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Investigation of the Relationship Between Restless Legs Syndrome and Sleep Quality in Multiple Sclerosis Patients

Multipl Skleroz Hastalarında Huzursuz Bacak Sendromu ile Uyku Kalitesi Arasındaki İlişkinin İncelenmesi

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Abstract

Objective: This study aimed to determine the prevalence of restless legs syndrome (RLS) in patients with multiple sclerosis (MS) and to evaluate its effect on sleep quality.

Materials and Methods: This cross–sectional study was approved by the Ethics Committee of Kütahya Health Sciences University. A total of 151 patients with a confirmed diagnosis of MS were included. The Cambridge–Hopkins RLS Questionnaire, RLS Severity Scale, and Pittsburgh Sleep Quality Index (PSQI) were administered. Demographic, clinical, and radiological data were recorded. Patients were divided into two groups according to the presence of RLS, and appropriate parametric and non–parametric statistical tests were used for comparisons.

Results: The mean age of the participants was 40.6 ± 8.6 years, and 68.9% were female. The prevalence of RLS was 37.7%. Patients with RLS were older and had higher Expanded Disability Status Scale scores, a greater proportion of secondary progressive MS and primary progressive MS subtypes, and more frequent spinal lesions ($p < 0.05$). Poor sleep quality was observed in 63.2% of patients with RLS ($p = 0.01$). Logistic regression analysis showed that the presence of RLS increased the risk of PSQI by 3.37–fold ($p = 0.006$), and a family history of RLS was also an independent risk factor ($p = 0.01$).

Conclusion: RLS is common among MS patients and is associated with PSQI. The presence of RLS, spinal lesions, higher disability levels, and older age negatively affect sleep quality. Early recognition and management of RLS in MS patients may improve sleep quality and overall quality of life.

Keywords: Multiple sclerosis, restless legs syndrome, sleep quality

Öz

Amaç: Bu çalışmada, multipl skleroz (MS) hastalarında huzursuz bacak sendromu (HBS) sıklığını belirlemek ve HBS'nin uyku kalitesi üzerindeki etkisini değerlendirmek amaçlanmıştır.

Gereç ve Yöntem: Kütahya Sağlık Bilimleri Üniversitesi Etik Kurulu onayıyla yürütülen kesitsel çalışmaya, MS tanısıyla izlenen 151 hasta dahil edilmiştir. Katılımcılara Cambridge–Hopkins HBS Anketi, HBS Şiddet Skalası ve Pittsburgh Uyku Kalitesi İndeksi uygulanmıştır. Demografik, klinik ve radyolojik veriler kaydedilmiştir. Gruplar HBS varlığına göre karşılaştırılmış, istatistiksel analizlerde uygun parametrik ve non–parametrik testler kullanılmıştır.

Bulgular: Katılımcıların yaş ortalaması 40,6 ± 8,6 yıl olup, %68,9'u kadındı. HBS sıklığı %37,7 olarak saptandı. HBS'si olan MS grubunda yaş, Genişletilmiş Özürlülük Durum Ölçeği skoru, sekonder progresif MS ve primer progresif MS oranları ile spinal lezyon varlığı anlamlı olarak daha yüksekti ($p < 0,05$). HBS'si olan hastaların %63,2'sinde uyku kalitesi kötü bulundu ($p = 0,01$). Lojistik regresyon analizine göre HBS varlığı kötü uyku kalitesi riskini 3,37 kat artırdı ($p = 0,006$); ailede HBS öyküsü de bağımsız risk faktörüydü ($p = 0,01$).

Sonuç: MS hastalarında HBS sık görülmekte ve kötü uyku kalitesiyle ilişkili bulunmaktadır. HBS varlığı, spinal lezyonlar, yüksek engellilik düzeyi ve ileri yaş ile birlikte uyku kalitesini olumsuz etkiler. MS hastalarının takibinde HBS'nin erken tanı ve tedavisi uyku kalitesinin iyileştirilmesi açısından önem taşır.

Anahtar Kelimeler: Multipl skleroz, huzursuz bacak sendromu, uyku kalitesi

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Introduction

Restless legs syndrome (RLS) is a chronic neurological disorder characterized by abnormal sensory symptoms. Although well known, it is still easily overlooked or misdiagnosed in clinical practice. RLS manifests as restlessness, sensations of burning or tingling in the legs, and a strong urge to move the legs. Although these sensations are not typically painful, they cause considerable discomfort. Symptoms predominantly occur during rest, intensify at night, and consequently lead to chronic sleep disturbances and emotional distress. Epidemiological studies show that RLS occurs in 1–15% of the population, with a higher frequency in women (1,2). Allen et al. (3) reported a prevalence of 7% in the general population.

