Original Article

Initial Cervical Spinal Cord Demyelinating Lesions are not Associated with Restless Legs Syndrome in Patients with Multiple Sclerosis

Neslihan Eskut, Asli Koskderelioglu, Muhtesem Gedizlioglu[1], Ozlem Onder[2]

Department of Neurology, University of Health Sciences, Izmir Bozyaka Education and Research Hospital, Izmir, [1]Department of Neurology, Atakalp Hospital, Izmir, [2]Department of Neurology, Fethiye State Hospital, Mugla, Turkey

Abstract

Purpose: This study aims to determine the prevalence and severity of restless legs syndrome (RLS) in patients with multiple sclerosis (MS) and its association with spinal cord lesions, fatigue, quality of life, and sleep disturbance. **Methods:** We recruited 222 consecutive MS patients admitted to MS outpatient clinic. Beck's Depression Inventory (BDI), Fatigue Severity Scale (FSS), Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), and MS Quality of Life-54 (MSQoL-54) questionnaire scores of all patients were measured. Initial cervical spinal cord magnetic resonance imaging (MRI) of the patients at first clinical evaluation for diagnosis was reviewed for accompanying demyelinating lesions. **Results:** RLS was diagnosed in 53 (23.87%) patients. RLS was associated with poor sleep, worse quality of life, increased fatigue, and depressive mood. The sleep quality index, FSS, and MSQoL-54 physical composite scores significantly correlated with RLS severity ($P < 0.001$, $P = 0.001$, $P < 0.001$, respectively). Of the 200 patients, 127 (63.5%) had spinal cord lesions. 22.83% of the patients with cervical spinal cord lesions had RLS comorbidity. We found no significant difference regarding spinal cord demyelinating lesions between RLS positives and negatives. ($P = 0.77$). In addition, having multiple spinal cord demyelinating lesions did not differ between the two groups ($P = 0.84$). Besides, the severity of RLS symptoms did not differ in patients who had a single cervical spinal lesion and those who had multiple lesions ($P = 0.35$). **Conclusion:** We have demonstrated the negative impact of comorbid RLS on fatigue, sleep quality, mood, and quality of life in MS patients. However, initial spinal cord lesions did not correlate with RLS comorbidity. The severity of RLS symptoms is associated with poor sleep and physical health.

Keywords: Fatigue, multiple sclerosis, quality of life, restless legs syndrome, sleep disturbance

Introduction

The restless legs syndrome is a common neurological disorder characterized by an irresistible urge to move legs accompanying unpleasant sensations.[1] Symptoms have a diurnal pattern that improves in the morning and worsens at night. Most patients experience insomnia affecting sleep onset and maintenance.[2] RLS is classified as idiopathic or primary if no other cause can be identified, or secondary when a comorbid medical condition is susceptible, such as multiple sclerosis (MS).[3] MS is one of the most debilitating neurological diseases in young adults. Recent studies showed that MS patients frequently suffer from sleep disturbances which limit their quality of life.[4] The prevalence of RLS is higher in MS patients than in the general population.[2,4-6] The restless legs syndrome in multiple sclerosis (REMS) study reported the frequency of restless legs syndrome to be 164/861 (19%) in MS and 27/649 (4.2%) in control subjects.[7]

RLS harms the sleep and quality of life (QOL) of patients with MS (PwMS).[4,8] Thus, RLS may lead to additional physical and emotional disability. One of the most common symptoms of MS is fatigue which has been related to sleep disturbances in recent studies. RLS may also play a role in exacerbating fatigue.[9] Consequently, patients with RLS may experience excessive daytime sleepiness. Furthermore, RLS-related sleep disruption and fatigue may be causal factors for depression or depressive symptoms.[10]

Treatment management of PwMS should not only be limited to disease-modifying therapies but should also include improving parameters that affect the quality of life and functional capabilities.[10] The treatment success of sleep disturbances in PwMS depends on the clinician's awareness of the typical features and obtaining detailed sleep history information.

