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Fatigue in multiple sclerosis is closely related to sleep disorders: a polysomnographic cross-sectional study

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Abstract

Background: Sleep disorders can cause tiredness. The relationship between sleep disorders and fatigue in patients with multiple sclerosis (MS) has not yet been investigated systematically.

Objective: To investigate the relationship between fatigue and sleep disorders in patients with MS.

Methods: Some 66 MS patients 20 to 66 years old were studied by overnight polysomnography. Using a cut-off point of 45 in the Modified Fatigue Impact Scale (MFIS), the entire cohort was stratified into a fatigued MS subgroup ($n = 26$) and a non-fatigued MS subgroup ($n = 40$).

Results: Of the fatigued MS patients, 96% ($n = 25$) were suffering from a relevant sleep disorder, along with 60% of the non-fatigued MS patients ($n = 24$) ($p = 0.001$). Sleep-related breathing disorders were more frequent in the fatigued MS patients (27%) than in the non-fatigued MS patients (2.5%). Significantly higher MFIS values were detected in all (fatigued and non-fatigued) patients with relevant sleep disorders (mean MFIS 42.8; SD 18.3) than in patients without relevant sleep disorders (mean MFIS 20.5; SD 17.0) ($p < 0.001$). Suffering from a sleep disorder was associated with an increased risk of fatigue in MS (odds ratio: 18.5; 95% CI 1.6–208; $p = 0.018$).

Conclusion: Our results demonstrate a clear and significant relationship between fatigue and sleep disorders.

Keywords

fatigue, insomnia, periodic limb movement disorder, polysomnography, restless legs syndrome, sleep apnoea syndromes, tiredness

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Introduction

Fatigue affects up to 87.5% of multiple sclerosis (MS) patients, and 26% of these view it as the most burdensome symptom of their illness.[1] Fatigue in MS is defined 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',[2] and is a major reason for early retirement.[3] Fatigue is usually measured with self-assessment rating scales: the Modified Fatigue Impact Scale (MFIS)[2,4] and the Fatigue Severity Scale (FSS).[4,5]

The mechanism of fatigue is not known,[2] and no specific successful treatment options exist.[2,6] Individual non-systematic studies have indicated a high prevalence of insomnia and periodic limb movement disorders (PLMDs) in MS.[7–9] A small cohort study compared polysomnographic parameters

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in fatigued and non-fatigued MS patients;[10] however, due to the study design no statement could be made regarding individual diagnoses and the frequency of sleep disorders. Actigraphic findings in a small case-control study[11] showed an increased frequency of disturbed sleep in fatigued versus non-fatigued MS patients and healthy controls. The authors concluded that systematic polysomnographic studies were needed, which have been lacking to date.

Therefore, we investigated the frequency of sleep disorders in unselected MS patients by two home-based overnight polysomnography (PSG) assessments. In addition, we aimed to compare the frequency of sleep disorders in fatigued versus non-fatigued MS patients, and to investigate the relationship between scores on self-rating fatigue questionnaires and the presence of sleep disorders.

Methods

Patients

In this cross-sectional study, all consecutive unselected patients with clinically definite MS and an Expanded Disability Status Scale (EDSS)[12] of 0–8 who presented to the MS outpatient clinic of the Cecilie-Vogt-Klinik, Charité and Helios-Klinikum in Berlin between 1 August 2008 and 31 January 2009, or who were admitted as inpatients between 1 March 2008 and 28 February 2009 in the Department of Neurology of the Hanse-Klinikum in Stralsund, were asked to participate, irrespective of the primary reason for their presentation. Clinically definite MS was determined according to the revised McDonald criteria.[13] The Berlin patients were referred to the outpatient clinic by their neurologists or general practitioners for reasons other than fatigue and sleep disorders (e.g. second opinion on MS diagnosis, evaluation of immunomodulatory treatment, etc.). Patients at the Hanse-Klinikum Stralsund were admitted for confirmation of the MS diagnosis or for treatment of a relapse. Exclusion criteria were severe medical comorbidities (decompensated cardiopulmonary disease, cancer, decompensated renal failure), drug and alcohol abuse, pregnancy and nursing. The study was approved by the local ethics committees in Stralsund and Berlin, and all participants gave written informed consent prior to the assessment.