Multiple sclerosis (MS) is a chronic autoimmune disease characterized by neuroinflammation and neurodegeneration and typically diagnosed between the ages of 20 and 40 years. Until recently, RLS in individuals with MS was considered a primary sensory manifestation of MS. However, subsequent studies have established MS as a secondary cause of RLS.

RLS occurs in approximately 30% of MS patients, a rate significantly higher than seen in general population (4). Auger et al. (5) identified RLS in 37.5% of 200 MS patients, compared to 16% in a control group of 100 individuals. Current literature suggests that RLS reduces sleep quality and increases fatigue in people with MS (6,7). In fact, greater RLS symptom severity in MS was shown to be associated with poorer sleep quality (8).

Given its high prevalence in MS patients, RLS is likely to contribute to impaired sleep quality and fatigue in these patients. However, there is a limited number of studies exploring the relationship between these variables. Therefore, this study aimed to investigate the effect of RLS on sleep quality and fatigue in patients with MS.

Materials and Methods

Patients aged 18 years and older with a diagnosis of MS were included in this cross–sectional study. Exclusion criteria were pregnancy, a diagnosis of any chronic disease other than MS (e.g., diabetes mellitus, renal failure, malignancy, rheumatological diseases, obstructive sleep apnea syndrome), and previous diagnosis or treatment for RLS. Following the provision of written informed consent, the Cambridge–Hopkins RLS Questionnaire was administered to 151 patients who had been followed with a definitive MS diagnosis for at least 6 months in the MS outpatient clinic (3). Based on the questionnaire results, patients were categorized into two groups: MS patients with RLS (n = 57) and MS patients without RLS (n = 94).

The Pittsburgh Sleep Quality Index (PSQI) was administered to all patients, and the RLS Severity Scale was also administered to patients with RLS. Routine neurological examinations were conducted and medical records were reviewed. Personal data forms were used to record demographic characteristics, MS subtype, disease duration, Expanded Disability Status Scale (EDSS) scores, lesion locations on brain and spinal (cervical and thoracic) magnetic resonance imaging (MRI), antidepressant medication use, immediate family history of RLS, and laboratory values including ferritin level. Immunotherapy was classified as first–line (interferon–beta, glatiramer acetate, teriflunomide, dimethyl fumarate) or second–line (fingolimod, natalizumab, cladribine, ocrelizumab, rituximab) treatment.

This study was approved by the Local Ethics Committee of Kütahya Health Sciences University (decision number: 2021/01–04, date: 20.01.2021).

Statistical Analysis

The normality of data distribution for continuous variables was assessed using the Kolmogorov–Smirnov test for continuous variables. Normally distributed variables were presented as mean and standard deviation, while non–normally distributed variables were expressed as median and range. Comparisons between groups for continuous variables were performed using the independent samples t–test or the Mann–Whitney U test, as appropriate. Categorical variables were compared using Pearson's chi–square test, continuity correction, or Fisher's exact test. Potential predictors of PSQI were evaluated using logistic regression analysis. IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY), and a p–value <0.05 was considered statistically significant.

Results

The mean age of the 151 patients included in the study was 40.62 ± 8.6 years. Of these, 47 (31.1%) were male and 104 (68.9%) were female. When grouped by the presence of RLS, 57 patients (37.7%) were included in the MS/RLS+ group and 94 patients (62.3%) in the MS/RLS–group. The demographic, clinical, and social characteristics of all patients are presented in Table 1.

In the comparison between groups, the mean age was significantly higher in the MS/RLS+ group than in the MS/RLS–group (43.07 ± 8.72 years vs. 39.13 ± 8.23 years, $p = 0.006$). Regarding MS disease course, the secondary progressive MS (SPMS) and primary progressive MS (PPMS) subtypes were more frequent in the MS/RLS+ group ($p = 0.006$). The median EDSS score was 2.5 (range, 0–8) in the MS/RLS+ group, which was significantly higher than in the MS/RLS– group (median 1.5, range 0–7.5; $p < 0.001$).

Comparison of MRI findings showed that spinal lesions were more common in the MS/RLS+ group, affecting 41 patients (71.9%) compared to 51 patients (54.3%) in the MS/RLS–group ($p = 0.04$). According to PSQI results, PSQI was identified in 36 patients (63.2%) in the MS/RLS+ group versus 39 patients (41.5%) in the MS/RLS– group ($p = 0.01$). Regarding employment status, the proportion of unemployed patients was significantly higher in the MS/RLS+ group (57.9% vs. 30.9%, $p = 0.02$). In terms of immunotherapy, significantly more patients in the MS/RLS+ group were receiving second–line treatment (59.6% vs. 38.3%, $p = 0.01$). No significant differences between the groups were found for other variables (Table 1).