Address for correspondence: Dr. Neslihan Eskut, Department of Neurology, University of Health Sciences, Izmir Bozyaka Education and Research Hospital, Bahar Mah. Saim Cikrikci Cad. No: 59 Karabaglar, 35170 Izmir, Turkey.
E-mail: nespur@hotmail.com

Submitted: 04-Apr-2023 **Revised:** 16-May-2023 **Accepted:** 01-Jun-2023
Published: 08-Aug-2023

DOI: 10.4103/aian.aian_289_23

We aimed to investigate the frequency of RLS and its possible relationship with sleep disturbance, depression, fatigue, excessive daytime sleepiness, and quality of life, as well as determine the link between RLS, and initial spinal cord lesions in MS patients.

Material and Methods

Study Design and Participants

This prospective, cross-sectional study, based on face-to-face interviews, was conducted at the Neurology Department of the University of Health Sciences, Izmir Bozyaka Education and Research Hospital from April 2019 until November 2019. All patients were informed by written consent before participation. The local ethics committee reviewed and approved the study protocol (Date: 13/2/2019; reference number: 6).

We evaluated 258 consecutive MS patients who attended our demyelinating diseases outpatient clinic. Participants had a definite clinical diagnosis of MS according to the 2017 McDonald criteria.[11,12] Patients with exacerbated infectious disease, traumatic, or other acute complications, or having an acute attack treated with intravenous corticosteroid in the previous three months were excluded. In addition, we did not include patients with pregnancy, opioid withdrawal, chronic kidney disease, chronic liver disease, rheumatoid arthritis, or varicose veins. We also excluded patients with a disease that may cause RLS and treated for either RLS or iron deficiency. The flowchart of the study is exhibited in Figure 1.

Clinical and demographic data were recorded. We used the EDSS scale to quantify disability in MS patients.[13] Two experienced neurologists scored the EDSS. RLS diagnosis was made based on the criteria defined by the International Restless Legs Syndrome Study Group (IRLSSG).[1] A neurologist subsequently examined those patients who fulfilled the diagnostic criteria and verified the diagnosis. Patients with RLS were evaluated for disease severity by the IRLSSG questionnaire.[14]

The MRI data of eligible patients with MS were extracted from the registry for the current study. We determined the initial cervical spinal cord involvement by reviewing MRI scans, radiological reports, and examination records. However, for a small group of patients (n = 22) whose spinal neuroimaging scans were not available at MS onset, their data on spinal demyelinating lesions were excluded from the analysis. Patients were grouped into two according to the accompanying initial cervical spinal cord demyelinating lesions at disease onset. Then, the number of lesions was noted (single or multiple lesions). In addition, the possible relationship between cervical spinal lesions and RLS and relevant test scores were evaluated.

Our study included standardized and validated questionnaires related to fatigue (Fatigue Severity Scale), sleepiness (Epworth Sleepiness Scale), sleep quality (Pittsburgh Sleep Quality Index), depression (Beck's Depression Inventory), and quality of life (multiple sclerosis QOL-54). A description of the standardized, validated questionnaires is as follows.

Fatigue was assessed by the Fatigue Severity Scale (FSS), composed of nine items with seven levels of agreement with each statement. The mean value of nine items provides FSS final score, and severe fatigue was defined as a score of ≥4.[15]

The Epworth Sleepiness Scale (ESS) was used to evaluate subjective daytime sleepiness. ESS is a self-report questionnaire,

