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Sleep and fatigue in multiple sclerosis: A questionnaire-based, cross-sectional, cohort study☆,☆☆

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ABSTRACT

Introduction: Fatigue and sleep disorders are frequently reported in patients affected by Multiple Sclerosis (MS) but the causes and the relationship are not yet fully understood. This study aimed at evaluating their prevalence, at determining the relationships between clinical findings of MS and the occurrence of sleep disorders and at investigating the relations between sleep disorders and fatigue.
Methods: One hundred and two MS patients were enrolled in the study. They were analyzed on both their clinical features (type of MS, disease duration, clinical severity, type of treatment, presence of spinal demyelinating lesions) and specific scales scores (Expanded Disability Status Scale, Modified Fatigue Impact Scale - MFIS, Self-Administered Anxiety Scale - SAS, Beck's Depression Inventory - BDI, Pittsburgh Sleep Quality Index - PSQI, Epworth Sleepiness Scale - ESS, and the Berlin's questionnaire for Obstruction Sleep Apnea Syndrome - OSAS).
Results: Patients with poor sleep quality are more frequently fatigued ($p = 0.001$), have higher MFIS global scores ($p < 0.001$), higher prevalence of RLS symptoms ($p = 0.049$), and show higher scores at BDI ($p = 0.017$) and SAS ($p \leq 0.001$). Conversely patients with fatigue show older age ($p = 0.005$), higher prevalence of sleepiness ($p = 0.021$), higher prevalence of RLS symptoms ($p = 0.030$), higher prevalence of poor sleep quality ($p < 0.001$) with higher PSQI scores ($p < 0.001$), higher scores on the BDI ($p < 0.001$) and SAS ($p \leq 0.001$).
Conclusion: This study shows that MS is associated with a high prevalence of sleep complaints, including subjectively poor sleep quality, excessive daytime sleepiness, RLS and symptoms of OSAS. Further, it demonstrated a strict relation between fatigue and sleep disorders. Finally, it underlines their relationship with anxiety and depression in MS patients.

1. Introduction

Multiple Sclerosis (MS) is a chronic disease of the central nervous system (CNS) characterized by loss of motor and sensory function, resulting from immune-mediated inflammation, demyelination and subsequent axonal damage [1].

The neurological symptoms can be various and heterogeneous, while fatigue and sleep disorders, even though extremely frequent, are often underestimated and underdiagnosed.

Fatigue is reported by 50–80% of the patients [2]. The attempt to find a correct definition of fatigue in MS has led to much controversy and so, to date, there isn't a sole description of it. We can describe fatigue in MS as "the subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities" [3]. Its pathophysiology is not completely understood but a cytokine influence, a role of cerebral lesions and cortical atrophy, a hypothalamus-pituitary-adrenal axis dysfunction and an activation of neural circuits have been discussed as possible causes [4]. Further, to date, no therapy for fatigue in MS has made a real clinical impact on the quality of life (QoL) of the patients.

Sleep is often disrupted in MS patients [5,6], with an incidence of about 50% of the patient population [7], and MS can be associated with a variety of sleep disorders, including sleep disordered breathing (SDB), rapid eye movement (REM) behaviour disorder, insomnia, symptomatic narcolepsy [8] and parasomnias [9,10]. Also Restless Legs

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Syndrome (RLS) has been observed with increased prevalence in MS patients [11,12], in particular in association with spinal demyelination. Another major problem derives from the underdiagnoses of sleep disorders in MS patients as shown by Brass et al. [13].

The relation between fatigue and sleep disorders in MS is intriguing. A previous study, by Cameron et al. [14], demonstrated a close relation between fatigue and sleep quality in MS patients with cognitive impairment while Strober et al. [15] have found a correlation between fatigue and poor sleep in a general MS population.

Kaminska et al. [16] and later Veauthier and Paul [17] wrote two exhaustive reviews about the existing studies of fatigue and sleep disorders in MS underlying their links and their importance in the QoL of the patients. Ghajarzadeh et al. [18] have studied 100 MS patients demonstrating the strict correlation between both sleep disorders, depression and fatigue, while Mills and Young [19] have further studied and confirmed their relationship by means of a cross-sectional study of 635 MS patients.

The nature of the connection between fatigue and sleep disturbances is not yet fully understood [18,20–26].

In particular fatigue has been considered as a symptom of impaired arousal [27] and treatments with central nervous system stimulants (namely, Modafinil) have been tested [28–30]. Strober and Arnett [31] have brilliantly studied how disease severity, depression and sleep disorders impact on fatigue finding, as more accurate, a model in which each of these three variables independently relates to fatigue.

The primary endpoint of the present study was to evaluate the prevalence of sleep disorders (in particular, poor sleep quality, daytime sleepiness, snoring and apneas, and RLS) in a cohort of adult patients with MS, by means of specific questionnaires. The other main objective of this study was to investigate the relations between sleep disorders and fatigue.