Procedures

Questionnaires, clinical and laboratory investigations. All patients completed the following questionnaires: the 21-item version of the MFIS,[2,4] FSS,[5] Nottingham Health Profile (NHP) in a German validation,[14] Epworth Sleepiness Scale (ESS),[15] Visual Analogue Scale (VAS) of fatigue, scored 0–10 cm,[5] and the 21-item version of the revised Beck Depression Inventory (BDI-IA).[16] We used the MFIS[2,18] in a German adaptation[4,17] for classification of fatigue. The patients were divided into fatigued patients (MFIS ≥ 45) and non-fatigued patients (MFIS < 45).

Figure 1 displays the sampling process. Of the gross sample, 215 outpatients and 11 inpatients fulfilled the inclusion criteria and were assessed for eligibility. Two patients were excluded (one due to severe cognitive impairment with inability to complete the questionnaires and one due to lack of knowledge of the German language), and 83 patients refused participation.

In the first stage, all 141 enrolled patients completed the questionnaires. Of these patients, 66 (47%) agreed to undergo PSG over two consecutive nights (PSG group), and 75 (53%) did not agree to the PSG (non-PSG group). The majority of these latter patients refused PSG because they could not imagine sleeping connected to cables. Other patients gave organizational matters as reasons for refusal (no time, wedding, new employment).

As we could not exclude that the high percentage (53%) of patients who refused PSG might lead to a substantial selection bias, we compared the patients who agreed to PSG with the patients who refused PSG. There was a marginal difference in disease duration ($p = 0.047$) between the two groups, but no significant difference between the two groups with respect to gender, age, EDSS, and the FSS, MFIS, ESS, VAS, NHP and BDI-IA scores (Table 1). In particular, there was no difference in MFIS, FSS and ESS.

The 66 patients who agreed to PSG were examined clinically for weight, height, body mass index, medication use, and history of nicotine abuse, and gave a blood sample (tested for vitamin B12, ferritin, iron, folic acid, blood count, creatinine, urea, TSH, HbA1c). The minimum time span between PSG and any steroid therapy was set at 4 weeks. In the week prior to PSG, patients kept a sleep diary. Immunomodulation was continued unchanged. Benzodiazepine dosages were tapered prior to PSG where possible. Reduction and cessation of treatment with antidepressants was decided on a case-by-case basis with regard to the risk of relapse of depression. Taking of further muscle relaxants was permitted up to 12 h before measurement began. Alcohol consumption was prohibited on the day of PSG.

Performance and evaluation of polysomnography. PSG was performed using a mobile polysomnographic device worn on the body, which has been validated

