The Relationship of Sleep Disturbances and Fatigue in Multiple Sclerosis

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Background: Fatigue is experienced by most patients with multiple sclerosis (MS) and often is profoundly debilitating. No large-scale studies to our knowledge have examined circadian rhythm abnormalities in MS patients or the relationship of fatigue to circadian rhythms.

Objective: To determine if patients with MS and fatigue have sleep disturbances or circadian rhythm abnormalities associated with fatigue.

Design: Case-control study.

Setting: Washington University School of Medicine, St Louis, Mo.

Patients: Fifteen patients with MS and fatigue were compared with 15 patients with MS without fatigue and 15 age- and sex-matched, healthy controls.

Main Outcome Measures: Sleep disturbances and circadian rhythm abnormalities were quantitated by actigraphy, fatigue by the Fatigue Descriptive Scale, and excessive sleepiness by the Epworth Sleepiness scale (ESS).

Results: Of the 15 fatigued patients with MS, 2 had delayed sleep phase, 10 had disrupted sleep, and 3 had normal sleep. One of the 15 nonfatigued MS patients had irregular sleep cycles, 2 others had disrupted sleep, and 12 had normal sleep. All 15 of the healthy controls had normal sleep. Nine patients with MS and fatigue scored 10 or higher on the ESS, suggesting excessive daytime sleepiness. Only 2 patients with MS without fatigue scored higher than 10 on the ESS. None of the healthy controls were fatigued, and 14 were not excessively sleepy. A relationship was found between fatigue and abnormal sleep cycles or disrupted sleep (Fisher exact test, \( P = .003 \)). There was also a relationship between subjective excessive daytime sleepiness and fatigue in MS patients \( (P = .02) \).

Conclusion: There is a significant correlation between fatigue in MS patients and disrupted sleep or abnormal sleep cycles.

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The Biological Clock, the circadian oscillator, is situated in the suprachiasmatic nucleus (SCN), a small paired structure just above the optic chiasm. In animal models circadian rhythms of sleep-wakefulness disappear when the SCN is destroyed, and transplantation of fetal or neonatal SCN into an animal with experimentally induced irregular circadian patterns restores circadian rhythm. A variety of degenerative neurological disorders affect human circadian rhythms.

Fatigue is the most frequent symptom in multiple sclerosis (MS) and is often difficult to treat. Fatigue is experienced by 76% to 92% of MS patients and often is profoundly debilitating. To our knowledge, no large-scale studies have been performed to examine circadian rhythm abnormalities in patients with MS, and none have looked at the relationship of fatigue to the circadian rhythms. Taphoorn et al assessed fatigue, sleep disturbances, and circadian rhythm in 16 patients with MS and assessed some of the patients’ partners (8 volunteers) as controls. No significant circadian rhythm abnormalities were found in the MS group, no correlation was found between fatigue and sleep disturbances, and the patients with MS who complained of fatigue were not directly compared with patients with MS who did not complain of fatigue. Soorensen et al found an absence of diurnal variation in cerebrospinal fluid somatostatin during MS relapses, which is suggestive of altered circadian rhythms. Other noncontrolled studies have also found various sleep disorders in the MS population. The objectives of the present study were to determine whether circadian rhythm abnormalities or disturbances of sleep exist in patients with MS and if they correlate with fatigue and excessive daytime sleepiness as assessed by standardized questionnaires. Circadian rhythm abnormalities include several clinical conditions: time zone
change (jet lag) syndrome, shift-work sleep disorder, irregular sleep-wake pattern, delayed sleep-phase syndrome, advanced sleep-phase syndrome, non–24-hour sleep-wake disorder, and circadian rhythm sleep disorder not otherwise specified.

The study protocol was reviewed and approved by the Washington University School of Medicine Human Studies Committee. Subjects were recruited through physician referrals and advertisements. Three groups of subjects were compared. The groups were age and sex matched. Group 1 consisted of 15 patients with relapsing-remitting and/or secondary progressive MS who had fatigue based on fatigue questionnaires, specifically the Fatigue Descriptive Scale (FDS)\textsuperscript{12} in which a score of 5 or higher was considered indicative of fatigue (range, 0-13). All patients were also rated with the Modified Fatigue Impact Scale (MFIS) (score range, 0-84)\textsuperscript{13}; however, the MFIS was not used to divide patients into fatigued and nonfatigued groups because the MFIS has no standardized norms. The literature reports the mean score of the MFIS for patients with MS fatigue as 27.24 vs 15.63 for healthy controls.\textsuperscript{14} The MFIS scores were compared with the FDS scores to look for major discrepancies between the two. None were found. Group 2 consisted of 15 patients with relapsing-remitting and/or secondary progressive MS without fatigue. Group 3 consisted of healthy volunteers who had no sleep complaints or fatigue, were not receiving medications that could possibly affect circadian rhythms, and had no neurological disorders. The male-female ratio in all groups was 4:11. Mean age was 45.1 years for healthy controls, 33.5 years for the nonfatigued group, and 46.4 years for the fatigued group. The mean Expanded Disability Status Scale (EDSS) was 3.4 for the nonfatigued group and 3.4 for the fatigued group.\textsuperscript{15} None of the female participants were pregnant during their participation in the study. None of the patients had a diagnosis of a chronic medical problem other than the MS. None were previously diagnosed as having any sleep disorder.

