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Sleep Disorders in Patients with Multiple Sclerosis

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Objective: Poor sleep is a frequent symptom in patients with multiple sclerosis (MS). The objective of the study was to assess the relationship between nocturnal polysomnographic (PSG) findings and quality of sleep, fatigue, and increased daytime sleepiness among patients with MS.

Methods: Clinical characteristics were collected. Pittsburgh Sleep Quality Index (PSQI), Fatigue Severity Scale (FSS), Epworth Sleepiness Scale (ESS), and International Restless Legs Syndrome Rating Scale were used to assess quality of sleep, fatigue, excessive daytime sleepiness, and the presence of restless legs syndrome (RLS). All patients underwent nocturnal diagnostic PSG examination.

Results: Fifty patients with MS were enrolled into the study. Age was the only independent variable significantly determining apnea-hypopnea index and desaturation index (DI) (beta = 0.369, p = 0.010, beta 0.301, p = 0.040). PSQI and ESS score were significantly higher in a population with RLS (p = 0.004, p = 0.011). FSS significantly correlated with DI (r = 0.400, p = 0.048). Presence of RLS was the only independent variable significantly determining PSQI and ESS (p = 0.005, p = 0.025). DI and presence of RLS were independent variables determining FSS (p = 0.015, p = 0.024).

Conclusion: Presence of RLS seems to be the main factor determining poor sleep, fatigue, and daytime somnolence. Sleep disordered breathing and its severity influences only fatigue in patients with MS.

Keywords: fatigue, multiple sclerosis, polysomnography, restless legs syndrome, sleep, sleep disordered breathing

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Multiple sclerosis is a chronic inflammatory and neurodegenerative disease of the central nervous system that most commonly affects young adults. The disease is characterized by neurological symptoms leading to long-term physical disability. Though often clinically underrecognized, sleep problems are seen in the MS population more frequently than in the general population, ranging from 25% to 54%.[1–3] Sleep disorders such as insomnia, nocturnal movement disorders, sleep disordered breathing (SDB), narcolepsy, and rapid eye movement sleep behavior disorder have all been reported in MS. Factors that may influence the quality of sleep in the MS population include nocturia, pain, depression, effect of medication, location of lesions, and disease severity.[4] Sleep disturbances can lead to daytime somnolence, increased fatigue, and depression. They have been associated with increased risk of mortality, cardiac diseases, obesity, and diabetes mellitus. Therefore, they have the potential to negatively affect overall health and quality of life.[5] The purpose of this prospective study was to assess the relationship between nocturnal PSG findings and a group of self- reported symptoms (quality of sleep, fatigue, and increased daytime sleepiness), among patients with MS referred for clinical polysomnography.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Sleep disorders remain often under-diagnosed in patients with MS, although they are frequent and have negative effect on overall health and quality of life. The aim of this study was to assess the relationship between nocturnal polysomnographic findings and a group of self-reported symptoms (quality of sleep, fatigue, and increased daytime sleepiness) among patients with MS.

Study Impact: Presence of restless legs syndrome seems to be the main factor determining poor sleep, fatigue, and daytime somnolence, sleep disordered breathing; its severity influences only fatigue in patients with MS. Targeted diagnosis and treatment of these disorders can help to improve overall care of MS patients.

MATERIAL AND METHODS

Patients

Patients attending MS Center of the 1st Department of Neurology, Bratislava, Slovakia, were recruited for the study over a 1-y period (January 2012–January 2013). We recruited adults with a diagnosis of MS based on the McDonald diagnostic criteria.[6] Age, sex, form of the disease (relapse-remitting, primary progressive, secondary progressive), duration of the disease, disease severity quantified by Expanded Disability Status Scale (EDSS) were registered. All cases were assessed while clinically stable, i.e., with absence of exacerbated infectious disease, traumatic or other acute complication, or use of corticosteroid drugs in the previous 3 mo as assessed by history and review of medical records. This study was approved by the institutional ethics committee. All patients provided informed consent.