Based on PSQI scores, 76 patients (50.3%) were classified as having good sleep quality and 75 patients (49.7%) as having PSQI. Demographic, clinical, and social variables were compared between these groups. Patients with PSQI had a

Table 1. Comparison of clinical and demographic characteristics of MS patients with and without RLS.

	Total (n = 151)	MS/RLS+ (n = 57, 37.7%)	MS/RLS- (n = 94, 62.3%)	Test statistics	p
Age (years), (mean ± SD)	40.62 ± 8.60	43.07 ± 8.72	39.13 ± 8.23	2.78	**0.006**
Gender, n (%)					
• Male • Female	47 (31.1) 104 (68.9)	20 (35.1) 37 (64.9)	27 (28.7) 67 (71.3)	0.40	0.52¥
MS duration (years), median (range)	7 (0.3-28)	7 (0.3-21)	7 (0.5-28)	2561	0.65
MS subtype, n (%) • RRMS • PPMS • SPMS	 127 (84.1) 4 (2.6) 20 (13.2)	 42 (73.7)[a] 4 (7)[a] 11 (19.3)[a]	 85 (90.4)[b] 0[b] 9 (9.6)[b]	10.31	**0.006**≠
EDSS, median (range)	1.5 (0-8)	2.5 (0-8)	1.5 (0-7.5)	1731	**<0.001**
Family history of RLS, n (%)	17 (11.3)	5 (8.8)	12 (12.8)	0.23	0.62¥
Antidepressant use, n (%) • Yes • No	 47 (31.1) 104 (68.9)	 22 (38.6) 35 (61.4)	 25 (26.6) 79 (63.4)	1.85	0.17¥
Ferritin, n (%) • Normal • Low	 128 (84.8) 23 (15.2)	 45 (78.9) 12 (21.1)	 83 (88.3) 11 (11.7)	1.73	0.18¥
MRI lesions, n (%) • Periventricular • Juxtacortical • Infratentorial • Spinal lesion	 146 (96.7) 88 (58.3) 68 (45) 92 (60.9)	 57 (10.0) 28 (49.1) 22 (38.6) 41 (71.9)	 89 (94.7) 60 (63.8) 46 (48.9) 51 (54.3)	 - 2.5 1.53 3.94	 0.15ǧ 0.10¥ 0.21≠ **0.04**¥
PSQI score, mean ± SD					
Poor sleep quality (PSQI <5), n (%) • Good • Bad	 76 (50.3) 75 (49.7)	 21 (36.8) 36 (63.2)	 55 (58.5) 39 (41.5)	6.66	**0.01**≠
Oligoclonal band positive, n (%)	142 (94)	53 (93)	89 (94.7)		0.61ǧ
Education, n (%) • Primary School • High School • University	 22 (14.6) 52 (34.4) 77 (51)	 12 (21.1) 22 (38.6) 23 (40.4)	 10 (10.6) 30 (31.9) 54 (57.4)	5.13	0.07≠
Marital status, n (%) • Married • Single	 133(88.1) 18 (11.9)	 53 (93) 4 (7)	 80 (85.1) 14 (14.9)	1.41	0.23¥
Employment status, n (%) • Employed • Unemployed	 89 (58.9) 62 (41.1)	 24 (42.1) 33 (57.9)	 65 (69.1) 29 (30.9)	9.63	**0.02**¥
Immunotherapy, n (%) • First-line treatment • Second-line treatment	 83 (53.6) 70 (46.4)	 23 (40.4) 34 (59.6)	 58 (61.7) 36 (38.3)	6.50	**0.01**≠
RLS severity score, n (%) • Mild • Moderate • Severe • Very severe	 5 (3.3) 28 (18.5) 18 (11.9) 6 (4)	 5 (3.3) 28 (18.5) 18 (11.9) 6 (4)	 - - - -		

¥Continuity correction, ≠Pearson chi-square test, ǧFisher's exact test.

a-b: Shows the difference between MS subtypes.

SD: Standard deviation, EDSS: Expanded Disability Status Scale, RLS: Restless legs syndrome, MS: Multiple sclerosis, MRI: Magnetic resonance imaging, PSQI: Pittsburgh Sleep Quality Index, RRMS: Relapsing-remitting MS, SPMS: Secondary progressive MS, PPMS: Primary progressive MS.

significantly higher rate of RLS (48.0% vs. 27.6%, p=0.01) and family history of RLS (17.3% vs. 5.3%, p=0.03) compared to those with good sleep quality. No significant differences in other variables were observed between the groups (Table 2).