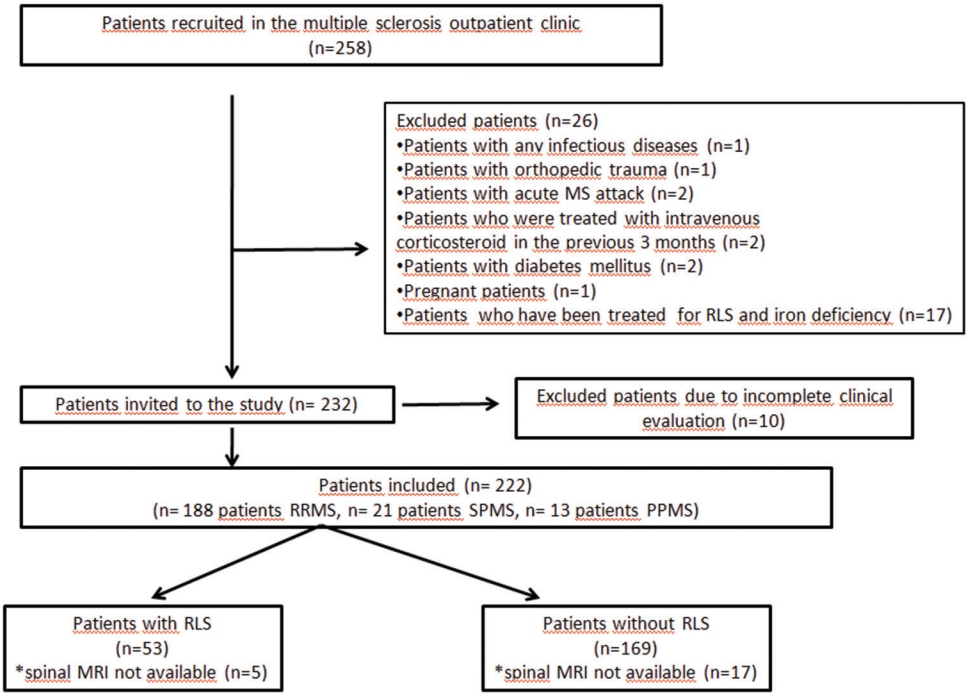

Figure 1: Flow-chart of the study

and the total score ranges from 0 to 24, by which an ESS score above 10 indicates excessive daytime sleepiness.[16]

The Pittsburgh Sleep Quality Index (PSQI) was achieved to evaluate sleep quality and habits over the last month. This questionnaire was adapted into Turkish by Agargun *et al*.[17] The sum of the seven components provides one global score of subjective sleep quality (range 0–21). Individuals with a global score above five were considered poor sleepers.[18]

Depression was assessed using Beck's Depression Inventory (BDI), a self-rating questionnaire consisting of 21 statements that evaluate the state of mood over the preceding two weeks. The test interpretation is based on a 0 to 63 total score. High scores greater than 10 indicate depression. Scores from 10 to 18 denote mild depression, 19–27 moderate, and greater than 27 severe. The BDI is one of the recommended screening scales to identify depressive symptoms in patients with MS.[19]

MS-specific HRQoL was assessed by multiple sclerosis QOL-54 (MSQOL-54). It is a structured, self-report questionnaire that contains 52 items distributed into 12 scales and two composite scores for "physical health" and "mental health," which range from 0 to 100.[20] The MSQOL-54 data were analyzed by calculating the Physical Health Composite Score and the Mental Health Composite Score. Higher scores indicate favorable QOL. Idiman *et al*.[21] translated and validated this questionnaire in Turkish.

Statistical analysis

Data were rationalized using the Statistical Package for the Social Sciences version 24.0 (SPSS Inc., Chicago, IL, USA). Continuous variables such as age, disease duration, EDSS, ESS, FSS, PSQI, BDI, and MSQoL-54 scores were expressed as mean ± standard deviation (± SD). The normality of continuous variables was assessed by Kolmogorov–Smirnov test. Comparisons between variables were performed using the Mann–Whitney U test for data not normally distributed. The gender variable was expressed as frequency (percentage), and its relationship with RLS was analyzed using the Chi-square test. After performing univariate analysis, we further explored the relationship between age, FSS, BDI, PSQI, MSQoL-54 scores, and RLS using binary logistic regression in multivariate analysis. The relationship between RLS and the abovementioned variables was assessed using the odds ratio (OR) and 95% confidence interval (95% CI). Spearman correlation analysis was used to determine the relationships between RLS severity scores and other continuous variables. A *P* value less than 0.05 was studied as statistically significant.

Results

A total of two hundred and twenty-two MS patients were included in the study. Of the 222 MS patients, 151 (68.02%) were female; the mean age was 40.46 ± 11.24 years. Most patients were mildly affected by the disease, as reflected by a mean EDSS of 2.11 ± 1.79 and mean disease duration of 9.17 ± 6.34 years. The majority of the patients were classified as having the relapsing-remitting form (N = 188, 84.68%). The clinical and demographic characteristics of participants are shown in Table 1.

Fifty-three MS patients (23.87%) fulfilled the diagnostic criteria for RLS. Most RLS patients (94.34%) experienced moderate to severe symptoms (IRLSSG score >11) with a mean severity score of 21.32 ± 8.05. Of the 53 patients with RLS, 3 (5.66%) of them had mild RLS symptoms, 25 (45.28%) had moderate, 16 (30.18%) had severe, and 10 (18.86%) had very severe symptoms according to IRLSSG score. RLS was present in 39 female subjects. Comparing RLS positive and RLS opposing groups, there was no difference in gender ($P = 0.31$). Twenty patients with RLS (37.74%) had EDSS scores of 3 or more. Patients with RLS were older than others ($P = 0.029$). We did not reveal significant differences between the two groups regarding disease duration and EDSS scores [Table 1].

