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The relationship between objective parameters of sleep and measures of fatigue, depression, and cognition in multiple sclerosis

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Abstract

Background: People with multiple sclerosis (MS) often report poor sleep, fatigue, sleepiness, depression and cognitive dysfunction. Interrelationships between symptoms and sleep are poorly understood.

Objectives: To document objective parameters of sleep measured by polysomnography (PSG) and multi-sleep latency tests (MSLTs) in patients experiencing fatigue or sleepiness and to determine whether they correlate with symptoms.

Methods: Thirty-two MS patients, not on therapy, with fatigue or sleepiness completed the Modified Fatigue Impact Scale, Fatigue Severity Scale, Epworth Sleepiness Scale, Beck Depression Index and NeuroTrax cognitive tests and underwent PSG and MSLTs.

Results: Sleep efficiency (SE) averaged 75.1%. wake after sleep onset (WASO), sleep onset latency and multi-sleep latency were 66.2, 43.4 and 10.43 min, respectively. Stage N3 and rapid eye movement sleep were absent in 10 and four patients, respectively. Increased limb movements were observed in eight patients. Obstructive sleep apnea was observed in 12 patients. Neither SE nor WASO correlated with fatigue or sleepiness. SE correlated with the global cognitive score and with executive function and information processing subscales.

Conclusions: Overall, 30/32 MS patients reporting fatigue or sleepiness had evidence of one or more sleep disturbances. PSG should be considered in MS patients reporting fatigue or sleepiness in order to rule out treatable disturbances.

***Keywords*:** Cognition, fatigue, hypersomnia, insomnia, multiple sclerosis, obstructive sleep apnea, polysomnography, periodic limb movement disorder

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Introduction

Compared to healthy controls, people with multiple sclerosis (MS) report more difficulty with poor sleep,[1] fatigue,[2] sleepiness,[3] mood disturbance[4] and cognitive dysfunction.[5] The interrelationship between these symptoms is poorly understood.

Fatigue and excessive daytime sleepiness are distinct symptoms. Fatigue has several related definitions. The MS Council defines it as ''a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities.''[6] More recently, it has been defined as reversible motor and cognitive impairment, with reduced motivation and desire to rest.[7]

Excessive daytime sleepiness (EDS) refers to an abnormal likelihood of dozing during normal waking hours. Fatigue is one of the most frequently reported symptoms in MS with a prevalence of over 75%.[8,9] EDS is less common than fatigue with several studies reporting rates from 19–34%, as measured by the Epworth Sleepiness Scale.[3,8,10–12] A relationship between fatigue and sleepiness has been reported in some studies, [3,8,10] while other studies found that these symptoms were independent.[12,13]

Conflicting measures of sleep disturbances are seen in different studies of MS patients. In some studies, sleep efficiency (SE) did not differ between MS patients and healthy controls, although MS patients

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had more sleep stage shifts or arousals.[14,15] In other studies, SE was reduced in MS patients compared to controls.[12,16] Some studies have shown a higher incidence of sleep disordered breathing in MS,[17,18] while other studies did not find an increased incidence of this symptom.[12,15,19] Relationships were found between the presence of fatigue and either reduced SE or disrupted sleep in several studies.[3,12,14,18]

The purpose of this study was to document objective parameters of sleep measured by polysomnography (PSG) and multi-sleep latency tests (MSLTs) in a population of MS patients experiencing fatigue or sleepiness and to determine whether they correlate with measures of fatigue, sleepiness, mood or cognition.