Predictors of PSQI identified by logistic regression analysis are presented in Table 3. The multivariate model was statistically significant (p<0.001) and demonstrated good fit with the data (p=0.01). The analysis revealed that the presence of RLS was a

Table 2. Comparison of variables associated with sleep quality among all MS patients.

	Good sleep quality (PSQI <5) (n = 76; 50.3%)	Poor sleep quality (PSQI >5) (n = 75; 49.7%)	Test statistics	p
Age (years), mean ± SD	40.59±9.02	40.65±8.22	-0.04	0.96
Gender, n (%)				
• Male	22 (28.9)	25 (33.3)	0.33	0.56[≠]
• Female	54 (71.1)	50 (66.7)		
MS duration (years), median (range)	7 (0.5-28)	7 (0.3-24)	2775	0.78
MS subtype, n (%)				
• RRMS	65 (85.5)	62 (82.7)	4.26	0.11[≠]
• PPMS	0	4 (5.3)		
• SPMS	11 (14.5)	9 (12)		
EDSS, median (range)	1.5 (0-7.5)	2 (0-8)	2818	0.90
RLS, n (%)				
• Yes	21 (27.6)	36 (48)	6.66	**0.01**[≠]
• No	55 (72.4)	39 (52)		
Family history of RLS, n (%)	4 (5.3)	13 (17.3)	4.36	**0.03**[¥]
Antidepressant use, n (%)				
• Yes	27 (35.5)	20 (26.7)	1.38	0.24[≠]
• No	49 (64.5)	55 (73.3)		
Ferritin, n (%)				
• Normal	66 (86.8)	62 (82.7)	0.23	0.62[¥]
• Low	10 (13.2)	13 (17.3)		
MRI lesions, n (%)				
• Periventricular	74 (97.4)	72 (96)	-	0.68[ǧ]
• Juxtacortical	41 (53.9)	47 (62.7)	1.18	0.27[≠]
• Infratentorial	36 (47.4)	32 (42.7)	0.33	0.56[≠]
• Spinal lesion	40 (52.6)	52 (69.3)	4.42	0.03[≠]
Oligoclonal band positive, n (%)	71 (93.4)	71 (94.7)	0.13	0.93[≠]
Education, n (%)				
• Primary School	12 (15.8)	10 (13.3)	0.60	0.74[≠]
• High School	24 (31.6)	28 (37.3)		
• University	40 (52.6)	37 (49.3)		
Marital status, n (%)				
• Married	65 (85.5)	68 (90.7)	0.52	0.46[¥]
• Single	11 (14.5)	7 (9.3)		
Employment status, n (%)				
• Employed	43 (56.6)	46 (61.3)	0.35	0.55[≠]
• Unemployed	33 (43.4)	29 (38.7)		
Immunotherapy, n (%)				
• First-line treatment	42 (55.3)	39 (52)	0.16	0.68[≠]
• Second-line treatment	34 (44. 7)	36 (48)		
RLS severity score, n (%)				
• Mild	1 (4.8)	4 (11.1)	2.17	0.53[≠]
• Moderate	11 (52.4)	17 (47.2)		
• Severe	8 (38.1)	10 (27.8)		
• Very severe	1 (4.8)	5 (13.9)		

[≠]Pearson chi-square test, [¥]Continuity correction, [ǧ]Fisher's exact test.

SD: Standard deviation, EDSS: Expanded Disability Status Scale, RLS: Restless legs syndrome, MS: Multiple sclerosis, MRI: Magnetic resonance imaging, PSQI: Pittsburgh Sleep Quality Index, RRMS: Relapsing-remitting MS, SPMS: Secondary progressive MS, PPMS: Primary progressive MS.

Table 3. Results of logistic regression analysis of predictors of sleep quality.

	Univariate logistic regression model		Multivariate logistic regression model (enter)	
	OR (95% CI)	p	OR (95% CI)	p
Presence of RLS	0.41 (0.21-0.81)	**0.01**	3.37 (0.18-0.75)	**0.006**
Family history of RLS	0.26 (0.08-0.85)	**0.02**	0.22 (0.06-0.75)	**0.01**
Constant			6.80	**0.003**

Cox & Snell $R^2 = 0.08$; Nagelkerke $R^2 = 0.11$; Hosmer-Lemeshow chi-square test = 0.01.