Assessment Procedures

Fatigue was assessed via the Fatigue Severity Scale (FSS).[7] This is a nine-item self-reported scale with seven levels of agreement with each statement. The scale developer defines

Table 1—Characteristics of 50 multiple sclerosis study subjects.

Variable	
Age (y)	40.3 ± 10.7
Sex (male)	15 (30%)
EDSS	2.5; 2.5 (0.0–6.5)
Disease duration (y)	5.0; 9.0 (0.5–23.0)
Disease type	
Relapsing remitting	38 (76.0%)
Secondary progressive	11 (22.0%)
Primary progressive	1 (2.0%)

Categorical variables expressed as numbers and proportions (%). Continuous variables expressed as median, interquartile range and range. EDSS, Expanded Disability Status Scale.

Table 2—Sleep characteristics of 50 multiple sclerosis study subjects.

Variable	
ESS	5.0; 5.0 (0.0–18.0)
PSQI	5.0; 4.5 (1.0–17.0)
RLS	14 (28.0%)
PLMS	10 (20.0%)
PLMS index	7.1; 7.6 (0.9–25.3)
FSS	4.7; 3.1 (1.0–6.9)
AHI (e/h)	3.0; 4.4 (0.0–14.6)
DI (e/h)	0.7; 3.5 (0.0–9.9)
AI (e/h)	8.0; 8.9 (2.6–67.0)

Categorical variables expressed as numbers and proportions (%). Continuous variables expressed as median, interquartile range and range. AHI, apnea-hypopnea index; AI, arousal index; DI, desaturation index; ESS, Epworth Sleepiness Scale; FSS, Fatigue Severity Scale; PLMS, periodic limb movement in sleep; PSQI, Pittsburgh Sleep Quality Index; RLS, restless legs syndrome.

severe fatigue as an FSS score ≥ 36 (an average of ≥ 4 across the nine questions). The Pittsburgh Sleep Quality Index (PSQI) is a 19-item self-reported scale primarily intended to measure sleep quality and to identify good and bad sleepers, not to provide clinical diagnosis.[8] Daytime somnolence was assessed by the Epworth Sleepiness Scale (ESS). This is a validated questionnaire containing eight items that ask about the expectation of dozing in eight hypothetical situations. Dozing probability ratings range from 0 (no probability) to 3 (high probability). ESS score of 10 or more indicates excessive daytime sleepiness.[9] Restless legs syndrome (RLS) was established using the minimum criteria defined by the International Restless Legs Syndrome Study Group (IRLSSG).[10] Severity of RLS was assessed via IRLSSG RLS severity rating scale.[11] The questionnaires were applied by a physician during a personal interview with a patient to avoid false-positive diagnosis.

Polysomnography

Overnight diagnostic polysomnography (PSG) with four electroencephalography (EEG) canals was performed (Alice 5, Philips-Respironics, The Netherlands). Sleep parameters and respiratory events were scored according to standardized criteria.[12] An apneic event was defined as cessation of airflow for ≥ 10 sec, hypopneic event was defined as a decrease in airflow for ≥ 10 sec by at least 50% or associated with an arousal or desaturation ≥ 4%. Apnea-hypopnea index (AHI) was calculated as the number of obstructive apneas, central apneas, or hypopneas per hour of sleep. SDB was diagnosed in patients with an AHI ≥ 5/h. SDB was classified as mild (AHI 5–15/h), moderate (AHI 15–30/h), and severe (AHI ≥ 30/h). Apneas were differentiated in obstructive, mixed, and central apneas according to standard criteria. A diagnosis of central sleep apnea was made in patients, in whom > 50% of all respiratory events were central. A periodic limb movements of sleep (PLMS) index (number of PLMS per hour of sleep) of > 15 for the whole night was considered pathological.