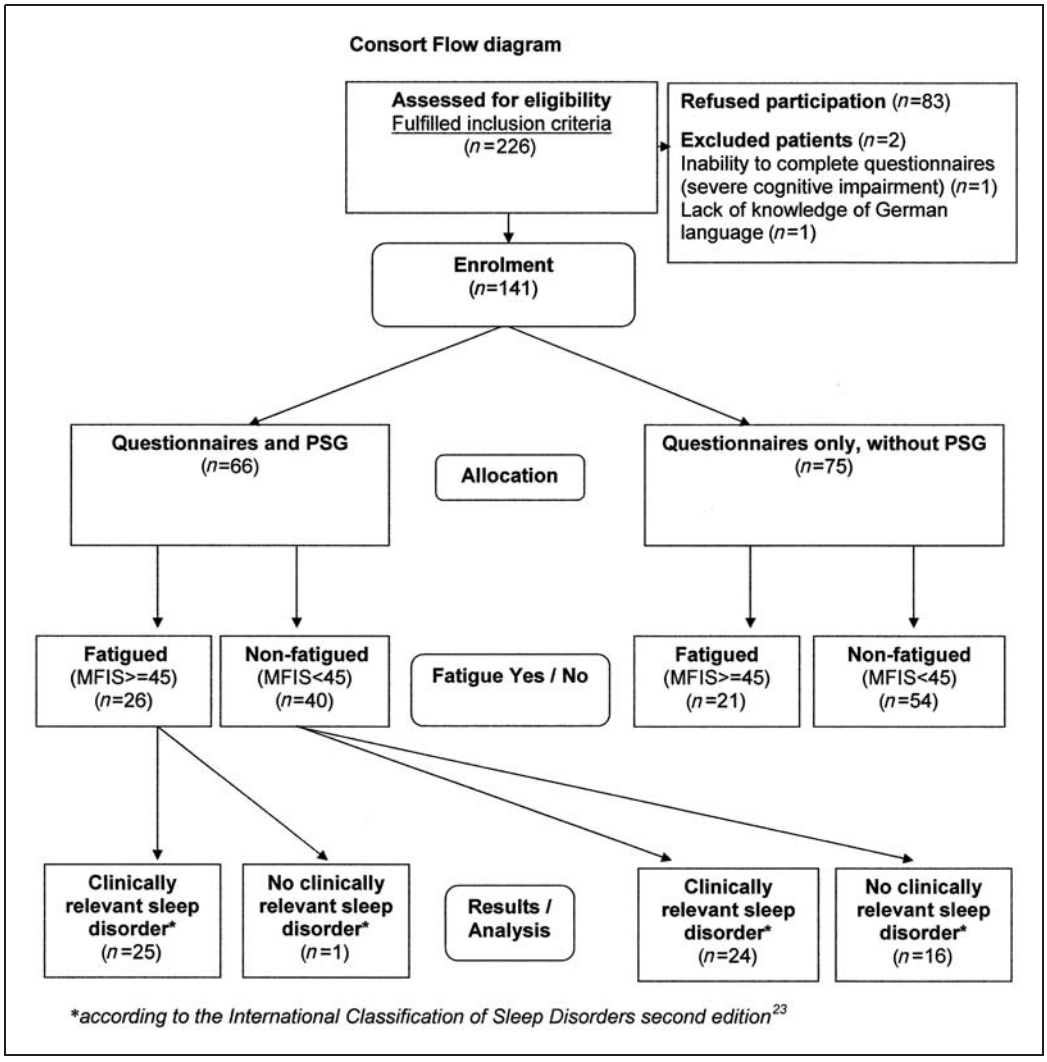

Figure 1. Prevalence of sleep disorders in MS patients with and without fatigue: consort flow diagram.

in three different sleep centres[19] (Somnocheck 2R&K, Weinmann Medical Technology; software: Somnolab; analysis software: Artisana, Hamburg, Germany) without a video or audio signal, but otherwise with full recording facilities as in a sleep laboratory.

Measurements were made over a period of 8 h: C3/C4-EEG electrodes to the contralateral mastoid electrode, ground electrode, electrooculogram on the ipsilateral mastoid electrode, bipolar chin electromyogram (EMG) of the muscle mentalis or muscle submentalis (according to biosignals testing and anatomical conditions), nasal airflow, thoracic breathing, abdominal breathing, position sensor, snoring signal, pulse oxymetry, pulse, electrocardiogram, bipolar 2-point EMG electrodes on both anterior tibial muscles. Prior to each measurement, an impedance test and a biosignal test were performed. A sleep specialist who was blinded to the clinical situation and the questionnaires analysed PSGs. Visual classification of sleep stages took place manually in accordance with Rechtschaffen and Kales.[20] Respiratory events were manually classified using the diagnostic guidelines of the Task Force of the American Academy of Sleep Medicine.[21] Periodic leg movements were pre-classified by the equipment's software and manually corrected using the Coleman criteria.[22] We also investigated the hypnogram: sleep efficiency, sleep onset latency, sleep stages, wake-time after sleep onset, number of waking events, number of changes in sleep stages, arousal index, periodic leg movement (PLM) index, PLM index in rapid-eye-movement (REM) sleep and non-REM sleep, PLM arousal index in REM sleep and non-REM sleep, respiratory disturbance index (RDI), blood oxygen desaturation, as well as chin EMG tonus, all respiratory events depending on position, arousal and sleep stage, and further standard polysomnographic parameters. Due to the first-night effect