Methods

Patients

Patients were recruited as part of the NAPS-MS study to determine whether natalizumab therapy affects parameters of sleep in MS patients reporting fatigue or sleepiness (ClinicalTrials.gov identifier NCT01591551). The study was also designed to determine interrelationships between objective parameters of sleep and measures of fatigue, sleepiness, mood and cognition. A cohort of 37 patients initiating natalizumab (Tysabri) therapy was recruited from three sites. At the time of study entry, patients were not on a disease-modifying agent. The study was approved by an institutional review board and all patients gave valid informed consent. For inclusion patients had to be naïve to natalizumab and have an Expanded Disability Status Scale (EDSS)[20] value from 0–6.0 and an age from 18–65 years. Patients were excluded if they did not speak English or had severe depression (score $\geq$32) on the Beck Depression Inventory II (BDI-II).[21] Patients were also excluded if they had severe cognitive impairment or coexisting medical conditions as determined by the site principal investigator. In order to select for a population with either fatigue or sleepiness, the patients needed to score over nine on the Epworth Sleepiness Scale (ESS),[22] over 30 on the Modified Fatigue Impact Scale (MFIS)[23] or over four on the Fatigue Severity Scale (FSS).[24] Of the 37 patients who were recruited, 33 passed the screen with three patients not meeting the fatigue or sleepiness criteria and one patient having severe depression. One patient withdrew consent before the sleep studies were performed and was excluded from the analysis. The remaining 32 patients underwent PSG. MSLTs were performed the next day in 31 of these patients. Patients often take medications for MS symptoms such as fatigue, spasticity, mood, pain, and insomnia. These medications may impact fatigue, daytime sleepiness, pain, mood, cognition, and objective measures on PSG or MSLT. Table 1 summarizes these medications and demographic data for the 32 patients.

Evaluations

During the screen visit, patient demographic data and a medical and MS history were obtained. The EDSS score was determined by an individual trained in this evaluation. The MFIS, FSS, Visual Analog Scale – Fatigue (VAS-F) and ESS were completed to assess fatigue and sleepiness. The 21 questions of the MFIS are grouped into the physical, cognitive and psychosocial subscales consisting of nine, 10 and two questions, respectively. Depression was assessed with the BDI-II. During the screen, cognition was assessed with NeuroTrax testing (Houston, Texas, USA), a computerized battery that has been validated for MS patients.[25] Normalized scores are standardized relative to cognitively healthy individuals of similar age and educational level. Results are fit to a scale with mean = 100 and standard deviation (SD) = 15. Patients underwent additional NeuroTrax testing on the day of their first infusion, an average of 29 days after the first test. The average of the two pre-treatment tests was used for analysis.

Overnight PSG was performed by certified technicians and interpreted by board certified physicians. The *AASM manual for the scoring of sleep and associated events: Rules, terminology and technical specifications* was used to perform the studies and to report the results.[26] PSG was scheduled to be performed within four weeks of the screen; however, two patients had the PSG/MSLT performed between four and eight weeks after the screen. The absolute time and percent of stage NI, stage N2, stage N3 and stage REM sleep were reported. Sleep onset latency (SOL), SE, and wakefulness after sleep onset (WASO) were determined. Respiratory measures including the apnea hypoxia index (AHI), respiratory disturbance index (RDI) and oxygenation nadir were measured. The periodic limb movement index (PLMI) and limb movement arousal index (PLMAI) were determined. The morning after the overnight PSG, patients underwent the MSLT.[27] The sleep latency of each of the four or five naps and presence or lack of REM sleep were reported.

Statistical analysis

Values are reported as the mean ± standard deviation (SD). Analysis was performed with SPSS V22.0 software (IBM). The Shapiro-Wilk test was used to

Table 1. Demographic data and concomitant medications.

Demographics	Mean	(SD)
Age (years)	45.66	(9.15)
Sex (percent female)	75%	
Race[a]		
Body mass index	28.86	(6.44)
Duration of MS (years)	7.45	(6.96)
Expanded Disability Severity Scale (EDSS)	2.72	(1.75)
Concomitant medications	No. of patients	
Antidepressants for mood	11/32	
Antidepressants for insomnia	4/32	
Benzodiazepines	6/32	
Anti-epileptic drugs (gabapentin)	3/32	
Wake-promoting agents	10/32	
Non-benzodiazepine hypnotics	4/32	
Dopamine agonists	1/32	
No concomitant medications	6/32	

MS: multiple sclerosis; SD: standard deviation.
Values are mean (SD).
[a]Race: 27/32 White, 3/32 African-American and 2/32 Hispanic.

determine whether a sample was normally distributed. Pearson's coefficient was used to determine the correlation between two normally distributed samples. When samples were not normally distributed, the non-parametric Spearman's correlation was used. For between-group analysis, the non-parametric Mann Whitney U-test was used. Significance was determined with a two-tailed test.

