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Original Article

Sleep quality can influence the outcome of patients with multiple sclerosis

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ABSTRACT

Objective: Sleep plays a role in some oligodendrocyte processes, including myelination. This study aimed to analyze the possible correlations between sleep quality and Multiple Sclerosis (MS) course.
Methods: Forty patients with Relapsing-Remitting MS were admitted. Based on the score obtained by the Pittsburgh Sleep Quality Index (PSQI), they were divided into good sleepers (<5) and bad sleepers (≥5). A set of data was collected retrospectively for each patient to investigate whether PSQI scores correlated with EDSS score changes, the number and the duration of each relapse and the cumulative day-number of MS reactivations over a three-year period.
Results: In a multivariate model, a PSQI score ≥5 independently and significantly correlated with an increase in number and duration of relapses ($p = 0.000$) and number of days of MS activity ($p = 0.000$) during the three-year retrospective observation period.
Conclusions: The results of this study show that the course of MS may be influenced by sleep quality. Assessment of sleep quality could be used to obtain reliable prognostic information in patients with relapsing-remitting MS. Further investigations are necessary to evaluate whether the correction of sleep disorders may be effective in improving the prognosis of MS patients.

1. Introduction

Sleep disturbances are common in multiple sclerosis (MS) [1,2]; alterations in sleep macro- and microstructure have been described in polysomnographic studies in a large percentage of patients [3].

Myelin production is a key function of oligodendrocytes [4]. Oligodendrocyte precursor cells (OPCs) are responsible for the production of new myelin in healthy brain, and they are recruited rapidly to prime the recovery processes in response to injury [5,6].

Simon et al. [7], showed that the endogenous population of adult brain parenchymal progenitors is subject to extensive modulation by environmental stimuli and voluntary physical exercise both a feature of the wake state. The wake state stimulates OPCs' exit from the cell cycle followed by an enhanced and fast differentiation into mature oligodendrocytes, thus reducing the staminal reserve.

Investigations using translating ribosome affinity purification technology combined with microarray analysis [8] found that the expression of hundreds of transcripts translated in oligodendrocytes, changes according to sleep and wake status and that many wake- and sleep-related genes have complementary or opposite functions. Further, direct evidence was provided that the proliferation of OPCs is affected negatively during wake but doubles during sleep whereas their differentiation is enhanced in the wake state. Several biological changes, differently expressed during wake and sleep can influence OPCs processes [9–11]. For example, glutamatergic transmission that is higher in wake than in sleep, can inhibit OPCs proliferation and affect their ability to produce myelin through AMPA-mediated excitatory currents [12].

The demonstrations supporting the role of sleep in some oligodendrocyte functions, including myelination, and in the proliferation of new immature oligodendrocytes, suggest that in some clinical conditions, characterized by oligodendrocyte involvement, sleep alterations could influence patients' prognosis. This study

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aimed to evaluate possible correlations between sleep quality and the course of MS, to verify whether the quality of sleep can be used as a prognostic indicator and then to suggest possible therapeutic intervention strategies.

2. Methods

2.1. Patients

Study subjects were recruited from patients attending the MS Center of the Neurological Department at the University Hospital of Ancona, Italy, over six months (January 2017–June 2017). Inclusion criteria were: age <50 years; Relapsing-Remitting form of MS (RRMS); years from disease onset >3 and ≤5 years; Expanded Disability Status Scale (EDSS) score ≤4.5 [13]; availability of accurate medical recordings in the three years preceding inclusion in the study including at least one medical assessment and a brain and spinal MR examination per year. All recruited patients were under first-line modifying therapy with interferon beta-1a; specifically, all patients had morning subcutaneous injection of 44 μg three times a week. Treatment tolerability for each patient was evaluated periodically. In the case of relapse, all patients received a standard therapy protocol within 24 h from symptoms' onset with intravenous methylprednisolone 1000 mg/day for five days [14].

Patients with symptoms clearly able to interfere with sleep quality, including spasticity, severe pain, and bladder dysfunctions as well as patients with psychiatric symptoms and cognitive deficits were excluded. Due to the possible confounding effect of fatigue, particular attention was paid to exclude patients with a score >36 on the fatigue severity scale [15]. Further exclusion criteria were the presence of major psychiatric or other neurological disease, ongoing treatments able to affect sleep architecture, drug abuse, work activities inducing sleep deprivation, and medical conditions including breathing and circulatory disorders potentially influencing sleep quality and structure.