Table 1. Demographic data and values of questionnaires of study participants

		PSG patients			Non-PSG patients		
		All	MFIS ≥45	MFIS <45	All	MFIS ≥45	MFIS <45
Number	*n* (%)	66 (46.8%)	26 (18.4%)	40 (28.4%)	75 (53.2%)	22 (15.6%)	53 (37.6%)
Sex	*N* = m, *N* = f/%	m = 21/14.9%	m = 7/5.0%	m = 14/9.9%	m = 25/17.7%	m = 10/7.1%	m = 15/10.6%
		w = 45/31.9%	w = 19/13.5%	w = 26/18.4%	w = 50/35.5%	w = 12/8.5%	w = 38/27.0%
Age (years)	mean	43.2	45.3	42.0	45.4	44.5	45.9
	SD	10.0	9.5	10.2	10.8	10.6	10.9
	min-max	20–66	24–66	20–64	21–71	26–66	21–71
EDSS	median	2.0	3.0	2.0	3.0	3.5	3.0
	SD	1.8	1.7	1.8	2.0	1.8	2.1
	min-max	0–7.5	0–7.5	0–7.5	0–8.0	0–6.5	0–8.0
Disease duration	mean months	137.4	131.1	141.4	107.8	85.6	116.4
	SD	108.2	101.0	113.7	103.7	80.4	110.9
	min-max	13–469	25–325	13–469	1–385	1–337	1–385
Disease course	PPMS *N*/%	4/2.8	2/1.4	2/1.4	5/3.5	1/0.7	4/2.8
	RRMS *N*/%	46/32.6	13/9.2	33/23.4	53/37.6	17/12.1	36/25.5
	SPMS *N*/%	16/11.3	11/7.8	5/3.5	17/12.1	4/2.8	13/ 9.2
MFIS	mean	37.0	57.2	24.0	34.5	52.9	26.9
	SD	20.4	8.4	14.2	17.1	7.5	13.8
	min-max	0–75	45–75	0–44	0–75	45–75	0–44
FSS	mean	4.5	6.0	3.6	4.8	5.9	4.4
	SD	1.8	1.0	1.6	1.7	1.0	1.7
	min-max	1.0–7.0	3.4–7.0	1.0–7.0	1.0–7.0	3.2–7.0	1.0–7.0
ESS	mean	8.9	11.3	7.5	8.2	9.8	7.6
	SD	4.7	4.2	4.5	4.6	4.4	4.5
	min-max	0–20	3–20	0–17	0–22	2–18	0–22
BDI-IA	mean	11.6	16.9	8.1	10.4	15.0	8.5
	SD	8.6	9.2	6.2	6.1	5.4	5.4
	min-max	0–33	1–33	0–21	0–29	9–29	0–21
NHP	mean	8.9	14.8	4.9	7.9	11.5	6.4
	SD	7.4	6.8	4.6	5.1	4.7	4.6
	min-max	0–28	2–28	0–21	0–19	4–19	0–17
VAS	mean	4.7	5.8	3.9	4.0	5.0	3.5
	SD	2.7	2.5	2.7	2.7	2.9	2.5
	min-max	0–9.8	0–9.8	0–8.9	0–10	0–10	0–9.6

Abbreviations: EDSS, Expanded Disability Status Scale; MFIS, Modified Fatigue Impact Scale; FSS, Fatigue Severity Scale; ESS, Epworth Sleepiness Scale; BDI-IA, revised Beck Depression Inventory; NHP, Nottingham Health Profile; VAS, Visual Analogue Scale of fatigue.

(patient is not yet familiar with the polysomnographic device), no pathological findings were assessed from the first-night hypnogram. On the first night, only PLMs and respiratory and cardiac events were considered. Following classification of the PSGs, sleep histories were obtained (CV), and a sleep diagnosis was made according to the International Classification of Sleep Disorders second edition (ICSD-2).[23] To avoid false conclusions with respect to mild sleep disorders as possible causes of tiredness, mild insomnias, nocturia, mild PLMDs and sleep-related breathing disorders with RDI below 10 per hour were not considered relevant sleep disorders. We classified as relevant sleep disorders only sleep disorders with disturbed hypnogram, which are able to cause consecutive daytime sleepiness. Following diagnosis, a specific therapy was initiated.

