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Evaluation of patients with multiple sclerosis and sleep disorders

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Ethics Committee Approval
Approval for the study was granted by the Medical Research Ethics Committee of Kahramanmaraş Sütçü Imam University Medical Faculty (Decision no:01, Dated: 08.11.2017). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Sleep disorders are often reported by MS patients and various studies have shown sleep disorders to be more widespread in MS patients than in healthy control groups. However, despite the high frequency, they are often overlooked. This study aimed to determine the characteristics of fatigue and daytime sleepiness in MS patients, the underlying factors, and their relationship for testing the reliability of subjective scales and establishing when patients presenting with these symptoms should be referred to a sleep specialist.

Methods: The patients enrolled in this cohort study were aged >18 years, had a confirmed diagnosis of relapsing remitting MS, were in the remission phase, had not taken steroids within the last 3 months, and had complaints of fatigue, daytime sleepiness, and sleep disorders. Patients with EDSS score <3 were admitted to the sleep laboratory for 2 days to perform 1 night of polysomnography (PSG) and a 5-nap multiple sleep latency test (MSLT) the following day. The results were evaluated with regards to the clinical scales.

Results: A total of 41 patients were evaluated. Excessive daytime sleepiness was found in 14 (34.1%), and sleep quality was poor in 28 (68.29%). According to the PSG-MSLT, a sleep disorder was found in 37 patients (90.24%). A diagnosis of hypersomnolence was made in 23 (56.1%) patients, and two (4.88%) were categorized as type 2.

Conclusion: It is necessary for every clinician involved in MS treatment to correctly diagnose and treat fatigue, excessive daytime sleepiness, and other sleep disorders, which increase the disability of disease. When the high prevalence of these types of disorders and the fact that they are multifactorial are taken into consideration, the timing of the referral of these patients to a sleep specialist and the implementation of objective tests become more important.

Keywords: Multiple sclerosis, Sleep disorders, Polysomnography

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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. Approximately 2.2 million people are affected worldwide, and the prevalence is expected to increase. It is more common in women compared to men. MS is a frequent cause of nontraumatic neurological disability in young adults. The neurological symptoms can be various and heterogeneous, while fatigue and sleep disorders, even though extremely frequent, are often underestimated and underdiagnosed. Comorbid conditions are common in MS and may contribute to disability. Many patients with MS report sleep disorders, more often than in the general population. Poor sleep quality in MS has been associated with negative outcomes, such as decreased quality of life, exacerbation rate and disease severity, and with other comorbidities such as fatigue, depression, anxiety, and pain [1].

This study aimed to determine the characteristics of fatigue and daytime sleepiness in MS patients, the underlying factors and their relationship for testing the reliability of subjective scales and establishing when patients presenting with these symptoms should be referred to a sleep specialist.

Materials and methods

This cohort study was conducted between 09.11.2017 and 01.11.2018. The patients enrolled in the study were aged >18 years, had a confirmed diagnosis of relapsing remitting MS (RRMS), were in the remission phase, had not taken steroids within the last 3 months, and had complaints of fatigue, daytime sleepiness, and sleep disorders.

Patients were excluded from the study if they were aged < 18 years, had any other disease which could be confused with MS (systemic lupus erythematosus, CNS vasculitis), were in the attack phase of RRMS, had experienced an attack within the last 3 months, had received steroid treatment within the last 3 months, had been diagnosed with sleep disorders because of other systemic diseases, especially respiratory, had been diagnosed with a psychiatric disorder such as depression or anxiety disorder before the MS diagnosis, had taken various treatments for a sleep disorder before the MS diagnosis, or were using drugs which have a direct effect on sleep such as benzodiazepines, modafinil or melatonin during the evaluation or in the recent past.

Approval for the study was granted by the Medical Research Ethics Committee of Kahramanmaraş Sütçü Imam University Medical Faculty (Decision no:01, Dated: 08.11.2017). The study was conducted per the Declaration of Helsinki. In the neurological evaluation, the neurologist applied the Expanded Disability Status Scale (EDSS) of Kurtze, and neuro-imaging methods were used. Those who presented with complaints of fatigue and sleep disorders, and those with an EDSS score <3 were admitted to the sleep laboratory for 2 days for 1 night of polysomnography (PSG) and a 5-nap multiple sleep latency test (MSLT) performed the following day. The results were evaluated with the clinical scales and demographic data. A total of 41 patients aged >18 years who met these criteria were included in the study.

