-0.197
	p-value	0.420
Health distress	r	-0.552
	p-value	0.114
Sexual function	r	0.375
	p-value	0.114
Overall quality of life	r	-0.245
	p-value	0.311

RLS: restless legs syndrome; BDI: Beck Depression Inventory; HAMA: Hamilton Anxiety Rating Scale; PSQI: Pittsburgh Sleep Quality Index; FSS: Fatigue Severity Scale; ESS: Epworth Sleepiness Scale; HRQoL: health-related quality of life. MCS: mental composite score; PCS: physical composite score; RLS: restless legs syndrome. Bold text indicates a statistically significant difference with a p-value<0.05.

DISCUSSION

In this study, we firstly presented data regarding HRQoL, psychiatric symptoms, sleep disturbances, and fatigue levels of MS patients with and without RLS/WED and data regarding RLS/WED symptom severity in MS patients. We found that MS patients had a high prevalence of RLS/WED. The MS-RLS/WED+ group experienced even further functional capacity impairment and had more cranial and spinal lesions compared to MS patients without RLS/WED. Moreover, RLS/WED symptom severity was significantly correlated with higher anxiety, reduced sleep quality, and lower mental HRQoL and pain scores.

MS is a neurological disease associated with long-term functional and physical disability. Levels of functional disability were significantly higher in RLS/WED patients than in those without RLS/WED. RLS/WED severity was not associated with the EDSS score in the current study. A recent study conducted by Giannaki et al. reported a negative effect of RLS/WED on the functional capacity of MS patients[6]. In addition, this study identified significant fatigue and reduced sleep quality in MS-RLS/WED+ patients. This finding might explain the differences between the two groups regarding functional capacity. In our sample of individuals with MS and RLS/WED, increased RLS/WED symptom severity was correlated with worse perceived sleep quality — patients with moderate-to-very severe RLS/WED reported significantly worse perceived sleep quality than those with mild RLS/WED severity, corroborating previous studies[18,19]. These results are not surprising because individuals with RLS/WED have longer sleep latency, shorter total sleep time, and a higher prevalence of insomnia symptoms than MS patients without RLS/WED[18,19]. Contrary to previous studies, MS-RLS/WED+ patients showed no difference in the fatigue index score compared to the MS-RLS/WED- group, and no significant correlation was found between the severity of RLS/WED symptoms and the fatigue index[20]. This scenario probably results from the low disability status of the patients and the small sample size. Furthermore, ESS scores were similar in both groups, and symptom severity did not affect daily sleepiness scale scores in our study.

MS patients are known to have impaired HRQoL. Impaired HRQoL has been associated with physical disability, sleep disturbances, depression, and fatigue[21]. In a previous study, the MS-RLS/WED+ group experienced further impairments on various factors associated with HRQoL in the MS population, such as sleep, depression, and functional capacity[6]. In another research conducted by Cederberg et al.[22], RLS/WED was associated with significantly worse mental and physical HRQoL, anxiety, depression, and fatigue, thereby suggesting that RLS/WED may negatively impact HRQoL and associated outcomes in adults with MS. In our study, lower mental HRQoL and greater anxiety scores were correlated with higher symptom severity in the MS-RLS/WED+ group, confirming previous studies. In contrast, no significant differences were found in terms of depression, physical HRQoL, and HRQoL subdomains, except sexual function and pain. This further suggests that sleep disturbances and anxiety symptoms may be essential mediators in the relationship between RLS/WED and HRQoL in adults with MS.

Many authors have suggested that demyelination sites are responsible for the development of RLS/WED among individuals with MS. These hypotheses are very speculative because the exact anatomical background of RLS/WED remains unclear[7]. Spinal lesions are suspected to be an anatomopathological substrate of RLS/WED[23]. The MS-RLS/WED+ group had more cranial and spinal lesions compared to MS patients without RLS/WED in our study. This fact may be explained by the sensory symptoms of patients with spinal lesions and the degeneration of spinal pathways resulting from demyelination, which may lead to the onset of RLS/WED symptoms. Besides, the number of lesions could be only a secondary association and not directly responsible for RLS/WED.

Significant limitations must be considered when interpreting our results. The present study had a cross-sectional design, restricting the conclusion about the direction of the association and precluding any inferences of causality or temporality. Since the study participants are RRMS patients, our results are not fully representative of the entire MS population. The low sample size was another limitation. The history of medication use other than MS drugs, such as antidepressants, was not investigated. This aspect presents another limitation while assessing the symptom severity of RLS/WED. Also, disease-modifying drugs may affect the RLS/WED prevalence among MS patients; however, the data available did not allow us to analyze this scenario.

In conclusion, we found that RLS/WED has a negative impact on functional capacity, anxiety, sleep quality, and HRQoL in MS patients. RLS/WED undertreatment is common in the MS population. Future prospective studies are necessary to understand whether RLS/WED treatment in MS patients can improve their overall health and quality of life.

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