Of the patients with RLS, 73.58% had depression, and 79.25% had fatigue. MS patients with RLS were more likely to present with depression and fatigue. There was a significant difference in FSS scores between RLS positive and negative groups ($P = 0.002$). Depression scores significantly differed between the two groups (<0.001). Of the 53 patients with RLS, 35.85% were involved in the mild depression group, 15.09% in the moderate depression group, and 22.64% in the severe depression group [Table 2].

Excessive daytime sleepiness (ESS) was higher in RLS positive group (30.19% vs 13.02%), but the ESS scores did not significantly differ between the RLS positive (7.02 ± 6.44) and opposing groups (4.92 ± 4.56) ($P = 0.084$). The PSQI scoring demonstrated that 61.26% of MS patients had poor sleep quality. MS patients with RLS had significantly worse sleep quality (<0.001).

Physical Health Composite Score and Mental Health Composite Scores were significantly lower in the RLS positive group (for both, $P < 0.001$). Moreover, we found that MSQOL-54 Physical Health Composite scores were independently associated with the presence of RLS according to multivariate logistic regression analysis [Table 3].

RLS severity was positively correlated with worse sleep quality (r = 0.48, $P < 0.001$) and negatively correlated with the physical health component of QOL (r = -0.42, $P = 0.001$) [Table 4].

We evaluated the cervical spinal cord MRI of 200 patients. Of the 200 patients, 127 (63.5%) had spinal cord lesions. 22.83% of the patients with cervical spinal cord lesions had RLS comorbidity. There was no significant difference between RLS positive and negative patients according to the presence of spinal cord demyelinating lesions. ($P = 0.77$). In addition, having multiple spinal cord demyelinating lesions did not differ between the two groups (36.17% vs. 34.67%, respectively; $P = 0.84$). Besides, the severity of RLS symptoms did not differ in patients who had a single lesion either multiple lesions ($P = 0.35$).

Table 1: Demographical and clinical characteristics of the study population

	All patients (*n*=222)	Presence of RLS		*P**
		Positive (*n*=53)	Negative (*n*=169)	
Age, years	40.46±11.24	43±9.93	39.67±11.63	0.029
Education, years	9.57±4.08	9.47±3.94	9.60±4.13	0.87
Disease Duration, years	9.17±6.34	9.76±5.94	8.98±6.46	0.29
EDSS	2.11±1.79	2.33±1.72	2.04±1.78	0.2
ESS	5.42±5.16	7.02±6.44	4.92±4.59	0.08
FSS	4.32±2.15	5.22±1.82	4.04±2.18	0.001
BDI	13±10.73	18.62±12.56	11.23±9.46	<0.001
PSQI	6.52±4.56	8.78±4.71	5.85±4.31	<0.001
MSQoL-54 Mental	60.24±21.75	50.17±20.91	63.40±21.09	<0.001
MSQoL-54 Physical	59.70±21.09	46.86±16.73	63.23±20.74	<0.001

EDSS; Expanded Disability Table 1: Demographical and clinical characteristics of the study population Status Scale, RLS; Restless Legs Syndrome, ESS; Epworth sleepiness scale, FSS; Fatigue Severity Scale, BDI; Beck's Depression Inventory, PSQI; Pittsburgh Sleep Quality Index, MSQoL-54 Mental; Multiple Sclerosis Quality of Life Questionnaire-54 Mental Composite, MSQoL-54 Physical; Multiple Sclerosis Quality of Life Questionnaire-54 Physical Composite; *P*<0.05 statistically significant; * Mann–Whitney *U* test