Statistical analysis

Following an exploratory analysis of the data and after a (negative) proof for normality of the underlying distributions, differences between two groups regarding

Table 2. Relevant sleep disorders able to cause consecutive daytime tiredness. Results of sleep medical investigations according to ICSD-2[23]

Relevant Sleep disorders		total	Fatigued patients (MFIS $\geq$ 45)	Non-fatigued patients (MFIS $<$ 45)
Number of patients		$n = 66$	$n = 26$	$n = 40$
Sleep related breathing disorders $n = 8$ (12.1 %)	Obstructive Sleep Apnoea Syndrome	6	5	1
	Central Sleep Apnoea Syndrome	1	1	0
	Central Alveolar Hypoventilation Syndrome	1	1	0
RLS, PLMD or leg pain $n = 24$ (36.4 %)	Severe RLS	4	2	2
	Moderate RLS	3	1	2
	Mild RLS	1	0	1
	Severe PLMD	2	2	0
	Severe NREM/-REM-PLM due to spasticity	1	1	0
	Severe PLMD and iron deficiency	1	0	1
	Moderate PLMD	9	1	8
	Moderate PLMD and muscle cramps	1	0	1
	Pain syndrome on the right-hand side of body	1	0	1
	PLM due to spasticity, inadequate sleep hygiene	1	1	0
Insomnia, inadeq.sleep hygiene $n = 17$ (25.75 %)	Moderate psychophysiological insomnia *	10	6	4
	Insomnia associated with depression **	5	3	2
	Inadequate sleep hygiene	2	1	1
No relevant Sleep disorder $n = 17$ (25.75 %)	Mild PLMD	6	1	5
	No sleep disturbance	11	0	11

RDI, respiratory disturbance index; RLS, Restless Legs Syndrome; PLMD, Periodic Limb Movement Disorder.
*=in 1 case additionally anaemia;
**=Insomnia associated with depression was assumed when further depressive symptoms were present and BDI values $\geq$21 (or alternatively under precedent psychiatric treatment BDI values $\geq$13).

age, disease duration, EDSS and questionnaires scores were analysed using the Mann–Whitney *U*-test and Fisher's exact test, respectively. Differences in the defined MFIS-groups (F-MS versus NF-MS) were not only univariately proved but also multivariately using the logistic regression and including age, disease duration, MS course, EDSS, presence of relevant sleep disorders and questionnaires scores as influencing factors. Odds ratios (OR) with 95% confidence intervals (CI) for those factors were determined in the logistic regression. For all calculations, statistical significance was established at $p < 0.05$. All tests should be understood as constituting exploratory data analysis, such that neither previous power calculations nor subsequent adjustments for multiple testing have been made. Statistical analysis was performed with SPSS 16 (SPSS, Chicago, IL, USA).

Results

Polysomnographic findings in the entire PSG group

Of the 66 patients who underwent PSG, 49 (74%) suffered from a relevant sleep disorder (according to ICSD-2), which can cause consecutive daytime tiredness (Table 2). Seven patients suffered from more than one sleep disorder. In these cases we classified only the more significant sleep disorder as the relevant diagnosis.

In the entire PSG group, eight patients (12.1%) suffered from sleep-related breathing disorders: three men 47–66 years old (14.2% of men; Body Mass Index: 26) and five women 42–57 years old (11.1% of women; Body Mass Index women: 25). Seven of these eight patients were in the fatigue subgroup (27%), whereas in the non-fatigue subgroup only one patient suffered from sleep-related breathing disorders (2.5%).

Classification fatigue/non-fatigue subgroups

In total, 26 of the 66 PSG patients were stratified in the fatigue subgroup (F-MS) (MFIS values of $\geq$45); of these 26 fatigued PSG patients, 25 (96%) suffered from a relevant sleep disorder which can cause consecutive daytime tiredness.

From 40 non-fatigued patients (NF-MS) (MFIS values of <45) 24 patients (60%) suffered from a

relevant sleep disorder, seven had only mild PLMD, and nine exhibited no sleep disorder (significant relationship between sleep disorders and fatigue; $p = 0.001$).

Classification of relevant/non-relevant sleep disorders

Even when disregarding the cut-off point of 45 in the MFIS and instead stratifying the entire group into patients with relevant sleep disorders ($n = 49$) and those without ($n = 17$), we found:

- relevant sleep disorders in *all* patients with secondary progressive MS;
- significantly higher MFIS values in patients with relevant sleep disorders (mean MFIS ± SD 18.3: **42.8**) than in those without (mean MFIS ± SD 17.0: **20.5**) (Fisher's exact test, $p < 0.001$);
- significantly higher FSS values in patients with relevant sleep disorders (mean FSS ± SD 1.7: **4.9** versus ± SD 1.7: **3.3**) ($p = 0.001$);
- no significant difference for ESS scores (mean ESS ± SD 4.4: **9.3** versus ± SD 4.8: **7.9**) ($p = 0.322$).