2.2. Sleep quality evaluation

Quality of sleep was assessed using the Pittsburgh Sleep Quality Index (PSQI), a self -administered questionnaire used to evaluate the previous month's quality of sleep. It contains 19 self-rated questions and five facultative questions [16]. Every item is constructed of 7 components: 1 = subjective sleep quality, 2 = sleep onset latency, 3 = sleep duration, 4 = sleep efficiency, 5 = sleep disturbance, 6 = use of hypnotic drugs and 7 = daytime dysfunction. Each component is scored from 0 to 3, giving a PSQI range from 0 to 21: the higher the score, the lower the quality of sleep. A cut off score of five divided good sleepers (<5) from bad sleepers (≥5). The validity of the PSQI score has been confirmed by several studies in different populations of patients [17,18]. We used the Italian version, validated in a general population and also in MS patients [19].

2.3. Main variables of disease course

From the MS Center's database we obtained the following variables: disease duration from MS onset; number of relapses during the three years preceding inclusion in the study; relapse duration defined as the number of days from the onset of new symptoms or increase of EDSS score until a stabilization of symptoms occurred, defined as a return to basal condition or documented stabilization of the clinical status for at least five consecutive days; number of days of MS activity calculated as duration in days of each relapse x number of relapses; EDSS score at the time of PSQI test administration (entry EDSS); EDSS score at the beginning of the three years preceding PSQI test administration (baseline EDSS); age and sex; number of lesions documented by MR (entry and baseline). All included patients were given the PSQI and then classified in two cohorts according to their PSQI score: good sleepers (PSQI <5) and bad sleepers (PSQI ≥5).

2.4. Statistical analysis

Age, baseline and entry EDSS score, baseline and entry number of lesions, number of MS relapses during the observation period, mean duration of MS relapses and number of days of MS activity were collected as continuous variables. PSQI was recoded into a dichotomous variable (<5 or ≥5). Sex was synthesized as a binary variable. Continuous variables were compared with t-tests for independent samples. The difference between baseline and entry EDSS score and number of lesions was evaluated with a t-test for repeated measures. Last, we prepared three different multivariate models adopting (i) the number of MS relapses in three years, (ii) the duration of MS reactivations and (iii) the number of days of MS activity. In each model, we adopted dichotomous PSQI as the main predictor and age, sex, baseline EDSS score and baseline number of MS lesions as covariates. To underline hidden relationships among variables, we also tested the effects of the clinical variables according to age in three mixed-effects models, treating age as a random-effect factor and sex, baseline EDSS score and baseline number of MS lesions as fixed-effect factors. Statistical analyses were performed with SPSS 13.0 for Windows Systems.

3. Results

Forty-four patients were selected. After the exclusion of four (two for the presence of spasticity, one for bladder dysfunction and one for a history of panic attacks), we obtained a final sample of 40 subjects. PSQI score was <5 in 20 and ≥ 5 in the other 20 patients. Baseline characteristics of the sample are shown in Table 1. Mean EDSS score and the number of lesions significantly increased from baseline to entry ($p < 0.0001$ and $p = 0.040$ respectively). Based on information recorded in the periodic evaluations during the three years of retrospective observation, all patients were compliant with interferon treatment, and no severe side-effects emerged. As shown in Table 2, according to the t-test, patients with PSQI ≥5 had a higher EDSS score ($p = 0.015$), greater number of lesions ($p < 0.0001$), greater number ($p < 0.0001$) and duration of relapses ($p < 0.0001$) and larger number of days of MS activity ($p < 0.0001$) detected at entry with respect to those with PSQI <5. No significant difference was found between the two groups for baseline EDSS score and number of lesions.