The age, gender, marital status, smoking status, comorbidities, nocturia, drugs used, duration of disease, body mass index (BMI), EDSS score, Epworth Sleepiness Scale (ESS), Fatigue Severity Scale (FSS), Hospital Anxiety Depression Scale scores (HAD-A, HAD-D), the presence of restless legs syndrome, widespread body pain scores according to the Visual Analog Scale (VAS), the Pittsburgh Sleep Quality Index (PSQI) score, and the data obtained from the PSG and 5-nap MSLT the following day were recorded for each patient. The patient scores obtained from the subjective scales were examined with respect to their relationship with each other and the diagnoses made with objective tests.

All patients provided written informed consent for participation in the study.

Statistical analysis

Data obtained in the study were statistically analyzed using Jamovi and JASP (Jamovi project (2018) version 0.9.6.9) and JASP Team (2019) version 0.10.2 software. Descriptive statistics were presented as mean (standard deviation) (SD), median, minimum, and maximum values and interquartile range for continuous variables according to distribution. Categorical variables were given as number (n) and percentage (%). Conformity of numerical variables to normal distribution was assessed with the Kolmogorov-Smirnov test. In the comparison of two independent groups, the Mann Whitney U-test was used for numerical variables not showing normal distribution. In the comparison of differences between categorical variables, the Pearson Chi-square test and Fisher's Exact test were used in 2x2 tables and RxC tables, respectively. The Spearman Rho correlation coefficient was used to examine the correlations between numerical variables. A value of $P<0.05$ was considered statistically significant.

Results

A total of 41 patients, comprising 30 (73.17%) females and 11 (26.83%) males, who were followed up in the Neurology Outpatient Clinic of Sütçü Imam University Medical Faculty Hospital were evaluated. The mean and median EDSS scores of the patients were 1 (range: 1-2.5) and 1.2 (0.4), respectively. Twenty-seven patients (65.85%) received injection treatment and fifteen patients (31.71%) were administered oral treatment. Among the patients receiving injections, interferon-ß was used in 25 (Table 1).

Table 1: Demographic and clinical data of the patients

	n (%) / mean (SD)	Median [Min - Max]
Gender		
Male	11 (26.83)	
Female	30 (73.17)	
EDSS	1.2 (0.4)	1 [1 - 2.5]
Treatment		
Injection treatment	27 (65.85)	
Oral	13 (31.71)	
Age (years)	35 (9)	34 [18 - 53]
Marital status		
Single	10 (24.39)	
Married	31 (75.61)	
Disease duration (years)	5.3 (3.04)	5 [1 - 13]
Smoker	12 (29.27)	
Body mass index	25.2 (4.59)	25.63 [17.3 - 36.05]

According to the HAD-A scale, 20 (48.8%) patients had anxiety, and according to the HAD-D scale, 24 (58.5%) had depression. The mean VAS score for widespread body pain was

4.73 (3.1). According to the FSS, fatigue was found in 30 (73.2%) patients.

According to the ESS, excessive daytime sleepiness was found in 14 (34.1%) patients. Based on PSQI, sleep quality was poor in 28 (68.29%) patients. Based on PSG-MSLT, there was a sleep disorder in 37 patients (90.24%), categorized as type 2 due to a medical condition, including obstructive sleep apnea syndrome (OSAS), hypersomnolence, restless legs syndrome (RLS), periodic limb movement disorder (PLMD). A diagnosis of hypersomnolence was made in 23 (56.1%) patients, and 2 patients (4.88%) had hypersomnolence type 2.

Following PSG, OSAS was found in 26 (63.41%) patients. The mean and median Apnea-Hypopnea Index (AHI) scores were 9, and 6 (range, 1-39), respectively. According to the AHI scores, OSAS was mild in 20 (48.78%), moderate in 4 (9.75%) and severe in 2 (4.87%) patients. Of the 26 patients diagnosed with OSAS, 6 (23.07%) were obese. The 2 patients diagnosed with severe OSAS were admitted to the sleep laboratory a second time and started on n-CPAP treatment. Two (4.87%) patients had central type apnea in addition to OSAS. A moderate, significant linear correlation was found between the PSQI scores and the HAD-A and HAD-D scores ($P<0.001$, $P=0.014$) (Table 2).