Results

Measurements of fatigue and sleepiness

The study population was moderately fatigued with an MFIS of 45.81 ± 13.83, FSS of 5.07 ± 0.98 and VAS-F of 5.94 ± 2.38 cm (Table 2). The FSS correlated with the MFIS (Pearson's $r = 0.525$, $p = 0.002$) and the VAS-F (Pearson's $r = 0.624$, $p < 0.001$). Just under half of the patient population reported hypersomnia (15/32 or 47%) on the ESS. In this population, sleepiness, as measured by the ESS, did not correlate with the FSS (Pearson's $r = 0.181$, $p = 0.320$) or the MFIS (Pearson's $r = 0.240$, $p = 0.186$); however, ESS mildly correlated with the cognitive component of the MFIS (Pearson's $r = 0.406$, $p = 0.021$). Disability (EDSS) did not correlate with the fatigue or sleepiness scales.

Sleep parameters

Patients underwent overnight PSG; the PSG data are summarized in Table 2. Patients averaged 7.41% stage 1, 68.55% stage 2, 7.97% stage 3 and 16.09% stage REM sleep. Ten patients had no stage 3 sleep and four patients had no REM sleep. Patients had a sleep onset latency of 43.36 ± 35.66 min (normal: ≤ 20 min), sleep efficiency of $75.1 \pm 15.1\%$ (normal: $\geq 85\%$) and WASO of 66.22 ± 48.35. No correlation between total MFIS, FSS or VAS-F and either sleep efficiency or WASO was found. However, the MFIS-Psychosocial subscales correlated with decreasing sleep efficiency (Spearman's $r = -0.3830$, $p = 0.031$) and increasing WASO (Spearman's $r = 0.372$, $p = 0.035$). The presence or absence of stage 3 sleep did not correlate with measures of fatigue, sleepiness or sleep latency on MSLT (Mann-Whitney U tests, $p > 0.2$). The spontaneous arousal index (SAI) and total arousal index (TAI) did not correlate with any of the fatigue or sleepiness measures.

Limb movements and REM behavior disorder

Eight of the 32 patients (25%) had periodic limb movements of sleep. These patients had a mean periodic limb movement of sleep (PLMS) index of 18.91 and PLMS arousal index of 3.1. Of these patients, three had mild PLMS with a PLM index between 5–15, four had moderate PLMS with an index between 15–30 and one had severe PLMS with an Index of 32. The mean PLMS index for all 32 patients was 5.22 and the overall mean PLMS arousal index was 0.91 (Table 2). PLMS had a significant impact on sleep quality in only

Table 2. Means and standard deviations for scores on self- reported scales and objective data from polysomnography (PSG), multi-sleep latency test (MSLT) and NeuroTrax cognitive tests.

Scales	Mean	(SD)
Epworth Sleepiness Scale	8.47	(5.12)
Fatigue Severity Scale	5.07	(0.98)
Modified Fatigue Impact Scale (MFIS)	45.81	(13.83)
MFIS – Physical	22.22	(7.11)
MFIS – Cognitive	19.31	(7.88)
MFIS – Psychosocial	4.25	(2.09)
Visual Analog Scale – Fatigue (VAS-F)	5.94	(2.38)
Visual Analog Scale – Pain (VAS-P)	2.83	(2.73)
Beck Depression Index	15.88	(8.44)
PSG/MSLT parameters		
Sleep efficiency	75.11%	(15.05%)
Sleep onset latency (min)	43.36	(35.66)
Percentage stage N1	7.41%	(5.86%)
Percentage stage N2	68.55%	(12.57%)
Percentage stage N3	7.97%	(11.49%)
Percent stage REM	16.09%	(11.54%)
Wake after sleep onset (min)	66.22	(48.35)
Apnea hypopnea index	8.68	(16.72)
Periodic limb movement of sleep (PLMS) index	5.22	(9.03)
PLMS arousal index	0.91	(1.89)
Respiratory arousal index	4.21	(5.88)
Spontaneous arousal index	7.76	(5.61)
Total arousal index	12.92	(8.25)
Mean sleep latency (min)	10.43	(5.53)
Patients with 2 or more sleep onset REM	3.13%	
NeuroTrax Tests		
Global	97.00	(10.19)
Memory	96.84	(16.82)
Executive function	97.04	(11.50)
Verbal fluency	99.34	(19.91)
Attention	96.56	(10.98)
Information processing	96.66	(12.38)
Motor	98.05	(12.64)

REM: rapid eye movement.
Values are means (standard deviation (SD)).

one patient with moderate PLMS who had a PLM arousal index of 9.5. Patients with PLMS (PLMS index $\geq$5) did not significantly differ from those without PLMS in regards to EDSS, ESS, FSS, MFIS, VAS-F, VAS-P, SE, WASO or SOL (Mann-Whitney U tests, $p > 0.05$). No patient showed REM behavior disorder during overnight PSG.