These observations were confirmed after correction for age, sex, baseline EDSS and baseline number of MS lesions in multivariate models for MS relapses, mean duration of MS reactivations and mean days of MS activity. The first multivariate model results were significant ($p = 0.0001$; observed power = 0.996). In this model, only PSQI significantly associated with the outcome ($p < 0.0001$). However, in the mixed model, accounting for the random-effect of age, female sex contributed significantly to the variation in the dependent variable ($p = 0.02$, Table 3). When comparing the estimated marginal means obtained from this model, we observed that the mean number of MS relapses in three years were significantly different according to PSQI score, correcting for covariates (PSQI < 5: 1.744; 95% CI: 1.220–2.269; PSQI ≥ 5: 2.940; 95% CI: 2.509–3.370; $p = 0.004$). The second model results were significant ($p = 0.001$; observed power = 0.967). In this model, only PSQI resulted in a significant association with the outcome ($p < 0.0001$). Similarly, in the mixed model, sex did not contribute significantly to variation in the dependent variable ($p = 0.594$, Table 4). When

Table 1
Baseline characteristics of the sample.

Continuous Variables	N	Minimum	Maximum	Mean	SD
EDSS (baseline)	40	0	3.0	1.038	0.7876
EDSS (entry)	40	1.0	4.5	2.188	1.0960
Number of MS lesions (baseline)	40	2	7	3.60	1.533
Number of MS lesions (entry)	40	2	18	6.83	3.137
Number of MS relapses	40	1	4	2.13	0.992
Mean duration of MS relapses (days)	40	3	22	9.90	3.699
Number of days of MS activity	40	3	52	22.03	14.766
PSQI at entry	40	1	13	5.40	3.128
Age	40	25	48	35.63	6.562
Dichotomous Variables	**n**	**Percent**			
Female sex (%)	26	65,0%			
PSQI $\geq$ 5 (%)	20	50,0%			

SD = standard deviation; **MS** = Multiple Sclerosis; **PSQI** = Pittsburgh Sleep Quality Index; **EDSS** = Expanded Disability Status Scale.

Table 2
Comparison of baseline characteristics of the sample with t-test.

		N	Mean	SD	SEM	p
EDSS (baseline)	PSQI < 5	20	1.150	0.8445	0.1888	0.373
	PSQI $\geq$ 5	20	0.925	0.7304	0.1633	
EDSS (entry)	PSQI < 5	20	1.775	0.9386	0.2099	**0.015**
	PSQI $\geq$ 5	20	2.600	1.1074	0.2476	
Number of lesions (baseline)	PSQI < 5	20	3.75	1.682	0.376	0.543
	PSQI $\geq$ 5	20	3.45	1.395	0.312	
Number of lesions (entry)	PSQI < 5	20	4.95	1.638	0.366	**0.000**
	PSQI $\geq$ 5	20	8.70	3.181	0.711	
Number of relapses	PSQI < 5	20	1.50	0.607	0.136	**0.000**
	PSQI $\geq$ 5	20	2.75	0.910	0.204	
Duration of relapses (days)	PSQI < 5	20	7.60	3.169	0.709	**0.000**
	PSQI $\geq$ 5	20	12.20	2.628	0.588	
Number of days of activity	PSQI < 5	20	10.85	5.174	1.157	**0.000**
	PSQI $\geq$ 5	20	33.20	12.564	2.809	

N = number of patients in the sample; **SD** = standard deviation; **SEM** = standard error of the mean; **EDSS** = Expanded Disability Status Scale.
Significant differences are in bold.

Table 3
Multivariate mixed model results for the mean number of MS relapses in three years.

Source		Type III Sum of Squares	df	Mean Square	F	p
Intercept	Hypothesis	4.499	1	4.499	5.994	**0.05**
	Error	4.248	5.658	0.751		
PSQI	Hypothesis	6.144	1	6.144	12.281	**0.004**
	Error	7.004	14	0.500		
Age	Hypothesis	11.828	21	0.563	1.126	0.42
	Error	7.004	14	0.500		
Sex	Hypothesis	3.270	1	3.270	6.536	**0.02**
	Error	7.004	14	0.500		
EDSS (baseline)	Hypothesis	0.196	1	0.196	0.392	0.54
	Error	7.004	14	0.500		
Lesions (baseline)	Hypothesis	0.029	1	0.029	0.058	0.81
	Error	7.004	14	0.500		

Intercept = estimate of the grand mean of the dependent variable when all the independent variables are 0; **Hypothesis** = null hypothesis testing if the means of each subgroup within the variable of interest are equal; **Error** = within-group estimate of variance; **df** = degrees of freedom; **F** = F-statistic; **PSQI** = Pittsburgh Sleep Quality Index; **EDSS** = Expanded Disability Status Scale.
Significant differences are in bold.