Table 2: Comparison between RLS positive and RLS negative MS patients

	RLS positive *n* (%)	RLS negative *n* (%)	*P*
FSS <4	11 (12.79)	75 (85.21)	0.002
FSS ≥4	42 (30.88)	94 (69.12)	
PSQI <5	12 (13.95)	74 (86.05)	0.006
PSQI ≥5	41 (30.15)	95 (69.85)	
ESS <11	37 (20.11)	147 (79.89)	0.004
ESS ≥11	22 (57.89)	16 (42.11)	
EDSS <3	33 (21.29)	122 (78.71)	0.170
EDSS ≥3	20 (29.85)	47 (79.15)	
BDI Mild	19 (30.65)	43 (69.35)	<0.001
Moderate	8 (22.86)	27 (77.14)	
Severe	12 (60)	8 (40)	

RLS; Restless Legs Syndrome, FSS; Fatigue Severity Scale, PSQI; Pittsburgh Sleep Quality Index, ESS; Epworth sleepiness scale, EDSS; Expanded Disability Status Scale, BDI; Beck's Depression Inventory, *P*<0.05 statistically significant

Table 3: Multivariate Logistic Regression Analysis in MS patients with RLS

	OR (%95 CI)	*P*
Age, years	1.02 (0.98-1.05)	0.341
FSS	1.14 (0.95-1.36)	0.160
BDI	1.03 (0.99-1.08)	0.158
PSQI	1.06 (0.98-1.15)	0.163
MSQoL-54 Physical Health	0.96 (0.93-0.99)	0.014
MSQoL-54 Mental Health	1.02 (0.99-1.06)	0.177

R^2=0.23 (Nagelkerke) FSS; Fatigue Severity Scale. BDI; Beck's Depression Inventory. PSQI; Pittsburgh Sleep Quality Index. MSQoL-54 Mental; Multiple Sclerosis Quality of Life Questionnaire-54 Mental Composite. MSQoL-54 Physical; Multiple Sclerosis Quality of Life Questionnaire-54 Physical Composite

Discussion

Our study showed nearly one in four MS patients suffer from RLS. Additionally, there was a significant correlation between RLS severity and QoL scores. It is revealed that patients with RLS had reduced QoL scores in both the physical and psychological domains. We demonstrated that MS patients with RLS have more significant sleep impairment and tend to have fatigue and depression more frequently. The results demonstrated a significant positive correlation between RLS severity and PSQI score.

Furthermore, a significant positive correlation was revealed between PSQI scores and ESS, FSS, and BDI scores. On the other hand, a significant negative correlation between PSQI score and MSQoL-54 physical and mental composite scores was found. Poor sleep quality was prominent in MS patients with RLS comorbidity. This finding is consistent with several previous studies showing that MS patients with RLS are more at risk of sleep disturbances leading to depression and fatigue.[8,9]

The pathophysiology of secondary RLS in different neurological disorders (i.e., MS, Parkinson's disease, spinal cord injury) remains uncertain. It has been considered that the etiology of RLS was associated with dopaminergic pathways projecting to striatum, hypothalamus, and the spinal cord, which cause suppression of sensory input and motor excitability. It is suggested that descending dopaminergic pathways can be destructed due to spinal cord lesions causing dysfunction.[22] Minár *et al*.[23] showed that PwMS with RLS had a higher prevalence of spinal cord lesions. They suggested decreased dopamine transmission to lower spinal regions as the pathological mechanism. Similarly, Manconi *et al*.[24] found a correlation between cervical cord damage and RLS in PwMS. It is reported that the presence of lesions in the spinal cord puts PwMS at a higher risk of RLS development. Also, lesions in the spinal cord can be evaluated as an independent risk factor for RLS.[23,24] Besides, in the current study, there was no significant difference in the rate of presence of single or multiple spinal cord demyelinating lesions between RLS positive and negative groups. Previously, a possible relationship was suggested between cervical located lesions

Table 4: Correlation analysis of RLS severity scores with clinical parameters in MS patients with RLS

	RLS severity ($n=53$)	
	r	*P**
Age, years	0.040	0.776
Education, years	0.057	0.683
Disease Duration, years	-0.014	0.922
EDSS	0.136	0.332
ESS	0.156	0.266
FSS	0.197	0.157
BDI	0.217	0.118
PSQI	0.483	<0.001
MSQoL-54 Physical Health	-0.429	0.001
MSQoL-54 Mental Health	-0.245	0.078