Respiratory parameters

Obstructive sleep apnea (OSA) was noted in 12 of the 32 patients. Eight of these patients had mild OSA with an apnea hypopnea index (AHI) between 5–15. One patient had moderate OSA (AHI between 15 and 30) with an AHI of 23.6 and three patients had severe OSA with AHI of 73.5, 56.3 and 37.2. One of these patients had 90 central apneas (Central Apnea Index = 30.7). Eleven of the 12 patients with OSA underwent MSLTs and seven showed moderate sleepiness with a sleep latency between 5–8 min. The body mass index (BMI) of patients with OSA was significantly higher than those without OSA (32.53 ± 5.77 vs 26.66 ± 5.90; Mann Whitney U test, $z = -2.74$, $p = 0.006$). MS patients with OSA

Table 3. Results of NeuroTrax tests normalized for age and education and correlation coefficients (significance) with objective sleep parameters.

	NeuroTrax test	Sleep efficiency	WASO
Global	95.7 (10.8)	**0.359 ($p = 0.043$)**	−0.258 ($p = 0.154$)
Memory	96.6 (18.1)	0.108 ($p = 0.556$)	−0.109 ($p = 0.554$)
Executive function	96.2 (11.3)	**0.405 ($p = 0.021$)**	−0.298 ($p = 0.097$)
Verbal function	95.4 (20.4)	0.334 ($p = 0.061$)	**−0.363 ($p = 0.041$)**
Attention	95.7 (12.2)	0.308 ($p = 0.086$)	−0.191 ($p = 0.296$)
Info. processing	94.3 (13.1)	**0.384 ($p = 0.030$)**	−0.333 ($p = 0.063$)
Motor function	98.5 (12.2)	0.066 ($p = 0.720$)	−0.003 ($p = 0.986$)

WASO: wake after sleep onset.
Normalized data is expressed as mean (standard deviation). Statistically significant associations are shown in bold type.

did not differ from those without OSA in regards to SE, WASO, mean sleep latency, FSS, MFIS, or ESS; however, all three patients with moderate or severe OSA who underwent MSLT testing had hypersomnia.

MSLT

Thirty-one of the 32 patients underwent MSLT testing. The average sleep latency (SL) on the MSLT was 10.43 min (Table 2). Fourteen patients (44%) met laboratory criteria for hypersomnia with a sleep latency $\leq$8 min and four patients (13%) had severe hypersomnia with a sleep latency $\leq$5 min. One patient with a mean sleep latency of 6 min met the laboratory criteria of narcolepsy with three sleep onset REM (SOREM) periods. Four other hypersomnia patients had one SOREM period. Mean latency on MSLT did not correlate with self-reported sleepiness on ESS (Spearman's $r = -0.232$, $p = 0.209$). Additionally, there was no correlation between the SL on MSLT and FSS, MFIS, SE, WASO or TAI.

Mood

The extent of depression, as measured by the BDI correlated with fatigue as measured by the MFIS (Spearman's $r = 0.688$, $p < 0.001$) and FSS (Spearman's $r = 0.426$, $p = 0.015$). The BDI did not correlate with measures of sleep efficiency (Spearman's $r = 0.166$, $p = 0.363$), WASO (Spearman's $r = -0.141$, $p = 0.442$), or sleep latency on MSLT (Spearman's $r = -0.185$, $p = 0.319$). The BDI mildly correlated with sleepiness as measured by the ESS (Spearman's $r = 0.402$, $p = 0.022$) and with pain as measured by the VAS-P (Spearman's $r = 0.366$, $p = 0.039$).

Cognition

The Mindstreams NeuroTrax computerized test was used to measure cognitive function in MS. Cognitive data was normalized for age and education and is displayed in Table 2. SE correlated with the global score as well as the executive function and information processing subscales (Table 3). Duration of WASO negatively correlated with the verbal function subscale but not the global scale or other subscales. The duration of the sleep onset latency negatively correlated with executive function and attention. The AHI and TAI did not correlate with cognitive measures. Furthermore, MS patients with OSA did not differ from those without OSA in the global score or any of the subscales (Mann-Whitney U tests, $p > 0.05$). The duration of daytime sleep latency on MSLT negatively correlated with the global cognition score.