comparing the estimated marginal means obtained from this model, we observed that the mean duration of MS reactivations were significantly different according to the PSQI score, correcting for covariates (PSQI < 5: 7.074; 95% CI:4.529–9.618; PSQI $\geq$ 5: 11.384; 95% CI: 9.748–13.920; p = 0.012). Furthermore, the third model results were significant (p = 0.0001; observed power = 0.999); only PSQI was significantly associated with the outcome (p < 0.0001). The mixed model, however, suggested that female sex contributed significantly to the variability of the dependent variable (p = 0.041, Table 5) when treating age as a random-effect variable. In this analysis, we compared the estimated means of days of MS activity and observed a significant difference according to PSQI score, correcting for covariates (PSQI < 5: 14.173; 95% CI:7.279–21.067; PSQI $\geq$ 5: 34.077; 95% CI: 28.425–39.729; p = 0.001).

4. Discussion

Our findings suggest a link between sleep quality and clinical evolution of MS. Patients with relapsing-remitting MS and poor sleep quality in the previous month, documented by a PSQI score $\geq$5, showed a significantly higher probability of a negative

Table 4
Multivariate mixed model results for the mean duration of MS reactivations.

Source		Type III Sum of Squares	df	Mean Square	F	p
Intercept	Hypothesis	264.125	1	264.125	24.315	**0.000**
	Error	166.920	15.366	10.863		
PSQI	Hypothesis	97.427	1	97.427	8.279	**0.012**
	Error	164.753	14	11.768		
Age	Hypothesis	148.952	21	7.093	0.603	0.857
	Error	164.753	14	11.768		
Sex	Hypothesis	3.499	1	3.499	0.297	0.594
	Error	164.753	14	11.768		
EDSS (baseline)	Hypothesis	0.014	1	0.014	0.001	0.973
	Error	164.753	14	11.768		
Lesions (baseline)	Hypothesis	25.950	1	25.950	2.205	0.160
	Error	164.753	14	11.768		

Intercept = estimate of the grand mean of the dependent variable when all the independent variables are 0; **Hypothesis** = null hypothesis testing if the means of each subgroup within the variable of interest are equal; **Error** = within-group estimate of variance; **df** = degrees of freedom; **F** = F-statistic; **PSQI** = Pittsburgh Sleep Quality Index; **EDSS** = Expanded Disability Status Scale.
Significant differences are in bold.

Table 5
Multivariate mixed model results for the mean number of MS activity days.

Source		Type III Sum of Squares	df	Mean Square	F	p
Intercept	Hypothesis	847.510	1	847.510	7.187	**0.031**
	Error	843,988	7.157	117.926		
PSQI	Hypothesis	1703,241	1	1703.241	19.721	**0.001**
	Error	1209,133	14	86.367		
Age	Hypothesis	1890,073	21	90.003	1.042	0.480
	Error	1209,133	14	86.367		
Sex	Hypothesis	437,059	1	437.059	5.061	**0.041**
	Error	1209,133	14	86.367		
EDSS (baseline)	Hypothesis	10,091	1	10.091	0.117	0.738
	Error	1209,133	14	86.367		
Lesions (baseline)	Hypothesis	14,438	1	14.438	0.167	0.689
	Error	1209,133	14	86.367		

Intercept = estimate of the grand mean of the dependent variable when all the independent variables are 0; **Hypothesis** = null hypothesis testing if the means of each subgroup within the variable of interest are equal; **Error** = within-group estimate of variance; **df** = degrees of freedom; **F** = F-statistic; **PSQI** = Pittsburgh Sleep Quality Index; **EDSS** = Expanded Disability Status Scale.
Significant differences are in bold.

progression of the disease; there was an increased rate of relapses of longer duration, supporting the hypothesis that a reduced sleep quality may impair the recovery capability from MS relapses, possibly due to a defect in myelin regeneration [9]. The short duration of the observation period could have been responsible for the lack of a significant independent association between poor sleep quality and an increase in the number of lesions and the EDSS score. In this regard, the repair capacity of the OPCs was probably not yet exhausted, resulting in a minor impact on anatomic and functional damage in spite of the longer duration of relapses. When adopting a mixed-model design, we observed a significant association between female sex and a higher number of MS relapses and duration in different age groups, suggesting that sex could modulate PSQI effects on these outcomes. This finding, however, needs to be confirmed in future studies that require a larger sample size than that of our study.