As a secondary endpoint, we aimed at evaluating the link between clinical findings (severity of the disease, disease duration, neuroimaging, treatments) and the occurrence of sleep disorders.

2. Methods

2.1. Patients

A cohort of 102 consecutive adult patients affected by MS were enrolled, 65 women and 37 men, the mean age was 43.1 ± 11.6 years (range: 28–66 years). Patients were recruited from the Center for Multiple Sclerosis of the Catholic University in Rome in a period of six months (from June 2014 to December 2014). The inclusion criteria were age >18 years, and a diagnosis of MS based on McDonald's Revised Criteria [32].

The main clinical features of the patients are described in Table 1.

No patient was receiving treatments for fatigue or for sleep disorders at the time of the study. Patients with relapsing-remitting MS (RR-MS) had to be in stable phase of the disease for at least three months at the time of the study. All patients underwent a medical and neurological examination. The local Ethical committee approved the study, and all patients gave their written consent to participate.

Table 1
Main clinical features of the patients.

	Mean	SD	Total
Male patients			37
Age	43.3	11.6	
Weight	69.6	13.2	
Height	1.7	0.1	
BMI	24.4	3.9	
SAS	38.3	9.1	
BDI	5.7	5.5	
SM (relapsing/remitting)			89
Disease duration (years)	10.6	6.6	
EDSS	2.4	1.8	
Severe MS			10
Spinal lesions			82
IFN treatment			75

2.2. MS clinical features

The following clinical features were evaluated: type of MS, disease duration, clinical severity, type of treatment, presence of spine demyelination.

2.3. Scales and questionnaires

The severity of the disease was measured by the Expanded Disability Status Scale (EDSS) score [33]. The EDSS quantifies disability in eight Functional Systems (FS) and allows to assign a Functional System Score (FSS) in each of these. In the present study we decided to consider affected by 'severe' MS (SMS) the patients with an EDSS score ≥5.

In order to evaluate the impact of fatigue, the Modified Fatigue Impact Scale (MFIS) was applied. The MFIS is a modified form of the Fatigue Impact Scale [34–36]; it measures how fatigue affects MS patient's life. This 21-items scale provides a global score, and also generates 3 subscales which measure the effects of fatigue in terms of physical, cognitive, and psychosocial functioning. The Total MFIS score can range from 0 to 84; we used a cut-off global score of 38 to discriminate fatigued from non-fatigued patients [37].

To evaluate the effects of anxiety and depression, a psychometric evaluation was performed, which included the Self-Administered Anxiety Scale (SAS #54) [38] and the Beck Depression Inventory (BDI) [39]. The SAS #54 [38] is a method of measuring the level of anxiety in patients who have anxiety-related symptoms. It uses a 4-point Likert-type scale, ranging from 1 to 4. The SAS contains 20 items with 15 increasing anxiety level questions and 5 items reverse scored. The total score ranges from 20 to 80; the normal range is from 20 to 44.

The BDI [39] is a 21-item well-validated self-report instrument measuring characteristic attitudes and symptoms of depression over the previous two weeks. Scores range from 0 to 36; scores >9 indicate a mild to severe depression [40].

Subjective evaluation of sleep quality was performed by means of the Pittsburgh Sleep Quality Index (PSQI). The validated Italian version was used [41]. A global score >5 was considered as an indicator of poor sleep quality [42]. For the evaluation of excessive daytime sleepiness (EDS), the validated Italian version of the Epworth Sleepiness Scale (ESS) [43] was applied. For diagnosis of RLS the validated four-item RLS criteria of the International Restless Leg Syndrome Study Group (IRLSSG) was used [44]. Fulfillment of all four criteria was required for diagnosis; moreover, we considered positive for RLS the patients who reported symptoms with a frequency >3 days per week. This was established by an unblinded face-to-face interview. Moreover, in all subjects, an evaluation for the symptoms and clinical signs predictors for OSAS was performed by means of the Berlin's Questionnaire [45]. Neck circumference and Body Mass Index (BMI), the best clinical predictors for OSAS, were measured in all patients.

2.4. Statistical analysis

The following variables were considered: age, gender, BMI, shift-work, duration of disease, type of MS disease (relapsing-remitting or progressive (Pr) form), type of treatment (interferon vs other) presence of spinal lesions at spinal cord Magnetic Resonance Imaging (MRI), disease disability degree (EDSS score), MFIS, SAS #54, BDI, PSQI, ESS, Berlin, IRLSSG score (RLS+ = 4; RLS− < 4).

In order to evaluate the link between clinical features and sleep parameters, in an univariate analysis, patients were divided into groups: RR-MS vs Pr-MS; SMS vs non-severe MS (nSMS); presence or absence of IFN treatment (IFN+ vs IFN−); presence or absence of spinal lesion (Sp + vs Sp−); presence or absence of fatigue (F+ vs F−).

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