Sleep disturbance

In this study, 30/32 MS patients reporting either fatigue or sleepiness had objective evidence of a sleep disturbance on either PSG or MSLT (Table 4). Over 70% of the MS patients experienced more than one sleep disturbance.

Discussion

Objective evidence of a sleep disturbance includes reduced sleep efficiency, increased WASO, absence of N3 slow wave sleep, absence of REM sleep, sleep disordered breathing, periodic limb movements and reduced daytime sleep latency. In this study, 30/32 MS patients reporting either fatigue or sleepiness had objective evidence of one or more of these sleep disturbances on either PSG or MSLT (summarized in Figure 3). Most patients (72%) experienced more than one disturbance. A similar high frequency of

Table 4. Summary of number of patients and percent of patients with abnormal objective parameters of sleep on polysomnography (PSG) or multi-sleep latency test (MSLT).

Criteria	No. of patients	%
Sleep efficiency ≤75%	10/32	37.50
Absence of REM sleep	4/32	12.50
Absence of stage 3 sleep	12/32	31.25
Sleep onset latency ≥40 min	16/32	50.00
Apnea hypoxia index ≥5	12/32	37.50
PLMS index ≥5	8/32	25.00
Multi-sleep latency ≤8 min	14/31	45.16
No disturbances	2/32	6.25
Any disturbances	30/32	93.75
1 disturbance	7/32	21.88
2 disturbances	6/32	18.75
3 disturbances	11/32	34.38
4 or more disturbances	6/32	18.75

PLMS: periodic limb movement of sleep; REM: rapid eye movement.

sleep disturbances was noted in a study of fatigued (MFIS ≥45) and non-fatigued MS patients. They found that 25/26 fatigued MS patients undergoing two nights of home PSG had objective evidence of relevant sleep disturbances.[18]

We found that this cohort of fatigued or sleepy MS patients had a reduced SE of 75.1% (normal ≥85%). This finding is in agreement with multiple studies that performed PSG and found SE ranging from 73.6–82.8%.[12,14–16,18,28,29] Furthermore, the MS patients in these studies had more WASO than the control patients. Our finding of an average of 66 min of WASO is similar to results from other studies, which found a range of 58.1–89 min.[12,15,16,18] Interestingly, we found that 10 of 32 patients had no stage 3 sleep and the average patient had less than 8% stage 3 sleep, compared to the normal value of 25%. This percent of stage 3 sleep is similar to the 9.5–10.8% found in two previous studies[14,18] but less than the near normal 21–28.2% seen in other studies.[12,15,16,18]

Obstructive sleep apnea was seen in 38% (25% mild and 13% moderate or severe OSA) of the patients in the current study. For our analysis, hypopneas required a 30% or more reduction in airflow and a 4% oxygen desaturation to be counted as defined in the 2007 *AASM scoring manual*.[26] An earlier definition requiring a 50% reduction in airflow and either a 4% oxygen desaturation or an arousal has been used in some studies.[30] The more recent criteria tends to be more stringent.[31] For example, one study diagnosed OSA in 58% of fatigued MS patients using the 1999 criteria and 11% using the 2007 criteria.[15] Most studies using the more stringent definition of hypopnea found a prevalence of OSA ranging from 0–19%.[12,15,16,18,19,28] Differences in BMI and disability may explain part of the discrepancy between studies. We found that higher BMI correlated with a higher likelihood of OSA. In one study of 62 patients, only 11% had OSA, but the patients had a lower BMI than those in the current study (BMI = 26.0 compared to 28.9 in the current study).[15] In a large cohort of 42 patients, some of whom were scored with the 1999 criteria and some with the 2007 criteria, 64% were found to have OSA.[17] This group had a mean BMI of 32.0. Additionally, 31% of those patients had an EDSS ≥6.0. Of the five patients in the current study with an EDSS ≥6.0, four had OSA.