In regard to the sub-classification of the relevant sleep disorders (Table 2) we have made three interesting observations:

- the PLMD/RLS/leg-pain subgroup had the lowest MFIS values (mean MFIS ± SD 19.4: 35.8) and the fatigued patients in this subgroup showed significantly higher arousal index ($p = 0.024$) than the non-fatigued patients (Table 3);
- this was followed by the patients with insomnia (mean MFIS ± SD 10.2: 47.9). The statistical analysis of sleep parameters between fatigued and non-fatigued patients with insomnia did not show any significant difference (Table 3);
- The highest MFIS values were present in patients with sleep-related breathing disorders (mean MFIS ± SD 18.1: 54.4).

Predictive values

We calculated the positive predictive values (risk factors) of fatigue (MFIS ≥ 45) with binary logistic regression. The OR of developing fatigue when sleep disorders were present was 18.5 (95% CI 1.6–208; $p = 0.018$). In patients suffering from a progressive MS course, the OR was 8.6 (CI 1.6–45; $p = 0.011$). The OR of the BDI was 1.1 (95% CI 1.0–1.3; $p = 0.012$). The OR of disease duration was reduced to 0.99 (95% CI 0.98–1.0; $p = 0.012$).

Laboratory findings

Three patients showed vitamin B12 deficiency (162 pmol, l/176 pmol, l/190 pmol/l; lower reference limit: 229 pmol/l), two showed low ferritin (11 µg/l, 15 µg/l; normal low range: 30 µg/l) and one female patient showed renal failure (creatinine 137 µmol/l; reference 58–96 µmol/l).

Discussion

Our study is the first large cross-sectional study to investigate the frequency of sleep disorders in consecutive unselected MS patients by home-based PSG. The most relevant findings were that (i) relevant sleep disorders, which can cause consecutive daytime tiredness, were frequent in MS patients (74%); (ii) all patients with a secondary progressive MS were suffering from a relevant sleep disorder; (iii) 96% of fatigued MS patients revealed a relevant sleep disorder according to ICSD-2 criteria which requires specific sleep medical treatment; (iv) a disproportionate number of these fatigued patients suffered from sleep-related breathing disorders (27%), (v) patients with sleep disorders scored significantly higher on self-rating fatigue questionnaires (FSS and MFIS) than those without; and (vi) sleep disorders are predictive of development of fatigue in MS (OR 18.5).

The fact that we found no significant difference when comparing the fatigue scales between those patients who refused and those who underwent PSG shows that not only patients interested in sleep medical investigations participated in this study and demonstrates that our results were not influenced by a substantial selection bias. Therefore, it can be assumed that a representative sample was investigated. We chose the home-based PSG instead of a sleep laboratory examination because we aimed to examine a large number of patients in their natural sleeping environment, and to minimize interruptions to their daily life.

In order to address the question of whether sleep disorders can cause fatigue or, at least, contribute to the development of fatigue in MS, it is not sufficient to compare the frequency of sleep disorders in MS versus the normal population. Even if the frequency of sleep disorders in MS were the same as in the normal population, this does not argue against a relationship between sleep disorders and fatigue, because there are problems with tiredness, fatigue and sleep disorders in the normal population as well. That means that a cohort study comparing the frequencies of sleep disorders in MS patients and in the normal population cannot highlight the relationship between fatigue and sleep disorders in MS. For this reason we conducted

