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SLEEP DISORDERS IN A SAMPLE OF EGYPTIAN PATIENTS WITH MULTIPLE SCLEROSIS

(CLINICAL AND POLYSOMNOGRAPHIC STUDY)

By

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ABSTRACT

Background: Sleep disturbances are common symptoms of multiple sclerosis (MS). Patients with multiple sclerosis (MS) often have unrecognized sleep disorders at higher frequency than the general population such as insomnia, sleep disordered breathing, circadian rhythm disorder, restless legs syndrome (RLS), narcolepsy, and rapid eye movement (REM) sleep behavior disorder.

Objective: To assess different types of sleep disorders in patients with multiple sclerosis in order to ensure early diagnosis and adequate treatment of such patients.

Patients and Methods: All patients with clinically confirmed MS were included in the current study from the MS unit of Neurology Department, Al-Azhar University Hospitals, during the period from October, 2018 to October, 2020. Those patients were furtherly assorted based on McDonald's Criteria, 2017.

Results: In the present study, 44 patients with confirmed diagnosis of multiple sclerosis were enrolled. Thirty one (70.45%) of the MS patients were classified as poor sleepers. They had decreased sleep efficiency, increased sleep latency, increased periodic limb movement (PLM) index, respiratory disturbance index (RDI), decreased REM sleep percentages, and decreased depth of sleep.

Conclusion: Sleep disorders are frequent in MS patients, prompt recognition and treatment, which is tailored toward the individual's clinical issues and potential underlying causes, are necessary to optimize functional status and quality-of-life.

Keywords: Multiple sclerosis, Polysomnography, Sleep disturbances.

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune disease which is the main cause of non-traumatic disability among young and middle-aged adults *(Rowitch et al., 2019).* Sleep disturbances are common symptoms of multiple sclerosis (MS), and their prevalence ranges from 47 to 62% *(Sakkas et al., 2019).* Patients with MS report Sleep disorders such as insomnia, sleep disordered breathing, circadian rhythm disorder, restless legs syndrome (RLS), narcolepsy and rapid eye movement (REM) sleep behavior disorder *(Kiziria et al., 2013).*

Sleep disturbances have been associated with increased risk of mortality, cardiac disease, obesity and diabetes and can contribute to depression, pain and fatigue symptoms that are

commonly seen in MS patients, and that are often disabling *(Michael et al., 2011).*

Causes of poor sleep are multiple and may stem from specific sleep disorders, MS-related symptoms, adverse effects from disease-modifying agents or to the effect of MS lesions located in specific CNS regions involved in sleep regulation and sleep quality. The most common causes of secondary sleep disorders in MS patients are neurogenic bladder dysfunction, depression, spasticity or spasms, pain and medication *(Lunde et al., 2012).*

Chronic insomnia disorder is common in the general population, with most studies reporting higher lifetime prevalence in women, and individuals with chronic medical disorders. Up to 40 % of MS patients may be at risk of having chronic insomnia disorder *(Giuseppe et al., 2016).*

The incidence of periodic limb movements (PLMS) and RLS is higher in patients with MS than in the general population, conservative estimates report RLS affecting about 10% of the general population with some studies showing a three to five times higher prevalence in patients with MS *(Marianna et al., 2014).*

Several risk factors in the MS cases were noted to be significant predictors for the presence of RLS including older age, leg jerks before sleep onset and primary progressive MS. It was reported that cervical cord affection correlates with RLS among patients with MS. Patients with MS and PLMS had higher magnetic resonance imaging lesion loads in infratentorial regions, compared with patients with MS without PLMS *(Zuzana et al., 2015).*

The present work aimed to assess different types of sleep disorders in patients with multiple sclerosis in order to ensure early diagnosis and adequate treatment of such patients.

SUBJECTS AND METHODS

This was a cross-sectional study which was carried out at the Multiple Sclerosis units of Al-Azhar Neurology Department at Al-Azhar University Hospitals during the period from October, 2018 to October, 2020.

The current investigation was executed based on the recommendations of the ethical committee, Faculty of Medicine for boys, Al-Azhar University, Cairo, Egypt. All clinical interventions were illustrated obviously to all participants prior to study processing. A written informed consent after a clear explanation of all study steps was obtained from every patient.

Inclusion criteria: All patients with clinically confirmed MS were included in the current study. Those patients were furtherly assorted based on McDonald's Criteria, 2017.

Exclusion criteria:

1. Patients with systemic disease that could affect sleep as: hepatic failure, renal failure, chest diseases, etc.
2. Patients received corticosteroid drugs in the previous 3 months.
3. Patients with psychiatric disorders that could affect sleep as: depression or bipolar disorder…..etc.

All patients were subjected to:

i. Full medical and neurological history and examination.

ii. Expanded Disability Status Scale (EDSS) for assessment of disease severity.

iii. Sleep scales:

-Epworth sleepiness scale for assessment of daytime sleepiness.

-Pittsburgh sleep scale for assessment of sleep quality.

iv. Polysomnography.

