Multiple Sclerosis, Fatigue, Expanded Disability Status Scale: A Cross-Sectional Exploration of Sleep Efficiency and Quantitative Sleep Parameters

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ABSTRACT

BACKGROUND: Poor sleep quality and sleep disorders are more prevalent in individuals with multiple sclerosis (MS) than in the general population. Poor sleep has been correlated with worse MS outcomes. Sleep efficiency (SE) is one of the most sensitive markers of sleep quality. There is very little written about SE and other polysomnography (PSG) parameters and MS measures.

METHODS: This is a retrospective review of 280 consecutive individuals with MS evaluated by PSGs and other standardized MS measures over 13 years at a comprehensive MS center. In addition, the cohort was assessed with 2 fatigue scales, the Epworth Sleepiness Scale, and the Expanded Disability Status Scale. A comparison of means test (independent *t* test) and a correlation coefficient (*r*) were used.

RESULTS: The PSG measures of SE and Total Sleep Time were significantly different between a group of individuals with MS with a disease duration of more than 5 years vs a group of individuals with MS with a disease duration less than or equal to 5 years. Prevalence of obstructive sleep apnea was 63%, higher than reported in the literature while the prevalence of moderate to severe obstructive sleep apnea was 33.4%, which was lower than reported.

CONCLUSIONS: Longer disease duration and worse disability correlate with sleep quality as measured by SE.

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Fatigue is very common among and quite disabling to individuals with multiple sclerosis (MS).[1] Sleep disorders, which occur with higher prevalence among individuals with MS than the general population,[1] can contribute to fatigue, mood disorders, and cognitive dysfunction in individuals with MS.[2] These disorders include obstructive sleep apnea (OSA),[3] insomnia,[4] restless legs syndrome,[5] and periodic limb movement disorder (PLMD).[6] When evaluated with polysomnography (PSG), more than 70% of patients with MS are impacted by 1 or more sleep disorders.[7] Targeted treatment of the specific sleep disorder can improve fatigue related to this underlying problem.[7] The cause of the high prevalence of sleep disorders and sleep disturbances in individuals with MS remains unknown. Several studies have suggested that disturbed sleep correlates with endogenous melatonin dysregulation,[8] lesions in the supplementary motor area,[9] and higher spinal cord plaque burden.[10] By contributing to systemic inflammation, OSA itself can impair the integrity of white matter.[11] One of the best markers for sleep quality is the percent sleep efficiency (SE) or total sleep time (TST) over time in bed times 100.[12] Poor sleep quality may lead to oxidative stress, which exerts toxic effects on oligodendrocytes and leads to progressive myelin destruction, possibly worsening MS symptoms.[1] Poor sleep quality may also influence the disease course of individuals with relapsing-remitting MS (RRMS). In a cohort of individuals with MS who were evaluated with the Pittsburg Sleep Quality Index and then grouped into good and bad sleepers, being a bad sleeper correlated significantly with an increase in the number and duration of MS relapses, as well as in the number of days of MS disease activity.[13] Very few studies have used objective metrics to assess SE in individuals with MS. All have been cross-sectional, using small cohorts of individuals with MS and controls, and most have shown, via PSG, lower SE in the MS group vs controls.[14-17]

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TABLE 1. Demographic Variables for Study Participants (N = 280)

Demographics	Multiple sclerosis duration ≥ 5 years n, (%)	Multiple sclerosis duration < 5 years n, (%)
Number of participants	148 (52.9)	133 (47.5)
Mean age in years	44	46.2
Sex		
Male	41 (27.7)	37 (27.8)
Female	107 (72.3)	96 (72.1)
Disease-modifying therapies	123 (83.1)	75 (56.4)
Mean EDSS score	2.94	2.02

EDSS, Expanded Disability Status Scale.

TABLE 2. Mean PSG Parameters (N = 280)

Variables	MS duration ≥ 5 years	MS duration < 5 years
Sleep efficiency, %	74.3 ± 14.3	80.5 ± 14.7
TST[a]	299.0 minutes (n = 88)	318.3 minutes (n = 89)
AHI	14.6	13.2
Periodic Limb Movement Index	3.93	2.76
N3 sleep, %	6.98	8.57
REM sleep, %	13.0	13.6
REM AHI	18.7	15.3
Arousal index, per hour	18.2	17.7
OSA (any), %	47 (31.8)	24 (18.0)

AHI, apnea-hypopnea index; N3, stage 3 non-REM sleep; OSA, obstructive sleep apnea; PSG, polysomnography; TST, total sleep time
[a] TST N = 177.

To the best of our knowledge, there are no studies looking at MS disease duration and objective sleep variables and their correlation with various disease measures. We postulated that the longer the disease duration, the poorer sleep quality would be. Full characterization of the multiple features of sleep architecture in individuals with MS has not been summarized in a large cohort, nor explored related to SE and the relationship to current normative sleep parameters. This summary analysis provides clinicians with an overview of the concept of SE in individuals with MS.