Because this study was designed to assess the biological and neurological effects of MS on circadian rhythms, patients were asked, when possible, to discontinue the use of medications that could possibly interfere with sleep-wake cycles or that could affect fatigue. Specifically excluded medications were melatonin, benzodiazepines, trazodone hydrochloride, zolpidem tartrate, zaleplon, methylphenidate, dextromethorphan, methylphenidate hydrochloride, dextromethorphan, and pemoline. Of 45 subjects, only 2, both in the group of MS with fatigue, were taking a medication from this list. Both were taking amantadine and both discontinued use for a week before and during the 2-week participation in the study. Twenty-six of the 30 patients with MS were undergoing disease-modifying treatments (interferon beta or glatiramer acetate), which were not discontinued. Of the 4 who were not undergoing disease-modifying treatments, 3 had disrupted sleep and 1 did not. All 4 were fatigued.

Patients were also screened for depression with the Beck Depression Inventory (BDI).\textsuperscript{16} Because depression has been associated with the complaint of fatigue, patients with a BDI score of higher than 16 were excluded.

The Epworth Sleepiness Scale (ESS)\textsuperscript{17} was used to determine the presence or absence of hypersomnia, a score of 10 or more being indicative of hypersomnia (range, 0-24). These data were used to establish the relationship between the severity of each subject’s fatigue and their degree of hyperomnia.

Patients were asked to keep sleep logs and wear an actigraph (Actiwatch; Mini-Mitter Co Inc, Bend, Ore) for 2 weeks. An actigraph is a simple, noninvasive, wrist-mounted device that consists of a movement detector and storage memory used to record activity during wakefulness and sleep.\textsuperscript{18} Actigraphy is based on the fact that, in general, there are fewer limb movements in sleep than in wakefulness.\textsuperscript{18} There is a close correlation between rest or activity recorded by the actigraph and the wake-sleep pattern determined by a polysomnogram.\textsuperscript{19} No electrode application is necessary, and a patient can wear the actigraph continuously for several days.\textsuperscript{19} Sleep-wake cycles were scored using specific computer software purchased from the manufacturer of the actigraphs. Study participants kept subjective sleep logs as well. The sleep log is a chart divided into 7 longitudinal bars, each for 1 day of the week. The bars themselves are divided into 24 boxes, and each box is divided into smaller boxes for each 15-minute interval. The participants color in the times that they think they have slept and leave blank the times they have remained awake. The sleep-wake scores from the actigraphic data were used to determine the timing of each subject’s major sleep period and its relationship to the standard 24-hour day. Subjects were aware of the function of the actigraphs. Subject insight into the mechanism of the actigraph did not affect the results. Subjects were considered to have circadian rhythm abnormalities if their major sleep period was delayed, advanced, or irregularly timed in relation to their desired sleep time and caused complaints of somnolence and/or insomnia.\textsuperscript{20} These determinations were based on the actigraphic readings and sleep log evaluations and not on the subject’s complaints of excessive sleepiness or insomnia. The Fisher exact test (2-tailed) was used to determine the significance of the results.

The actigraphs and the sleep logs were evaluated in a blinded fashion without prior knowledge of the results of the questionnaires. The blinded evaluator (H.P.A.) compared the objective sleep-wake cycles of the actigraph with the subject’s sleep and wake cycles as reflected in the sleep logs. Disrupted sleep on actigraphy was defined as at least 3 or more awake periods of 15 minutes or longer during the major sleep period, occurring at least 3 nights per week.