Table 3. Comparison of the sleep parameters in the subgroups

	MFIS	*N*	m	Sleep efficacy (%)	Number of awakenings	Arousal-Index (/h)	PLM-Index during sleep (n/h)	PLM-Arousal-Index (n/h)	Slow wave sleep (% time in bed)	Wake after sleep onset (minutes)	ESS	BDI
Total patients	0–84	66	Mean	76.3	26.7	19.9	23.0	2.8	10.4	83.8	8.9	11.7
			SD	12.3	12.4	10.3	29.7	4.2	6.4	57.3	4.7	8.6
			min-max	48	6	1.1	0	0	0	8	0	0
				93.7	72	47.1	125.7	19.7	24.6	258	20	33
	≥45	26	Mean	73.6	28.2	21.6	23.5	4.0	9.5	89.0	11.3	16.9
			SD	13.0	13.2	11.9	29.4	5.4	6.3	62.0	4.2	9.2
			min-max	48.0	8	1.1	0.0	0.0	0.9	30	3	1
				93.7	72	46.4	123.3	19.7	24.1	245	20	33
	<45	40	Mean	78.1	25.7	18.8	22.7	2.0	11.1	80.3	7.5	8.4
			SD	11.6	11.9	9.0	30.2	3.0	6.4	54.6	4.5	6.3
			min-max	49.9	6	3.9	0.0	0.0	0.0	8	0	0
				92.6	60	47.1	125.7	12.7	24.6	258	17	24
Patients with PLMD, RLS, leg pain	0–84	24	Mean	76.9	24.4	18.2	45.8	4.4	8.6	69.3	8.4	11.1
			SD	11.1	9.7	7.6	35.9	4.1	5.7	43.8	4.6	8.0
			min-max	54.5	6	4.1	1.2	0.0	1.0	8	1	1
				93.7	45	34.4	125.7	12.7	24.6	173	20	31
	≥45	8	Mean	77.4	26.1	23.0	45.1	5.5	7.8	58.0	9.4	15.8
			SD	11.2	7.9	7.0	39.0	4.4	4.7	38.8	6.0	10.3
			min-max	61.4	8	14.3	4.9	0.0	2.6	30	3	1
				93.7	33	32.6	121.3	12.7	17.6	139	20	31
	<45	16	Mean	76.6	23.6	15.9	46.2	3.8	9.0	75.0	8.0	8.8
			SD	11.4	10.6	7.0	35.4	3.9	6.3	46.2	3.9	5.6
			min-max	54.5	6	4.1	1.2	0.1	1.0	8	1	2
				89.2	45	34.4	125.7	12.7	24.6	173	15	22
	Comparison MFIS ≥45/<45 *p*-values			0.976	0.508	0.024	0.752	0.466	0.557	0.230	0.666	0.101
Patients with insomnia	0–84	17	Mean	71.9	31.9	20.8	5.3	1.5	9.7	103.9	10.2	15.8
			SD	13.8	15.7	11.8	8.6	4.7	6.6	69.2	5.5	7.7
			min-max	49.9	9	3.9	0.0	0.0	0.0	32	0	5
				92.8	72	43.9	36.7	19.7	21.6	258	19	32
	≥45	10	Mean	72.9	31.2	23.8	6.6	2.5	9.9	91.4	11.8	16.8
			SD	13.8	17.2	13.5	11.1	6.1	6.8	61.4	3.8	7.9
			min-max	51.9	9	8.2	0.0	0.0	0.9	32	7	6
				92.8	72	43.9	36.7	19.7	21.6	221	19	32
	<45	7	Mean	70.1	32.9	16.6	3.3	0.2	9.3	121.9	8.0	14.2
			SD	14.7	14.4	7.8	2.9	0.4	6.9	80.6	7.0	7.7
			min-max	49.9	14	3.9	0.2	0.0	0.0	47	0	5
				87.0	60	23.9	7.6	1.0	19.4	258	17	24
	Comparison MFIS ≥45/<45 *p*-values			0.671	0.809	0.452	0.863	0.191	0.958	0.274	0.305	0.585
Patients with sleep-related	0–84	8	Mean	71.8	32.1	22.0	25.8	4.7	11.9	125.8	10.9	16.1
			SD	14.8	14.3	13.5	20.8	5.3	7.8	71.7	4.2	11.7

(continued)