We found that 25% of the patients in the current study had PLMS on overnight PSG, but only one individual had a PLMS arousal index of greater than five. Therefore, in our cohort, PLMS appears to play a minimal role in sleep disruption. The mean PLMS index of 5.22 reported in this study is much lower than mean indices of 16–18 reported in three other studies.[12,14,15]

The mean sleep latency for daytime naps of 10.43 min in this study is similar to that reported by several other studies[12,15,28] but shorter than the 16–17 min observed in some studies.[29,32,33] Narcolepsy is rare with only one patient meeting the criteria in the

current study with documented hypersomnia and two or more SOREM periods. Kaminska et al. found similar results with 1/62 patients in their cohort meeting the diagnostic criteria.[15] As with these other studies in MS, there was no correlation between MSLT and ESS.

To our knowledge, this is the first paper investigating a relationship between objective parameters of sleep and cognition in MS patients reporting fatigue or sleepiness. We found that reduced SE correlated with reduced scores on the global cognitive scores and the executive function and information processing subscales. Patients with longer WASO performed worse on the verbal function subscale. Other studies have shown that OSA negatively affects performance on cognitive testing;[34] however, we found no association between the presence or absence of OSA and cognitive performance in this study.

The current study is limited by the absence of a control arm of non-fatigued MS patients. To enter the study, patients needed to present with either moderate or severe fatigue and/or sleepiness. Only one patient presented with sleepiness without fatigue. Another study with objective measures of sleep that included a non-fatigued arm found no significant difference between SE or WASO but did find a higher total arousal index in patients with fatigue.[12] As this study only enrolled patients who were planning on initiating natalizumab therapy, the results may not be generalizable to all MS patients

In conclusion, sleep disturbances are common in MS patients reporting fatigue. Poor SE may contribute to reduced cognitive function. PSG should be considered in fatigued MS patients to exclude treatable sleep disorders.

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Conflict of interest

RAS has served as a speaker and/or consultant for Acorda, Biogen Idec, EMD Serono, Genzyme, and Novartis. MG has served as a speaker and/or consultant for Acorda, Biogen Idec, EMD Serono, Genzyme, and Teva. KKR has served as a speaker and/or consultant for Acorda, Biogen Idec, EMD Serono, Genzyme, Pfizer, Novartis, and Teva. DWB has served as a speaker and/or consultant for Acorda, Avanir, Biogen Idec, Genzyme, Novartis, Questcor, and Teva. PAS has no conflict of interest to declare.

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References

1. Bamer AM, Johnson KL, Amtmann D, et al. Prevalence of sleep problems in individuals with multiple sclerosis. *Mult Scler* 2008; 14: 1127–1130.
2. Téllez N, Río J, Tintoré M, et al. Does the Modified Fatigue Impact Scale offer a more comprehensive assessment of fatigue in MS? *Mult Scler* 2005; 11: 198–202.
3. Attarian HP, Brown KM, Duntley SP, et al. The relationship of sleep disturbances and fatigue in multiple sclerosis. *Arch Neurol* 2004; 61: 525–528.
4. Galeazzi GM, Ferrari S, Giaroli G, et al. Psychiatric disorders and depression in multiple sclerosis outpatients: Impact of disability and interferon beta therapy. *Neurol Sci* 2005; 26: 255–262.
5. Rao SM, Leo GJ, Bernardin L, et al. Cognitive dysfunction in multiple sclerosis. *I. Frequency, patterns, and prediction. Neurology* 1991; 41: 685–691.
6. Multiple Sclerosis Council for Clinical Practice Guidelines. *Fatigue and multiple sclerosis. Evidence-based management strategies for fatigue in multiple sclerosis*. Washington, DC: Paralyzed Veterans of America, 1998.
7. Mills RJ and Young CA. A medical definition of fatigue in multiple sclerosis. *QJM* 2008; 101: 49–60.
8. Stanton B, Barnes F and Silber E. Sleep and fatigue in multiple sclerosis. *Mult Scler* 2006; 12: 481–486.
9. Krupp LB. Fatigue in multiple sclerosis: Definition, pathophysiology and treatment. *CNS Drugs* 2003; 17: 225–234.
10. Merkelbach S, Schulz H, Kölmel HW, et al. Fatigue, sleepiness, and physical activity in patients with multiple sclerosis. *J Neurol* 2011; 258: 74–79.
11. Pokryszko-Dragan A, Bilińska M, Gruszka E, et al. Sleep disturbances in patients with multiple sclerosis. *Neurol Sci* 2013; 34: 1291–1296.
12. Kaynak H, Altintas, A, Kaynak D, et al. Fatigue and sleep disturbance in multiple sclerosis. *Eur J Neurol* 2006; 13: 1333–1339.
13. Pokryszko-Dragan A, Frydecka I, Kosmaczewska A, et al. Stimulated peripheral production of interferon-gamma is related to fatigue and depression in multiple sclerosis. *Clin Neurol Neurosurg* 2012; 114: 1153–1158.
14. Braley TJ, Chervin RD and Segal BM. Fatigue, tiredness, lack of energy, and sleepiness in multiple