EDSS; Expanded Disability Status Scale, ESS; Epworth sleepiness scale, FSS; Fatigue Severity Scale, BDI; Beck's Depression Inventory, PSQI; Pittsburgh Sleep Quality Index, MSQoL-54 Mental; Multiple Sclerosis Quality of Life Questionnaire-54 Mental Composite, MSQoL-54 Physical; Multiple Sclerosis Quality of Life Questionnaire-54 Physical Composite; *Spearman Correlation test

and RLS.[24] Although the spinal cord lesions may have an essential effect on the ethiopathological mechanism of RLS, there are probably multiple etiological factors in PwMS.[25]

Sleep disorders have been expected in patients with MS. Giannaki *et al*.[9] used face-to-face interviews and reported the prevalence of RLS in their MS population at 20%. Recently, in a meta-analyze study, conducted by Zali *et al*.[26] showed the pooled prevalence of RLS in PwMS was estimated as 28%, while the pooled prevalence in control group was estimated as 8%. Similarly, 23.87% of our PwMS had RLS. According to the assessment method, the prevalence of RLS varies between 13.3 and 65.1%.[2] The sleep disruption resulting from RLS may lead to decreased quality of life relevant to poor sleep. RLS could be an etiological factor for other sleep disorders such as insomnia, and reduced sleep quality may lead to excessive daytime sleepiness and mood disorders.[4,24,26,27] However, our patient population had no significant daytime sleepiness related to poor sleep; patients with RLS symptoms more frequently experienced sleep disorders, fatigue, and depression. We saw that this result is consistent with the study by Seferoğlu *et al*.[25]

Fatigue affects up to 90% of patients with MS. It can be reported as the most disabling and the earliest symptoms by MS patients.[28] It is well known that sleep is an essential contributing factor to fatigue and tiredness in MS patients.[9] We should indicate that patients with RLS had poor sleep quality due to PSQI. In line with previous studies, we showed that MS patients with RLS struggle with significantly poor sleep quality and fatigue compared to those without RLS.[8,24] The fatigue severity in MS patients with RLS may be explained by the adverse effects of the RLS on sleep, QoL, and mood following the literature.[9,25,29] However, we did not observe a significant association between RLS severity and fatigue among MS patients with RLS. Treating the symptoms of RLS in MS patients may reduce RLS-related fatigue and improve quality of life measures.

EDSS, in the current study, evaluated the disability level of the patients. Previously, disabilities were significantly higher in MS patients with RLS comorbidity.[23,24] In our study, although 41% of the patients with RLS had EDSS scores of 3 or more, there was no significant difference in EDSS scores between the groups. This result may be related to most of our study group's mildly disabled ones.

Multiple Sclerosis Quality of Life Instrument (MSQoL-54) is one of the most commonly used qualities of life scales specific to MS.[20] MSQoL-54 assessment provides unique information for MS-related disability, clinical disease activity, and also impact of the disease on patients' life from the patient's perspective.[30] According to the MSQoL-54 questionnaire, patients' health conditions can be evaluated in two domains, including physical and mental health. Numerous factors have been reported to be associated with impaired QoL of PwMS, such as fatigue, sleep disturbance, depression, and disability.[9] We found that the patients with RLS reported lower MSQOL-54 scores than patients without RLS in both physical and mental domains. Moreover, according to the current study, patients in the RLS group experienced more significant sleep impairment. They had more severe fatigue and depression, which were known to be associated with QoL in PwMS, in line with previous reports.[9,25]

To our knowledge, there have not been any studies investigating the relationship between RLS and spinal cord lesions in MS patients. Our results supported the hypothesis that RLS might be responsible for sleep disturbance leading to impaired QOL in MS. Additionally, the prospective nature of the study allowed us to examine RLS symptoms and properly evaluate for medication. To understand several conditions which might have affected the QOL measures, we evaluated fatigue, depression, sleep quality, and excessive sleepiness.

Using proper QOL measures may provide neurologists an insight into MS patients' health perspectives. By improving knowledge about sleep disturbances and the potential role of RLS on QoL of PwMS, clinicians would be able to choose appropriate interventions for sleep disorders. In clinical practice, it is essential to recognize RLS symptoms while managing the care of MS patients. The association between several subscales of QOL and MS-related problems, including fatigue, depression, and sleep disruption, has been firmly identified.[31,32] MS population with a high prevalence of RLS deserves special attention and specific treatment for a better quality of life. We can speculate that adequate and effective treatment of RLS will provide physical and mental improvement and improvement in QoL measures and prevent the need for additional treatment for possible comorbid conditions.