METHODS

This is a retrospective review of 280 consecutive adults with MS who were seen and evaluated at South Shore Neurologic Associates, a comprehensive MS care center, from September 17, 2014, to November 19, 2021, and who underwent overnight PSG during routine care. The PSGs were performed to evaluate fatigue and various sleep complaints. Informed consent was obtained prior to inclusion in the study. Approval for the retrospective review of deidentified clinical data was obtained by the South Shore Neurologic Associates institutional review board.

The data collected included, age, sex, MS duration, disease-modifying treatments (DMTs), and several validated outcome measures, including scores of the Expanded Disability Status Scale (EDSS), Epworth Sleepiness Scale (ESS), Modified Fatigue Impact Scale (MFIS) and Fatigue Severity Scale (FSS). The EDSS assesses disability in individuals with MS on a scale of 0 to 10.[18] The ESS is a measure of subjective sleepiness with a score range of 0 to 24. Scores of 11 and higher are suggestive of excessive daytime sleepiness.[19] The MFIS has 3 subscales and the total score ranges from 0 to 84. It assesses the impact of fatigue on various functional domains including physical, cognitive, and psychosocial functioning.[20] The FSS measures fatigue, in MS and systemic lupus erythematosus, over the previous week. Scores range from 0 to 63, and 36 or higher is suggestive of fatigue.[21] Data extracted from the PSG included SE, sleep onset latency (SOL; ie, time to initially fall asleep), relative REM latency (ie, time it takes from sleep onset to first REM period), total apnea-hypopnea indices (AHI; ie, number of respiratory events per hour), REM AHIs, spontaneous arousal indices (AI; ie, number of arousals per hour), periodic leg movements indices (PLMI) without arousals and with arousals (PLMAI) each per hour, and respiratory arousal indices (RAI). Additionally, sleep architecture metrics were collected, including percentage spent in REM sleep and in the 3 nonREM (N) stages, N1, N2, N3. Researchers also recorded participants' Total Sleep Time (TST) and any prior diagnosis of OSA.

Statistical Analysis

Data were analyzed by using a comparison of means test (independent *t* test) through MedCalc (https://www.medcalc.org). Mean SE was compared between 2 groups of individuals with MS: those with a disease duration of more than 5 years and those with a disease duration of 5 years or less. This same test was used to compare mean AHI, REM AHI, PLMI, AI, percentages of N3 and REM

sleep, age, whether individuals were on DMTs, MFIS, ESS, and FSS between the 2 groups. The cohort's SE and EDSS scores were compared to these scales and a 2-tailed test was used. We calculated the correlation coefficient using Excel.

RESULTS

Of the 280 individuals with MS, 148 (52.9%) had MS for more than 5 years (group 1), while 133 (47.5%) had MS for 5 years or less (group 2). Patient characteristics are in **TABLE 1**. Of the total 148 in group 1, 107 (72.3%) were female, the mean age was 44 years, and 123 (83.1%) were on DMTs. Of the total 133 in group 2, 96 (72.1%) were female, the mean age was 46.2 years, and 75 (56.4%) were on DMTs at the time of PSG. In group 2, some patients were not yet on DMT because they were newly diagnosed with MS. Because some of the data was not entered in the original database, TST was only available for 88 subjects in the first group and 89 in the second group. **TABLE 2** lists all data collected for each group. Group 1 had a significantly lower SE than group 2, (74.3%, SD 14.3 vs 80.5%, SD 14.7; P = .0004, 95% CI 2.8-9.7). The 2 groups also had different TSTs; the mean TST in group 1 was 299 minutes (SD 78.35 min) and the mean TST in group 2 was 318.26 minutes (SD 76.2 min) (difference = −19.224 min, standard error = 11.619 min, 95% CI, −42.1551 to 3.7067, t statistic −1.655, DF 175, significance level P = .0998). There were no significant differences between the groups in AHI, PLMI, PLMAI, AI, REM AHI, percentage of N3 sleep, or percentage of REM sleep.

Abnormal sleep parameters were found in group 2. Mean AHI at 13.2 (55.6%), PLM at 2.76, and mean AI at 17.7 (56.4%) were all above the normal range. SE was inversely correlated with EDSS (r = −0.22, 2-tailed P = .0005). No other correlations between SE and other outcome measures were identified. Age correlated with EDSS in the total cohort (r = 0.27, 2-tailed P = .000023), but not with SE (r = −0.11, 2-tailed P = .086174). Because we did not have TST values for all the subjects, we did not run correlations among TST and other measures.