Table 2: Descriptive statistics of various data

	n (%) / mean (SD)	Median [Min - Max]
ESS	8 (6)	7 [0 - 23]
FSS	45 (17)	50 [9 - 63]
HAD-A	10 (4)	9 [0 - 21]
HAD-D	8 (5)	8 [1 - 20]
VAS	4.7 (3.1)	4.5 [0 - 10]
RLS	5 (12.2)	
OSAS	26 (63.41)	
AHI	9 (9)	6 [1 - 39]
Hypersomnolence	23 (56.1)	
Narcolepsy	2 (4.88)	
PLMD	12 (29.3)	
PLMI	16 (35)	0 [0 - 188]
Sleep Efficacy (%)	86.17 (10.72)	87 [52.6 - 99]
PSQI	8 (4)	8 [1 - 15]
PSQI sleep quality		
Good	13 (31.71)	
Poor	28 (68.29)	
Obesity	6 (14.63)	
Sleep latency (mins)	22.7 (27.3)	11.5 [1 - 109]
N1 (%)	2.59 (2.62)	2 [0.3 - 17]
N2 (%)	52.5 (9.64)	52.2 [28.6 - 71.3]
N3 (%)	29.45 (6.74)	28.6 [14.5 - 45.8]
REM (%)	15.76 (7.33)	16.8 [1.8 - 34.7]
First REM Latency	147.1 (90.5)	116.5 [46 - 376]
MSLT sleep latency	8.2 (4.5)	7.7 [0.8 - 17.5]
SOREM	1 (1)	0 [0 - 4]
Interferon Beta Treatment		
Using	25 (61.0)	
Not using	16 (39.0)	

Considering the effects of injection on quality of life and sleep disturbance, some clinical parameters were compared according to Interferon-ß use. The median sleep latency values in the MSLT significantly differed between those using and not using interferon beta ($P=0.048$) (Table 3).

Table 3: Comparisons of various clinical and objective parameters according to the treatment used

	Interferon Beta Treatment		
	Using (n=25)	Not using (n=16)	*P*-value
OSAS (%)	15 (60.0)	11 (68.8)	0.814
RLS (%)	2 (8.0)	3 (18.8)	0.362
Hypersomnolence (%)	16 (64.0)	7 (43.8)	0.341
ESS (median [IQR])	8.0 [4.0 - 12.0]	6.5 [4.2 - 8.8]	0.376
FSS (median [IQR])	50.0 [31.0 - 61.0]	45.5 [33.2 - 57.8]	0.355
HAD-A (median [IQR])	9.0 [6.0 - 14.0]	9.5 [7.0 - 12.2]	0.861
HAD-D (median [IQR])	8.0 [4.0 - 9.0]	7.5 [5.8 - 11.0]	0.397
PLMI (median [IQR])	0.0 [0.0 - 16.0]	2.0 [0.0 - 18.0]	0.652
PSQI (median [IQR])	8.0 [5.0 - 11.0]	7.0 [4.0 - 12.0]	0.957
MSLT sleep latency (median [IQR])	6.1 [3.9 - 10.6]	9.1 [6.7 - 13.8]	0.048
Sleep latency - mins (median [IQR])	10.0 [4.0 - 32.0]	12.5 [4.9 - 35.0]	0.678
N1 (median [IQR])	1.7 [1.3 - 2.4]	2.5 [1.6 - 3.0]	0.177
N2 (median [IQR])	51.2 [46.3 - 56.1]	54.0 [46.8 - 60.1]	0.530
N3 (median [IQR])	28.6 [26.0 - 31.5]	28.2 [24.8 - 32.3]	0.820
REM (median [IQR])	17.0 [9.3 - 21.1]	15.2 [9.9 - 20.6]	0.602
First REM Latency (median [IQR])	105.0 [84.0 - 171.5]	140.2 [88.8 - 190.1]	0.593
Minimum O2 Saturation (median [IQR])	92.0 [90.0 - 93.0]	92.0 [91.0 - 93.2]	0.580
SOREM (median [IQR])	0.0 [0.0 - 0.0]	0.0 [0.0 - 1.0]	0.693

Discussion

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating, and neurodegenerative disease of the central nervous system. It is a heterogenous, multifactorial, immune-mediated disease caused by complex genetic-environmental interactions with the demyelination occurring in the white and grey matters of the brain and the spinal cord, and axonal damage. In addition to the disease itself primarily leading to disability, secondary factors such as fatigue, excessive daytime sleepiness, anxiety, depression, sleep disorders and pain also increase disability and affect the daily activities of the patient.

Due to many factors which contribute to their existing disability, several MS patients find themselves not being able to complete their academic life or being fired from work as a person who quickly tires and cannot resist sleep. When motor and sensory symptoms develop, although the majority of patients understand that they have suffered an attack and present to a physician, they may not be able to easily express complaints such as excessive daytime sleepiness or not pay enough importance, since it is overshadowed by other major symptoms. In addition, patients may mistakenly use the two distinct but closely related and intertwined concepts of fatigue and daytime sleepiness interchangeably.