Nevertheless, this study has some limitations. First, our study had a small sample size from a single MS center; therefore, a multicenter, considerable case-control study is necessary to provide supportive data. In addition, MRI examinations in

this study are not standardized because each patient had spinal neuroimaging at a different time frame related to MS onset. Furthermore, nerve conduction studies should be required to optimize the RLS diagnosis. However, only a few patients had nerve conduction studies to exclude neuropathy. In addition, polysomnography (PSG) would be an appropriate diagnostic tool to detect sleep apnea and certain other sleep disorders such as periodic limb movements; however, we could not perform PSG in our study. Finally, our study did not evaluate the biochemical parameters aside from iron deficiency related to RLS.

However, the strengths of our study lie in its design of face-to-face interviews conducted by experienced neurologists in the MS field. Detailed physical and neurological examination and detailed medical history screening ensured the exclusion of other medical conditions mimicking RLS.

Conclusions

In conclusion, we detected a higher prevalence of RLS in MS patients. Compared to those without RLS, sleep was more disturbed in MS patients with comorbid RLS. Furthermore, we showed that MS patients with RLS had worse mental and physical health. RLS harmed both mental and physical health. The PSQI scores and RLS severity negatively correlated with mental and physical health composite scores. Initial spinal cord demyelinating lesions did not associate with comorbid RLS. In light of these results, with a holistic approach in the clinical follow-up of MS patients, it can be predicted that recognition and treatment of RLS will improve both sleep and QoL. Prospective studies in a larger sample of MS patients would be instructive to enhance the evidence of RLS's impact on QOL and sleep.

Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelman WJ, *et al*. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: Updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria-history, rationale, description, and significance. Sleep Med 2014;15:860-73.
2. Sieminski M, Losy J, Partinen M. Restless legs syndrome in multiple sclerosis. Sleep Med Rev 2015;22:15-22.
3. Gonzalez-Latapi P, Malkani R. Update on restless legs syndrome: From mechanisms to treatment. Curr Neurol Neurosci Rep 2019;19:54.
4. Cederberg KLJ, Jeng B, Sasaki JE, Braley TJ, Walters AS, Motl RW. Restless legs syndrome and health-related quality of life in adults with multiple sclerosis. J Sleep Res 2020;29:e12880.
5. Contentti EC, López PA, Nadur D, Balbuena ME, Finkelstein AM, Tkachuk V. Impact, frequency, and severity of restless legs syndrome in patients with multiple sclerosis in Argentina. Int J MS Care 2019;21:157-65.
6. Schürks M, Bussfeld P. Multiple sclerosis and restless legs syndrome: A systematic review and meta□analysis. Eur J Neurol 2013;20:605-15.
7. Italian REMS Study Group, Manconi M, Ferini-Strambi L, Filippi M, Bonanni E, Iudice A, *et al*. Multi center case-control study on restless legs syndrome in multiple sclerosis: The REMS study. Sleep 2008;31:944-52.
8. Kotterba S, Neusser T, Norenberg C, Bussfeld P, Glaser T, Dörner M, *et al*. Sleep quality, day time sleepiness, fatigue, and quality of life in patients with multiple sclerosis treated with interferon beta-1b: Results from a prospective observational cohort study. BMC Neurol 2018;18:123.
9. Giannaki CD, Aristotelous P, Stefanakis M, Hadjigeorgiou GM, Manconi M, Leonidou E, *et al*. Restless legs syndrome in multiple sclerosis patients: A contributing factor for fatigue, impaired functional capacity, and diminished health-related quality of life. Neurol Res 2018;40:586-92.
10. Becker PM, Novak M. Diagnosis, comorbidities, and management of restless legs syndrome. Curr Med Res Opin 2014;30:1441-60.
11. Frohman TC, Castro W, Shah A, Courtney A, Ortstadt J, Davis SL, *et al*. Symptomatic therapy in multiples clerosis. Ther Adv Neurol Disord 2011;4:83-98.
12. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, *et al*. Diagnosis of multiples clerosis: 2017 revisions of the Mc Donald criteria. Lancet Neurol 2018;17:162-73.
13. Kurtzke JF. Rating neurological impairment in multiple sclerosis: An expanded disability status scale (EDSS). Neurology 1983;33:1444-52.
14. Walters AS, LeBrocq C, Dhar A, Hening W, Rosen R, Allen RP, *et al*. Validation of the International restless legs syndrome study group rating scale for restless legs syndrome. Sleep Med 2003;4:121-32.
15. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989;46:1121-23.
16. Johns MW. A new method for measuring daytime sleepiness: The Epworth sleepiness scale. Sleep 1991;14:540–45.
17. Agargun MY, Kara H, Anlar O. The validity and reliability of the Pittsburgh sleep quality ındex [in Turkish]. J Psychiatry 1996;7:107–15.
18. Tomfohr LM, Schweizer CA, Dimsdale JE, Loredo JS. Psychometric characteristics of the Pittsburgh Sleep Quality Index in English speaking non-Hispanic whites and English and Spanish speaking Hispanics of Mexican descent. J Clin Sleep Med 2013;9:61-6.
19. Minden SL, Feinstein A, Kalb RC, Miller D, Mohr DC, Patten SB, *et al*. Evidence based guideline: Assessment and management of psychiatric disorders in individuals with MS: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2014;82:174–81.
20. Vickrey BG, Hays RD, Harooni R, Myers LW, Ellison GW. A health-related quality of life measure for multiple sclerosis. Qual Life Res 1995;4:187-206.
21. Idiman E, Uzunel F, Ozakbas S, Yozbatiran N, Oguz M, Callioglu B, *et al*. Cross-cultural adaptation and validation of multiple sclerosis quality of life questionnaire (MSQOL-54) in a Turkish multiple sclerosis sample. J Neurol Sci 2006;240:77-80.
22. Trenkwalder C, Allen R, Hög B, Paulus W, Winkelmann J. Restless legs syndrome associated with major diseases: A systematic review and new concept, Neurology 2016;86:1336-43.
23. Minár M, Petrleničová D, Valkovič P. Higher prevalence of restless legs syndrome/Willis-Ekbom disease in multiple sclerosis patients is related to spinal cord lesions. Mult Scler Relat Disord 2017;12:54-8.
24. Manconi M, Rocca MA, Ferini-Strambi L, Tortorella P, Agosta F, Comi G, *et al*. Restless legs syndrome is a common finding in multiple sclerosis and correlates with cervical cord damage. Mult Scler 2008;14:86-93.
25. Seferoğlu M, Sivaci AÖ, Tunç A. Restless legs syndrome/Willis-Ekbom disease in multiple sclerosis: A contributing factor for anxiety, disability, sleep disorder, and quality of life. Arq Neuropsiquiatr 2020;78:708-12.
26. Zali A, Motavaf M, Safari S, Ebrahimi N, Ghajarzadeh M, Khoshnood RJ, *et al*. The prevalence of restless legs syndrome (RLS) in patients with

multiple sclerosis (MS): A systematic review and meta-analysis—An update. Neurol Sci 2023;44:67-82.
27. Popp RF, Fierlbeck AK, Knüttel H, König N, Rupprecht R, Weissert R, *et al*. Daytime sleepiness versus fatigue in patients with multiple sclerosis: A systematic review on the Epworth sleepiness scale as an assessment tool. Sleep Med Rev 2017;32:95-108.
28. Wood B, van der Mei IA, Ponsonby AL, Pittas F, Quinn S, Dwyer T, *et al*. Prevalence and concurrence of anxiety, depression and fatigue over time in multiple sclerosis. Mult Scler 2013;19:217-24.
29. Braley TJ, Chervin RD. Fatigue in multiple sclerosis: Mechanisms, evaluation, and treatment. Sleep 2010;33:1061-7.
30. Nortvedt MW, Riise T, Myhr KM, Nyland HI. Quality of life in multiple sclerosis: Measuring the disease effects more broadly. Neurology 1999;53:1098-103.
31. Plow M, Finlayson M, Motl RW, Bethoux F. Randomized controlled trial of a teleconference fatigue management plus physical activity intervention in adults with multiple sclerosis: Rationale and research protocol. BMC Neurol 2012;12:122.
32. Boeschoten RE, Dekker J, Uitdehaag BM, Polman CH, Collette EH, Cuijpers P, *et al*. Internet-based self-help treatment for depression in multiple sclerosis: Study protocol of a randomized controlled trial. BMC Psychiatry 2012;12:137.