Among the 30 patients with MS, there was concordance between the person’s subjective assessment of their own sleep (sleep logs) and that of the objective measure (actigraphy). Of 15 fatigued patients with MS, 2 had a circadian rhythm abnormality of a delayed sleep phase, and 10 had disrupted sleep. Three had normal sleep cycles with no significant nighttime disruptions. One of the 15 nonfatigued MS patients had a circadian rhythm abnormality of irregular sleep phase. Two others had disrupted sleep, and 12 had normal sleep cycles with no significant nighttime disruptions. All 15 of the healthy controls had normal, nondisrupted sleep cycles, and only 1 of the controls had a significant discrepancy between subjective and objective sleep, such as that seen in sleep state misperception insomnia.\textsuperscript{20}

All of the healthy controls scored less than 5 on the FDS, and 14 scored less than 10 on the ESS. Only 1 scored 13 on the ESS, suggesting excessive daytime sleepiness. Nine patients with fatigue scored 10 or higher on the ESS, indicating excessive daytime sleepiness: 2 had normal sleep and 7 had disrupted sleep. Only 2 patients without fatigue scored higher than 10 on the ESS. Both had normal sleep. None of the patients without fatigue but with abnormal sleep scored 10 or higher. A significantly high probability of a relationship between the presence of fatigue and abnormal sleep cycles or disrupted sleep...
was found (Fisher exact test, \( P = .003 \)). There was also a significantly high probability of a relationship between excessive daytime sleepiness and subjective fatigue complaints in MS patients \( (P = .02) \).

For fatigued patients, the range of FDS scores was 5 to 11 (median, 7), the range of ESS scores was 2 to 24 (median, 12), the MFIS range was 17 to 62 (median, 44), and the range of BDI scores was 4 to 14 (median, 7). For nonfatigued patients with MS, the FDS range was 1 to 4 (median, 3), the ESS range was 0 to 19 (median, 5), the MFIS range was 12 to 41 (median, 21), and the BDI range was 0 to 9 (median, 5). The healthy controls had an FDS range of 0 to 4 (median, 1), an ESS range of 2 to 13 (median, 6), an MFIS range of 0 to 33 (median, 10), and a BDI range of 0 to 11 (median, 2).

### COMMENT

In our series of patients with MS, there was a significantly high probability of a relationship between fatigue and disrupted sleep or abnormal sleep cycles. These abnormalities may be playing a role in the pathophysiology of poorly understood and disabling MS fatigue. There was also a significantly high probability of a relationship between excessive sleepiness as measured by the ESS and complaints of fatigue.

Our study used the actigraph as an objective measure of sleep disruption and/or circadian rhythm disturbances. Although the actigraph is ideal for evaluating sleep-wake cycles during long periods and in the subjects’ home environment, it does not show the causes of those disruptions. A larger-scale study, one that uses 2 or 3 consecutive, all-night polysomnograms and daytime, multiple sleep latency tests to assess the cause of those sleep disturbances, is needed. Sleep disorders, such as restless legs syndrome, periodic limb movement disorder, and obstructive sleep apnea, are more common in patients with MS.\(^{11,22}\) Also, once the underlying sleep disorder is identified, assessing the impact of successful treatment of those disorders on the complaints and objective measurements of fatigue is warranted.

Additional studies are also needed to correlate the specific sleep disorders with the location of the demyelinating plaques seen on brain magnetic resonance imaging studies. Several case reports and small studies\(^ {11,21,22}\) of plaque location and relationship to fatigue have been published. In one study,\(^ {23}\) regional lesion load did not differ between fatigued and nonfatigued patients. The authors concluded that differences in the levels of self-reported fatigue in patients with MS could not merely be explained by the degree of clinical disease activity, neurological disability, or the extent of magnetic resonance image abnormalities.

The results of our study differ somewhat from those of Taphoorn et al.\(^ {8}\) This may be because we assessed both sleep disruptions and circadian rhythm problems, whereas the other study assessed only circadian rhythm abnormalities. In addition, we compared fatigued MS patients with age- and sex-matched, nonfatigued MS patients and healthy controls, whereas the other study did not compare fatigued with nonfatigued patients. Finally, our method of measuring excessive sleepiness was the ESS, which is more sensitive in detecting hypersomnolence than the Multiple Sleep Latency Test, which was used by the other study to identify sleepiness.\(^ {24}\)

Although our study involved only a limited number of subjects, it raises the question of the role of sleep disorders in the development of MS fatigue. The FDS and ESS may be used as screening tools in patients with MS and fatigue to screen for potentially reversible sleep disorders. Increasing awareness among the medical community may contribute to early detection and treatment of these sleep abnormalities. However, additional large-scale studies using polysomnography are needed to confirm their utility.

### Author contributions:

Study concept and design (Drs Attarian, Brown, and Cross); acquisition of data (Drs Attarian and Cross and Ms Carter); analysis and interpretation of data (Drs Attarian, Brown, Duntley, and Cross); drafting of the manuscript (Drs Attarian and Brown); critical revision of the manuscript for important intellectual content (Drs Attarian, Brown, Duntley, and Cross and Ms Carter); statistical expertise (Dr Attarian); obtained funding (Drs Attarian and Cross); administrative, technical, and material support (Drs Brown and Duntley and Ms Carter).

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### REFERENCES


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