Our study results differed from other studies of adults in terms of sleep parameters. The mean AHI and AI were both higher among our cohorts at 13.9 and 17.7, respectively, as compared with historic norms recorded at less than 5 and 12.6, respectively.[22] Mean SE was lower at 74.96% compared with 85.7% among controls.[22] Our study cohort also demonstrated a statistically significant increase in individuals with OSA, which is defined as an AHI of 5 or higher. Of the 280 total in the cohort, 168 (60.1%) had OSA, 94 (33.4%) had moderate or severe OSA (AHI ≥ 15/hour). Only 25.3% of our cohort had an OSA diagnosis prior to undergoing the PSGs reported here. Historically, the prevalence of any OSA among smaller cohorts of individuals with MS is reported between 15.04%[23] and 30%,[24] and that of moderate to severe OSA has been reported at 58%.[25] The prevalence of OSA among the general population using the same criteria (ie, AHI ≥ 5) is reported to be between 9% and 38%[26] with moderate to severe OSA (ie, AHI ≥ 15) at 7% to 17%.[26] There was an increase in the prevalence of OSA with age.[26]

DISCUSSION

To our knowledge, this study is the first to explore the relationship of SE and multiple objective quantitative measures of sleep disorders in individuals with MS by both disease duration and EDSS quantified disability. It is also a relatively large cohort of individuals with MS. SE was not related to changes in sleep stage distribution (N3, R percentages), severity of OSA (AHI), PLMD (PLMI), or even AI. In this cohort, as previously reported in smaller cohorts, DMT did not impact SE independently of disease duration.[27] SE declines with the duration of illness, but other sleep parameters may change early in the illness and remain abnormal throughout. SE correlated with disease duration but not age in our cohort, even though age positively correlated with EDSS. This could be due to polypharmacy, pain, bladder dysfunction, and other comorbidities that tend to increase with disease duration and may impact sleep independent of the age of the person. The lack of these data is mentioned below in the study limitations. With the limited TST data we have, we can postulate that SE was lower in the individuals with a disease duration less than or equal to 5 years because their TST was shorter.

Perhaps due to increased plaque burden causing more significant neurodegeneration (and its resultant poorer sleep quality)[27-29] or because impaired sleep worsens disability due to microstructural white matter damage,[27] individuals with MS who have higher EDSS scores and longer disease duration are more likely to have impaired SE.[30] Although related to SE, EDSS-defined disability is unrelated to the presence of OSA or PLMD. These findings are consistent with previous smaller cohorts.[30] The reason for the discrepancy in the OSA prevalence when compared with previously published reports is the age and the size of the cohorts. Chinnadurai et al excluded anyone over age 50.[23] All other studies included cohorts smaller than ours with Ns ranging from 23 to 113.[23,25,31] Perhaps Chinnadurai et al did not find a correlation between SE and disease duration because of their age limits as well as the smaller cohort.[23] Another potential explanation for the discrepancy between OSA prevalence and severity among our cohort vs others is the way hypopneas are defined. In this study, the more sensitive American Academy of Sleep Medicine rule 1A was used; it defines hypopneas as a 50%

PRACTICE POINTS

Sleep efficiency, the percentage of time in bed spent sleeping, independently and inversely correlates with scores on the Expanded Disability Status Scale in multiple sclerosis (MS).

In individuals with MS with longer sleep duration, sleep efficiency is significantly lower than in individuals with MS with shorter sleep duration. ■

reduction in airflow associated with either a 3% or more oxygen desaturation and/or an arousal.

Our study has several limitations. Our cohort did not differentiate between currently defined RRMS, primary progressive MS, or secondary progressive MS. This was a cross-sectional study allowing analysis of disease duration limited to over 5 years or less than or equal to 5 years; whether or not additional disease duration information would impact SE or other PSG measures remains undetermined. We also only had incomplete TST data with scores for only 177 of 280 (63.21%) participants instead of the entire cohort. Whether additional geographic variability or analysis by ethnicity will impact SE or other PSG measures also remains unknown. Longitudinal impact of individual DMT or DMT mechanism of action on SE or PSG measures remains to be defined. The study does not include data on other potentially relevant MS-related variables, such as pain, polypharmacy, and bladder dysfunction, which also can interfere with sleep. These MS-related variables are more likely to be prevalent among individuals with a duration of disease of more than 5 years. The majority of our study participants with less than or equal to disease duration of 5 years were not on any DMTs, and the most likely explanation for that is their shorter duration of illness. Interferons are known to impact sleep architecture, which may explain why unmedicated patients had better sleep efficiencies. It is also prudent to note that only 241 of our 280 study participants had recorded EDSS. There was a low threshold to send patients experiencing fatigue for polysomnogram tests. These studies were performed in different labs and were read by different professionals who implement or follow different criteria to achieve a diagnosis of OSA. These could have potentially impacted other sleep parameters and could explain why they were not statistically significant.

CONCLUSIONS

This study demonstrates how lower sleep efficiency correlates with additional EDSS-defined disability and longer disease duration. Further clarification of this association can be achieved by pursuing PSGs as part of routine clinical care. This will give clinicians better insight into sleep disorders in individuals with MS and help them make more informed treatment decisions. This, in turn, could improve patient outcomes and reduce overall disability. ■

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