Fatigue is defined subjectively as a decrease in mental and physical energy leading to difficulty in performing routine daily activities, which is noticed by the patient or their caregiver [2]. The patient feels exhausted, fatigued, burnt-out, and listless. The social and professional life of the patient can be affected. It can be evaluated subjectively with some scales but there is no test with proven reliability and validity for objective evaluation. In subjective evaluations, the Fatigue Severity Scale (FSS), which has a critical cutoff of ≥36 points, is used. Fatigue has been reported in 50-80% of MS patients [3]. Approximately 55% of MS patients report that fatigue is one of the worst symptoms [4] and 40% of patients state that it is the complaint that disables them most [5]. There are many studies in the literature which evaluate the frequency of fatigue and the reasons, and the rates found in most of these studies are similar.

In this study, we only included ambulatory RRMS patients who presented to the outpatient clinic with complaints of fatigue, excessive daytime sleepiness, and poor sleep and those who had an EDSS score of <3, and a relatively short duration of disease. When these inclusion criteria are considered, it can be

assumed that the effects of factors such as spasticity, pain, disability, anxiety and depression on sleep and fatigue are relatively low. According to the FSS, fatigue was found in 30 (73.2%) of the 41 patients.

In a study by Veauthier et al. [6] assessing which MS patients with fatigue should be referred to a sleep specialist, the optimal cutoff for PSQI was 5 points, and sensitivity was higher in those with positivity in the PQSI and fatigue scales. It was emphasized that each patient with fatigue should be evaluated carefully in terms of sleep disorders, and patients with a PQSI score >5 and Modified Fatigue Impact Scale (MFIS) score of >34 should certainly be referred to a sleep specialist and PSG should be used. In that study, only PSG was used to objectively evaluate sleep disorders, while in our current study, we used both the nocturnal PSG and the 5-nap MSLT performed the following day, along with the FSS, which evaluates fatigue.

In our patients, the sensitivity of the PSQI to sleep disorders, and whether there was accompanying fatigue were similar with the literature. In the analysis of the PSG-MSLT data of the patients with fatigue, an underlying sleep disorder was found in 86.6%. If a patient presented with other symptoms and fatigue was found in subjective scales, the patient was referred to a sleep specialist. It is recommended to perform MSLT the following day in addition to PSG.

Sleepiness is different from fatigue. When it is necessary to remain awake during the day, fatigue is the difficulty in remaining awake, feeling the need to sleep and not being able to prevent falling asleep. The ESS is used for subjective evaluation, and the critical cutoff value is >10. In objective evaluations, the maintaining awakeness test or MSLT are used. Therefore, the physician must differentiate these two concepts, for which the diagnosis and treatment are different [7]. Evaluation with differentiation of these two concepts will be beneficial in understanding the underlying biological mechanisms of these pathologies.

Merkelbach et al. [8] reported that 20% of MS patients had pathological sleepiness. According to the ESS scores in the current study, excessive daytime sleepiness was found in only 14 (34.1%) patients. According to the PSG-MSLT, a diagnosis of hypersomnolence was made in 23 (56.1%) patients. Two (4.88%) patients had narcolepsy. According to the objective data, there was pathological sleepiness in a total of 25 (60.9%) patients. When examined in this respect, if excessive daytime sleepiness in patients with symptoms is evaluated with a single subjective scale, those with non-pathological scores are considered normal and the objective tests are not applied, approximately half of the patients could be missed. Therefore, the ESS alone is not sufficient in the evaluation of excessive daytime sleepiness, and it is necessary for patients with this complaint to undergo PSG and more importantly, the MSLT the following day.

In the PSQI, which is a subjective scale for sleep quality, the cutoff value was >5, and sleep quality was poor in 28 (68.29%) patients. Thirty-seven (90.24%) patients were diagnosed with a sleep disorder according to the PSG-MSLT results. The rate in PSQI is of good guidance in the evaluation of sleep quality in MS patients, irrespective of whether they have fatigue.

Several studies in recent years have shown that sleep disorders contribute to fatigue and excessive daytime sleepiness, which can be intertwined with fatigue. There are many publications in the literature related to the reasons for MS fatigue and associated conditions. However, there are no systematic studies which evaluate fatigue and its frequency in MS patients. In 2017, Popp et al. [7] conducted a systematic review by screening all the studies in literature which used the ESS evaluation scale. A total of 48 original articles were examined. There was a correlation between the ESS and FSS in 19 studies. The results of the current study do not support this information as we found no correlation between the two (P=0.256).