Table 3. Continued

	MFIS	*N*	m	Sleep efficacy (%)	Number of awakenings	Arousal-Index (/h)	PLM-Index during sleep (n/h)	PLM-Arousal-Index (n/h)	Slow wave sleep (% time in bed)	Wake after sleep onset (minutes)	ESS	BDI
breathing disorders			min-	48.0	18	6.4	1.8	0.0	3.2	36	3	3
			max	90.0	55	46.4	64.0	14.2	24.1	245	15	33
	≥45	7	Mean	70.6	28.9	19.9	25.0	4.8	10.9	123.0	12.2	18.0
			SD	15.5	11.8	13.1	22.3	5.7	7.9	77.0	2.6	11.3
			min-	48.0	18	6.4	1.8	0.0	3.2	36	9	3
			max	90.0	52	46.4	64.0	14.2	24.1	245	15	33
	<45	1*	Mean	79.9	55.0	36.5	31.3	3.3	18.9	145.0	3.0	3.0
			SD									
			min-	79.9	55	36.5	31.3	3.3	18.9	145	3	3
			max	79.9	55	36.5	31.3	3.3	18.9	145	3	3
No relevant sleep disorders (no sleep disorders or mild PLMD)	0–84	17	Mean	82.1	22.1	20.3	7.3	1.8	13.1	64.2	7.5	6.5
			SD	9.2	9.1	10.8	9.3	3.8	5.7	38.8	4.1	5.7
			min-	63.8	8	1.1	0.0	0.0	1.0	20	2	0
			max	92.6	41	47.1	34.9	14.1	22.1	144	15	19
	≥45	1*	Mean	72.2	11.0	1.1	8.5	0.5	8.7	76.0	13.0	19.0
			SD									
			min-	72.2	11	1.1	8.5	0.5	8.7	76	13	19
			max	72.2	11	1.1	8.5	0.5	8.7	76	13	19
	<45	16	Mean	82.8	22.8	21.5	7.2	0.8	13.4	63.4	7.1	5.8
			SD	9.1	8.9	10.0	9.6	1.4	5.7	39.9	3.9	4.9
			min-	63.8	8	6.5	0.0	0.0	1.0	20	2	0
			max	92.6	41	47.1	34.9	5.8	22.1	144	15	19

*Due to small number of patients in the subgroups, we could not calculate statistical significance for these parameters.

a cross-sectional study only in MS patients. Due to our study design, a precise statement about the comparison of the frequency of sleep-related breathing disorders, insomnia and PLM/PLMD in MS with the normal population cannot be made. In general it is conceivable, however, that mental stress/depression or paraparesis could increase the incidence of insomnia or PLM/PLMD.

In the past, various hypotheses regarding the pathophysiological explanation for fatigue have been discussed. For example, a neuroendocrine origin with hyperreactivity of the hypothalamo–pituitary–adrenal axis and cytokine-mediated proinflammatory mechanisms,[24,25] as well as a relationship to brain lesions in specific neuroanatomical pathways[26,27] and to depression[27,28] has been described. With regard to the relationship between depression and fatigue, our results now undeniable argue against an explanation of fatigue only through depression, as some previous studies have suggested.[28] On the other hand, however, there is an often-neglected relationship between depression and sleep-related breathing disorders: the treatment of sleep-related breathing disorders can reduce symptoms of depression in patients with depression and coexisting sleep apnoea.[29,30]

As the mechanism of fatigue in MS is not known, it has not been possible thus far to decide whether 'fatigue' exists as a nosological entity in its own right, or is only a multifactorial feature of various underlying conditions.

We do not yet have well-defined diagnostic criteria to distinguish between fatigue and tiredness. We have to pose the question of why we call, in general, the lack of energy described by MS patients 'fatigue' and not 'tiredness', as we do in healthy subjects. Distinguishing fatigue/tiredness from sleepiness is (more) important. The term 'sleepiness' includes the propensity to fall asleep, often associated with an effort to avoid sleeping. This increased sleep pressure can be measured with objective tests (multiple sleep latency test,[31] multiple sleep wakefulness test,[32] pupillography,[33] driving simulator,[34] neuropsychological tests[35]) and questionnaires

such as the ESS.[15] With regard to tiredness, however, such objective tests or validated questionnaires are not readily available. For this reason, it is almost impossible to differentiate between tiredness and fatigue.

Drug therapy of MS-related fatigue remains without proven efficacy.[2,6,18] In order to address the question of whether sleep disorders can cause fatigue or, at least, contribute to the development of fatigue in MS, further studies are needed to verify if treatment of sleep disorders can reduce fatigue in MS.

MS patients in particular may be denied access to sleep diagnostic procedures, as the treating physician may attribute daytime tiredness to MS-related fatigue and thus regard a PSG as unnecessary. However, our results show a substantial contribution of sleep disorders to fatigue in MS; they are treatable and should not be misdiagnosed. Therefore, in all MS patients suffering from fatigue, a careful history assessing for disturbances of sleep and polysomnographic investigations should regularly be performed.

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Conflict of interest statement

The authors declare that they have no conflicts of interest.

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