Statistical Analysis

Categorical variables were expressed as numbers and proportions (%). Continuous variables were expressed as means ± standard deviation or median, interquartile range (IQR), and minimal and maximal values. Normal distribution of variables was investigated visually by histograms and by Kolmogorov-Smirnov normality test. Pearson or Spearman correlation coefficients were used to determine relationships between sleep related indices and clinical characteristics of the patients. Stepwise multiple linear regression analysis was used to identify factors that contributed to AHI, PSQI, FSS, and ESS. To compare groups, Mann–Whitney *U* test was used for ordinal or abnormally distributed parametric variables. All tests were two sided. A p value < 0.05 was considered statistically significant. All analyses were conducted using SPSS version 18 (SPSS Inc., Chicago, IL, USA).

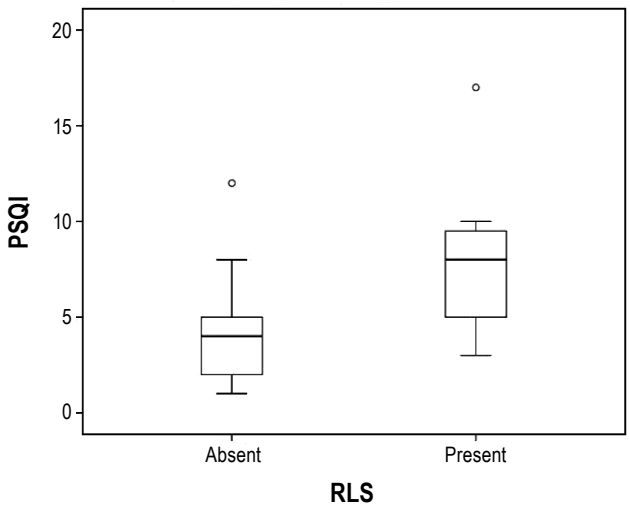
RESULTS

The baseline characteristics of the population are presented in **Table 1**. A total of 50 subjects (35 females, 15 males, mean age 40.3 ± 10.71 y) were included in the study. The median MS duration was 5 y (IQR 9, range 0.5–23.0 y), the median EDSS score was 2.5 (IQR 2.5, range 0–6.5). The number of patients affected by the relapsing-remitting form of MS was 38 (76%), 11 patients with MS (22%) presented a secondary-progressive form, and one patient (2%) had a primary-progressive form. PSG characteristics and questionnaire scores are presented in **Table 2**. Impaired sleep was present in 19 (38%), excessive daytime sleepiness in 9 (18%), and fatigue was present in 19 cases (38%). The median global PSQI score was 5 (IQR 4.5, range 1–17), median ESS score was 5 (IQR 5, range 0–18) and median FSS score 4.65 (IQR 3.10, range 1.0–6.9). RLS was present in 14 patients (28%), and PLMS were present in 10 patients (20%). A PLMS index of > 15 for the entire night was considered pathological.

In two cases, both RLS and PLMS were reported together. Median PLMS index was 7.1 (IQR 7.63, range 0.9–25.3). Using a cutoff AHI value of five events per hour of sleep, 14 patients (28%) met criteria for mild sleep apnea (3 patients with

central sleep apnea [CSA], 11 patients with obstructive sleep apnea [OSA]). We found that the AHI and desaturation index (DI), respectively, significantly correlated with age (r = 0.424, p = 0.002; r = 0.305, p = 0.033), EDSS (r = 0.384, p = 0.006; r = 0.289, p = 0.047), disease duration (r = 0.321, p = 0.025; r = 0.435, p = 0.002). Based on the linear regression analysis, age was the only independent variable significantly determining AHI and DI (beta = 0.369, p = 0.010; beta 0.301, p = 0.040). PSQI score was significantly higher in a population with RLS (p = 0.004). ESS was significantly higher in the RLS population (p = 0.011). There was a trend toward higher score of FSS in the RLS population, but the association was not significant (p = 0.052). Presence of RLS was the only independent variable significantly determining PSQI and ESS, respectively (beta = 0.535, p = 0.005; beta = 0.389, p = 0.025). DI and presence of RLS, respectively, were the only independent variables determining FSS (beta = 0.456, p = 0.015; beta = 0.418, p = 0.024). The association between PSQI and RLS is shown in **Figure 1**. We failed to find any significant intergroup difference in AHI, DI, PSQI, FSS, and ESS in populations with presence and absence of PLMS. We failed to find any significant correlation of PLMS index and sleep related indices or clinical characteristics of the patients.