sclerosis patients referred for clinical polysomnography. *Mult Scler Int* 2012; 2012: 673936.

15. Kaminska M, Kimoff RJ, Benedetti A, et al. Obstructive sleep apnea is associated with fatigue in multiple sclerosis. *Mult Scler* 2012; 18: 1159–1169.
16. Ferini-Strambi L, Filippi M, Martinelli V, et al. Nocturnal sleep study in multiple sclerosis: Correlations with clinical and brain magnetic resonance imaging findings. *J Neurol Sci* 1994; 125: 194–197.
17. Braley TJ, Segal BM and Chervin RD. Sleep-disordered breathing in multiple sclerosis. *Neurology* 2012; 79: 929–936.
18. Veauthier C, Radbruch H, Gaede G, et al. Fatigue in multiple sclerosis is closely related to sleep disorders: A polysomnographic cross-sectional study. *Mult Scler* 2011; 17: 613–622.
19. Tachibana N, Howard RS and Hirsch NP. Sleep problems in multiple sclerosis. *Eur Neurol* 1994; 34: 320–323.
20. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An Expanded Disability Status Scale (EDSS). *Neurology* 1983; 33: 1444–1452.
21. Beck AT, Steer RA, Ball R, et al. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. *J Pers Assess* 1996; 67: 588–597.
22. Johns MW. A new method for measuring daytime sleepiness: The Epworth sleepiness scale. *Sleep* 1991; 14: 540–545.
23. Fisk JD, Ritvo PG, Ross L, et al. Measuring the functional impact of fatigue: Initial validation of the fatigue impact scale. *Clin Infect Dis* 1994; 18: S79–S83.
24. Krupp LB, LaRocca NG, Muir-Nash J, et al. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989; 46: 1121–1123.
25. Achiron A, Doniger GM, Harel Y, et al. Prolonged response times characterize cognitive performance in multiple sclerosis. *Eur J Neurol* 2007; 14: 1102–1108.
26. Iber C, Ancoli-Israel S, Chesson A and Quan S. *The AASM manual for the scoring of sleep and associated events: Rules, terminology and technical specifications*, 1st edn, Westchester, Illinois: American Academy of Sleep Medicine, 2007.
27. Arand D, Bonnet M, Hurwitz T, et al. The clinical use of the MSLT and MWT. *Sleep* 2005; 28: 123–144.
28. Neau J-P, Paquereau J, Auche V, et al. Sleep disorders and multiple sclerosis: A clinical and polysomnography study. *Eur Neurol* 2012; 68: 8–15.
29. Vetrugno R, Stecchi S, Scandellari C, et al. Sleep–wake and body core temperature rhythms in multiple sclerosis with fatigue. *Clin Neurophysiol* 2007; 118: 228–234.
30. American Academy of Sleep Medicine. Sleep-related breathing disorders in adults: Recommendations for syndrome definition and measurement techniques in clinical research. *The Report of an American Academy of Sleep Medicine Task Force. Sleep* 1999; 22: 667–689.
31. Ruehland WR, Rochford PD, O'Donoghue FJ, et al. The new AASM criteria for scoring hypopneas: Impact on the apnea hypopnea index. *Sleep* 2009; 32: 150–157.
32. Poirier G, Montplaisir J, Dumont M, et al. Clinical and Sleep laboratory study of narcoleptic symptoms in multiple sclerosis. *Neurology* 1987; 37: 693–695.
33. Taphoorn MJ, van Someren E, Snoek FJ, et al. Fatigue, sleep disturbances and circadian rhythm in multiple sclerosis. *J Neuro* 1993; 240: 446–448.
34. Lal C, Strange C and Bachman D. Neurocognitive impairment in obstructive sleep apnea. *Chest* 2012; 141: 1601–1610.