RLS: Restless legs syndrome, OR: Odds ratio, CI: Confidence interval.

significant independent predictor, with 3.37 times higher odds of PSQI in these patients (p=0.006). A family history of RLS was also an independent predictor, associated with 78% lower odds of PSQI (p=0.01).

Discussion

In our study, the frequency of RLS among patients with MS was 37.7%, which falls within the range of 13.3% to 65.1% reported in the literature (8).

Our findings indicated that spinal lesions were more common in the MS/RLS+ group, consistent with numerous studies suggesting that such lesions increase the risk of RLS in patients with MS. This association is likely driven by multiple mechanisms. The spinal cord serves as the primary relay for sensory signals from the legs and for descending dopaminergic inhibition. Lesions in this region can disrupt the spinothalamic and dorsal column pathways, leading to the disorganized sensory input and the subsequent urge to move that characterizes RLS. Furthermore, reduced dopaminergic inhibition promotes hyperexcitability in spinal neurons. The combination of sensory impairment, increased neuronal excitability, and disrupted motor control provides a robust explanation for the higher prevalence of RLS among MS patients with spinal cord involvement (9-12).

The frequent occurrence of RLS in MS may be attributed to sensory symptoms of MS that mimic RLS (13,14). Beyond symptomatic overlap, several clinical factors have been identified as risk factors for RLS in this population, including older age, longer disease duration, greater pyramidal and sensory dysfunction, and the PPMS subtype (15). In contrast, Vávrová et al. (16) reported that RLS was most common in the SPMS subtype. Consistent with this finding, our study revealed a higher frequency of RLS in the SPMS and PPMS subtypes, with a particularly significant association with SPMS, while no significant difference was observed in RRMS patients. Although Güneş et al. (17) similarly found that RLS was more frequent in SPMS patients, they also reported a higher frequency of RLS in RRMS patients.

Several studies have shown that patients with MS and comorbid RLS tend to have higher EDSS scores. Patients with a higher EDSS score may develop RLS more easily, and the pathological processes underlying RLS may concurrently worsen the course of MS (18). Consistent with this, both EDSS scores and mean age were substantially higher in the MS/RLS+ group compared to the MS/RLS– group in our study.

The higher rate of RLS among patients receiving second–line immunotherapy in our study may be attributable to the higher prevalence of RLS in the SPMS and PPMS subtypes, rather than a direct relationship with the medications themselves. Furthermore, older age and higher disability levels in the second–line immunotherapy group are other likely contributing factors. Younis et al. (19) examined the relationship between immunotherapies and RLS in MS patients and found that RLS was more severe in those receiving fingolimod and teriflunomide. While their study suggests that RLS severity may vary depending on immunotherapy type, the results remain inconclusive because of the small sample size. In contrast, Monschein et al. (12) found no relationship between immunotherapies and the frequency and severity of RLS in patients with MS. A limitation of our study is that the specific relationship between individual immunotherapy agents and RLS was not directly examined.

Another finding of this study was the significantly higher proportion of unemployed individuals in the MS/RLS+ group. This may be related to the higher mean age, higher EDSS scores, and longer disease duration in the unemployed group.

Consistent with previous research, our results underscore the clinical impact of RLS on patient well–being. Moreira et al. (6) confirmed that RLS is common in MS patients and is associated with PSQI and fatigue. Similarly, Manconi et al. (4) and Miri et al. (20) demonstrated that insomnia is highly prevalent among MS patients with RLS. In our study, 49.7% of MS patients were found to have PSQI, and this rate increased to 63.2% among those with RLS.

Conclusion

Patients with MS and RLS demonstrated poorer sleep quality, higher levels of physical disability, and a greater prevalence of spinal lesions compared to those without RLS. Additionally, the RLS group was characterized by a higher mean age, lower employment rate, and larger proportions of the SPMS and PPMS subtypes. While PSQI in MS was associated with personal and family history of RLS, there was no relationship with RLS severity. Given that early detection and management of RLS can significantly improve sleep quality, clinicians should routinely screen for RLS during the follow–up of patients with MS.

Ethics

Ethics Committee Approval: This study was approved by the local ethics committee of Kütahya Health Sciences University (decision number: 2021/01–04, date: 20.01.2021).

Informed Consent: Informed consent was obtained.

Footnotes

Authorship Contributions: Concept: F.A.A., M.Ç., S.C.K., Design: G.A., M.Ç., S.C.K., Data Collection or Processing: F.A.A., G.A., M.Ç., Analysis or Interpretation: F.A.A., G.A., S.C.K., Literature Search: F.A.A., M.Ç., Writing: F.A.A.

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