Figure 1—The PSQI in population with and without RLS.



PSQI, Pittsburgh Sleep Quality Index; RLS, restless legs syndrome.

DISCUSSION

Poor sleep is a common finding in patients with MS. Previous studies have shown a prevalence ranging from 25% to 54% in this patient group.[1,3] In our patients with MS, poor sleep was present in 38%, excessive daytime sleepiness in 18%, and fatigue in 38%. The focus of this study was to assess the relationship between these subjective complaints using self-reported scales and nocturnal PSG findings and clinical characteristics of the population. Poor sleep, daytime sleepiness, and fatigue were significantly influenced by the presence of RLS. Fatigue was also determined by DI score. We failed to find any significant association between sleep related indices and clinical characteristics of the MS population (including EDSS, form, and duration of the disease).

In our MS population, 28% patients met the criteria for RLS, which is similar to other studies. A recent meta-analysis indicated that RLS prevalence among patients with MS ranges from 12.12% to 57.50% and is higher compared with healthy controls (2.56% to 18.33%).[13] In a large multicenter study of RLS, several risk factors in the MS cases were noted to be significant predictors for the presence of RLS including older age, leg jerks before sleep onset and primary progressive MS.

Patients with MS and with RLS were more likely to use hypnotic medications for sleep complaints than MS patients without RLS.[14] Moreira et al. reported that RLS is related to poor sleep quality and fatigue, and patients with RLS showed worse scores in several sleep domains such as sleep latency, sleep efficiency, and sleep duration.[15] In agreement with this study, we identified the presence of RLS as the only independent variable significantly determining poor sleep and daytime sleepiness. RLS and DI were independent predictors of fatigue in our population. The strength of our study was the objective assessment of sleep using the PSG measurement, which helped us to recognize other possible causes of poor sleep; for example, SDB or PLMS.

There are several studies suggesting MS as one of the causes of symptomatic RLS. The cause of increased prevalence of RLS in patients with MS is still not clear. There is biological plausibility for a link between MS and RLS. Current concepts of RLS assume a dysfunction of the dopaminergic system, spinal pathogenesis, that attributes the occurrence of the symptoms to an interruption of descending and ascending hypothalamic-spinal pathways.[16–18] It was reported that cervical cord affection correlates with RLS among patients with MS.[19,20] The exact cause of increased prevalence of RLS in MS population is beyond the aim of our study.

Motor and sensory symptoms such as leg spasms and paresthesias are common symptoms in MS and may complicate the diagnosis of RLS. For this reason, a detailed assessment of the four essential diagnostic criteria for RLS is necessary to avoid false-positive diagnosis. Because RLS is usually unresponsive to treatment with benzodiazepines and because symptoms sometimes worsen with the use of some antidepressant drugs, an early recognition of RLS in patients in MS may avoid ineffective drug treatment in favor of a more successful therapy, such as a low evening dose of dopamine agonists.[21]

PLMS are characterized by brief (0.5–5.0-sec lower extremity movements during sleep, which typically occur at 20- to 40-sec intervals, most commonly during the first 3 h of sleep. The affected individual is usually not aware of the movements or of the transient partial arousals.[12] The prevalence of PLMS in the Ferini-Strambi et al. study of patients with MS was 36% compared to healthy controls (8%). They have also found that patients with MS and PLMS had higher magnetic resonance imaging lesion loads in infratentorial regions, compared with patients with MS without PLMS.[22] A number of patients with RLS may have PLMS during sleep. PLMS may be accompanied by arousals leading to sleep fragmentation and excessive daytime sleepiness. Generally, PLMS have been found in approximately 80–90% of patients with RLS.[23] In our sample,