Popp et al. [7] found 9 PSG studies and 2 actigraphy studies which objectively evaluated sleep disorders in MS patients. While most studies emphasized the clinical importance of fatigue in MS patients, excessive daytime sleepiness was less frequent and of a lower severity. In this study, we stressed the importance of fatigue, consistent with the literature. However, the lower frequency of excessive daytime sleepiness in the literature can be attributed to the use of subjective scales only, such as the ESS. In the current study, while the rate was 34.1% according to the ESS, the actual rate of pathological sleepiness was 60.9% according to the PSG and MSLT data. Therefore, it must be emphasized again that subjective scales are not sufficient in the evaluation of excessive daytime sleepiness. Generally, fatigue and excessive daytime sleepiness have been associated with respiratory disorders and PLMD. In an earlier study, it was concluded that while fatigue without accompanying excessive daytime sleepiness was frequent, excessive daytime sleepiness without fatigue was uncommon. Consistent with this finding, in our study, the most common underlying reasons were respiratory disorders and PLMD.

In an actigraphy study by Mendozzi et al. [9] conducted to examine the effect of long-term treatment of Interferon beta on sleep quality and fatigue, 42 ambulatory RRMS patients were monitored for at least 7 nights. Sleep quality was evaluated every day through actigraphy. The data were compared by grouping the patients as those did not receive immunomodulator treatment, those using glatiramer acetate, those using Interferon beta 3 days a week, and those using Interferon beta 1 day a week. There was a 5% decrease in sleep efficacy in two-thirds of the nights when Interferon beta injection was made, and sleep efficacy was lower in patients using glatiramer acetate compared to those not using the drug. It was emphasized that these types of side-effects on sleep should be taken into consideration when planning long-term treatment. In the current study, the scores obtained from the subjective scales, the diagnoses of sleep disorders obtained and the PSG-MSLT data were compared by separating the patients as those using and not using Interferon-ß, and a significant difference was found between the median MSLT sleep latency values only. It would be useful for physicians treating MS to know the effects of the treatments on sleep.

In a study by Shahrbanian et al. [10] that compared 79 and 110 MS patients with and without pain, respectively, the prevalence of pain among MS patients was 42%. The presence of pain and the pain severity were the factors most related to disability in MS. Fatigue was also one of the main factors contributing to pain. Moreover, a relationship was found between

pain and higher rates of depression and anxiety, sleep problems and impaired cognition. In our study, the mean VAS score of the patients was 4.7 (0.31). This may be attributed to the fact that spasticity and disability have not yet developed, as the study sample included a selected group of RRMS patients with EDSS scores of <3.

There are studies in literature which report that RLS is seen in 32.7% of MS patients, and in the primary progressive form of MS, this rate increases and leads to higher disability scores [11]. Predictive factors for RLS in MS patients are advanced age, a long duration of disease, primary progressive form, higher disability score, and shaking the legs before sleeping. RLS symptoms related to MS are more severe compared to RLS with no association with MS [12]. In the current study, RLS was found in 5 patients (12.2%).

In a PSG study, Ferini-Stramb et al. [13] showed a higher prevalence of PLMD in MS patients compared with a control group (36% vs. 8%). These movements can partially explain the disrupted sleep among individuals with PLMD, but anatomically, a specific region or neurophysiological mechanisms are still not fully known. In the current study, PLMD was found in 12 (29.3%) patients.

In their review, Marrieve et al. [14] reported that OSAS prevalence ranged between 7.14%-58.1%. While central sleep apnea is seen in <1% of the normal population, in some studies, it is reported to range between 0-8% in MS, especially in those with brain stem involvement [15]. In the current study, OSAS was found in 26 (63.41%) patients, 2 of which (4.88%) had mixed type with a combination with central apnea.

The prevalence of narcolepsy in the general population is approximately 4-5 per 10,000, or 0.047% [16]. Although its prevalence in MS patients is still not clearly known, in their systematic review, Marrieve et al. [14] reported the prevalence of narcolepsy in MS patients as varying between 0-1.6%. In the current study, a type 2 diagnosis was made because of a medical condition in 2 (4.88%) patients.

Our study has some limitations. The low number of cases and the use of single-center data may impede the generalizability of the results.

Conclusion

It is necessary for every clinician treating MS and its components to correctly diagnose and treat fatigue, excessive daytime sleepiness, and other sleep disorders, which increase the disability of disease. When the high prevalence of these disorders and their multifactorial nature are taken into consideration, however reliable subjective scales are, the timing of referral of these types of patients to a sleep specialist and the implementation of objective tests become more important.

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