In spite of their frequency, potential pathogenetic role in different clinical conditions and social implications [20–22], sleep disturbances typically are not systematically and carefully investigated in the clinical setting and thus, they are often underestimated [23]. Neurological bladder, pain, spasticity, anxiety or depression that are common features in MS patients may strongly influence the occurrence of chronic insomnia [24]. There is substantial evidence that sleep-disordered breathing (obstructive and central apneas), restless leg syndrome (RLS) and periodic limb movements (PLM) are widely prevalent in MS patients. These can be due to several reasons, including demyelinating lesions in the brainstem and spinal cord that may negatively influence breathing control and upper airway muscle activity and induce unstable ventilatory drive. The use of narcotic medications for pain, sedatives and muscle relaxant drugs can exacerbate the occurrence of apnea [25,26]. Different and complex pathogenic mechanisms may be involved in RLS. Neurophysiological findings showed the involvement of intracortical and cortical-subcortical generators, resulting in enhanced cortical excitability and/or decreased inhibition [27]. Moreover, brainstem or spinal lesions with interruption of the hypothalamic-spinal pathway and consequent motor neuron hyperexcitability are a possible cause of RLS and PLM [28,29].

Pathophysiologic considerations strongly support the relevant role played by correct sleep hygiene on structural and functional recovery processes. Maturation and activity of OPCs that represent 5–8% of the adult nervous system glial population and that primarily contribute to repair processes after white matters damage, are appreciably influenced by the sleep-wake rhythms [7–9]. Specifically, their proliferation increases during sleep but is reduced after sleep deprivation. Cerebral gene expression considerably changes from sleep to wake and several transcripts involved in the production and maintenance of membranes, including myelin, show higher levels during sleep; while others, whose levels increase during waking state, are involved in apoptosis and the mechanisms of cellular stress [7,10,11]. These considerations support the hypothesis that an alteration in sleep quality can have negative influences on remyelination processes and therefore, on recovery capacities after MS relapses.

Our study has some points of weakness. First, patients were retrospectively investigated. Even if we had the opportunity to

consult reliable and standardized databases, the possibility of missing some relevant data could not be completely excluded. Our decision to not conduct a prospective investigation is justified by the need to keep patients from an unnecessary exposure to a condition potentially involved in the promotion of different pathological events. In recent years, strong recommendations to improve the quality of sleep have emerged from several studies demonstrating that correct sleep hygiene is strategic to preserve anatomical and functional integrity of the brain and other organs [20–22,30]. Further, evaluation of sleep quality was implemented with the PSQI whose results refer to the last month's patients' sleep quality. In this case, we are quite confident, after a careful investigation of every single patient, that what we documented in terms of sleep quality was a stable and typical characteristic. For this reason, it is highly probable that a PSQI score $\geq$5 characterized a general long-term poor sleep quality in every patient. However, this approach cannot completely exclude that sleep quality varied during the three years of the observation period. No patient had a polysomnographic evaluation during the study period. Therefore, we were unable to deliver specific information about sleep features. Given these considerations, the results of the present study are considered preliminary, hopefully able to stimulate further research on the issue that would include instrumental investigations. The possibility that sleep quality can be negatively influenced by treatments deserves consideration. In the present study, we were not able to deliver specific information on this issue, even if the procedure of beta-1a treatment in morning administration three times a week, is considered an acceptable approach for reducing the probability of a negative influence on sleep quality [31].

In conclusion, our investigation suggests that sleep alterations are involved in the clinical expression of MS. Considering the role of sleep in myelin regeneration and consequently on the outcome of the disease and the possibility that sleep alterations can be involved in promoting fatigue, cognitive dysfunction, mood alterations and other common clinical features of MS [32–35]. Moreover, further studies on the issue are warranted. For clinical purposes, in MS patients with an alteration of sleep quality, a careful evaluation including, in selected cases, a polysomnographic study, should be recommended for a specific diagnosis and treatment.

Conflict of interest

The authors report no conflict of interest and no financial interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.02.020.

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