PLMS were present in 20% of cases. In two cases, both RLS and PLMS were reported together. RLS is a clinical diagnosis, but PSG is required for detecting PLMS. We failed to find any significant intergroup difference in PSQI, FSS, and ESS in populations with presence and absence of PLMS. We failed to find any significant correlation of PLMS index and sleep related indices or clinical characteristics of the patients. RLS compared to PLMS seems to be a superior factor determining poor sleep, daytime sleepiness, and fatigue in patients with MS. We confirm that nocturnal movement disorders are frequent in MS, compared to other studies. Despite the fact that symptomatic treatment for RLS is available, it is still an underrecognized condition and frequently patients with MS remain undiagnosed and untreated. Because of its significant effect on sleep, it should be always investigated in patients with MS.[24]

Although some data suggest an increased prevalence of SDB in patients with MS, other studies have produced conflicting results. SDB has also been proposed as a potential risk factor for fatigue in MS. In our current survey, SDB was found in 28% of patients and was mild in all cases. SDB was obstructive in 11 patients, and central in three patients. Although SDB was associated with age, clinical status, disease duration, and the presence of fatigue, age was the only independent variable determining SDB severity. Ferini-Strambi et al. compared 25 consecutive patients with MS to 25 healthy controls and found three of the patients with MS had an AHI greater than 5 versus none of the controls.[22] However, Kaynak et al. found no subjects on PSG to have an AHI greater than 5 in their analysis of 27 patients with fatigue, 17 patients with MS without fatigue, and 10 healthy controls.[25] However, Veauthier and colleagues reported increased prevalence of clinically relevant sleep disorders, including SDB, in fatigued patients with MS (27%) compared to nonfatigued patients (2.5%) as defined by the Modified Fatigue Impact Scale.[26] Another prospective PSG study in MS subjects and controls suggests that severe obstructive sleep apnea (defined as an AHI $\geq$ 30) is independently associated with fatigue in MS, as defined by the Fatigue Severity Scale.[5] Braley et al. suggest a predisposition for obstructive sleep apnea and accompanying central apneas among patients with MS, particularly among those with brainstem involvement.[27] Very recent studies have reported a significant improvement of fatigue after treatment of SDB and other sleep disorders.[28,29] Kallweit et al. have found a SDB frequency of 41% among patients with MS with severe fatigue and demonstrated that continuous positive airway pressure therapy was associated with a significant improvement of fatigue severity, whereas sleepiness remained unchanged.[30] All the studies mentioned illustrate different prevalence and severity of SDB in MS and its relationship to fatigue. Differences between studies may be due to disparities of included patient cohorts, and technical and methodological differences. We found DI to be one of independent predictors of fatigue in the MS population.

Psychiatric disorders, especially depression, are common in patients with MS. Sleep disruption and depression are closely linked. The number of patients with MS who have a clinical diagnosis of depression is higher among poor sleepers.[2,31] The relationship between sleep and depression seems to be bidirectional; in fact, poor sleep can predict depression and a depressed mood may be a predictor of a disrupted sleep. [32]

In conclusion, we suggest that the presence of RLS seems to be the main factor determining poor sleep and daytime somnolence in patients with MS. RLS together with DI were significantly associated with fatigue. Presence of SDB and its severity was associated with age, clinical status of a patient, and disease duration, but age was the only independent variable determining SDB severity. In our MS population, SDB was mild in all patients. We have to acknowledge several limitations in our study. First of all was the small sample size. Second, we did not include a control group, and third, we did not assess possible confounders such as psychiatric or internal disorders or influence of any therapy. Nevertheless, we believe that our study may provide another clinical experience to the current discussion about the role of sleep disorders in patients with MS.

ABBREVIATIONS

AHI, apnea-hypopnea index
AI, arousal index
CSA, central sleep apnea
DI, desaturation index
EDSS, Expanded Disability Status Scale
ESS, Epworth Sleepiness Scale
FSS, Fatigue Severity Scale
IQR, interquartile range
IRLSSG, International Restless Legs Syndrome Study Group
MS, multiple sclerosis
OSA, obstructive sleep apnea
PLMS, periodic limb movement in sleep
PSG, polysomnography
PSQI, Pittsburg Sleep Quality Index
RLS, restless legs syndrome
SDB, sleep disordered breathing

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