Imaging: All patients were radiologically evaluated using MRI on brain and spine using 1.5 Tesla scanners and when needed intravenous contrast (Gadolinium) has been used to highlighten the lesions. This test can illustrate the nature and the distribution of the lesions for differential diagnosis.

MRI Brain:

- Axial T1 weighted image without contrast (and post contrast when needed).
- Axial T2 weighted image.
- Axial FLAIR sequence for lesion detection and lesion load estimation.
- Sagittal FLAIR sequence for better evaluation of lesion location in reference to the lateral ventricle.

MRI Spine:

- Sagittal T1 without contrast (and post contrast when needed).
- Sagittal T2 weighted image.
- Axial T2 weighted image.

Statistical Analysis:

Data were collected, revised coded and entered to the statistical package for the social sciences (SPSS), version 10. Qualitative data were presented as number and percentages, while quantitative data were presented as mean, and standard deviations. The comparisons between two groups with qualitative data were done using Chi-square test. The comparison between two groups regarding quantitative data with parametric distribution was done using Independent t-test and Mann-Whitney U test. P-value was considered significant when P was < 0.05.

RESULTS

The present study included 44 definite multiple sclerosis patients recruited from Al-Azhar University Hospitals from October 2018 to October 2020. The mean age of patients was 31.27 ± 8.49years. The patients were sixteen males and twenty-eight females. The mean age at onset of MS was 26.55±8.22 years. Twenty-two (50 %) of MS patients had RRMS, while eighteen patients (40.9%) had SPMS, four patients (9.1 %) had primary progressive (PPMS).

Twenty-six (59.1%) of patients had pain and reported presence of leg spasm in sixteen patients (36.36%). Twenty-four (54.55%) of patients had mild disability, twelve had moderate (27.27%) clinical disability, while eight (18.2%) had severe disability.

Thirty (68.2 %) of patients had fatigue, while fourteen (31.82 %) were none fatigued. Eight patients (18.2 %) had narcoleptic symptoms **(Table 1)**.

Table (1): Clinical presentation among patients of the studied group

ITEM	No.	%
Disease duration	5.59±2.98	46.1%
Age of onset	26.55 ± 8.22	
Mild disability	24	54.55
Moderate disability	12	27.27
Severe disability	8	18.2%
Narcolepsy	8	18.2%
Fatigue	30	68.2%
Pain and parathesia	26	59.1%
Nocturia	26	59.1%
RRMS	22	50%
SPMS	18	40.9
PPMS	4	9.1

Sleep parameters in patients with MS Vs controls **(Table 2)** MS patients had highly significantly delayed sleep onset latency, reduced sleep efficiency (P=0.001). Regarding sleep architectures, MS patients had significant decrease in sleep stage N3 (P<0.05) and significant increase in RDI and PLM index (P = 0.008 and P=0.002 respectively) compared to control group. REM sleep analysis including REM%, REM latency, and REM periods revealed decrease in the percentage of REM sleep (P=0.001) in MS patients compared to control group **(Table 2)**.

Table (2): Clinical and sleep parameters in MS patient VS control

Parameter \ Groups		Control group No = 15	Patients group No = 44	P-value
Age (years)	**Mean ± SD**	28.26 + 6.52	31.27 ± 8.49	0.164
Sex(F/M)	**No.**	9/6	28/16	0.110
Epworth sleepiness scale	**Mean ± SD**	2.44 ± 1.78	9.74 ± 7.13	**0.000**
Pittsburg scale	**Mean ± SD**	3.68 ± 1.95	10.46 ± 5.34	**0.000**
Sleep latency	**Mean ± SD**	10.73±2.47	38.45±23.65	**0.000**
Sleep efficiency %	**Mean ± SD**	89.76 ± 4.43	66.08 ± 21.54	**0.001**
N1%	**Mean ± SD**	5.24 ± 2.68	11.02 ± 6.06	**0.001**
N2%	**Mean ± SD**	50.24 ± 3.26	55.46 ± 5.63	**0.002**
N3%	**Mean ± SD**	20.00 ± 1.44	17.32 ± 6.02	**0.001**
REM Latency (Min)	**Mean ± SD**	67.48 ± 6.97	59.94 ± 41.20	0.063
REM%	**Mean ± SD**	24.72 ± 3.62	16.06 ± 6.42	**0.001**
PLMI	**Mean ± SD**	3.79±1.18	10.29±7.35	**0.002**
RDI	**Mean ± SD**	0.40 ± 0.50	7.64 ± 8.62	**0.008**

About half of MS patients (54.55%) complained of difficulty in initiation of sleep (initial insomnia), while (middle insomnia) were found in twenty patients (45.45%), sixteen patients (36.36%) complained of early morning awakening (terminal insomnia), twenty six (59.1%) complained of hypersomnolence, and sixteen patients (36.36%) had repeated abnormal leg movements during night **(Table 3)**.

Table (3): Prevalence of sleep complaints in patients

Variable	No.	Percent
Insomnia	31	70.45%
Initial insomnia	24	54.55%
Middle insomna	20	45.45%
Late insomnia	16	36.36%
EDTS	26	59.1%
Apnea $_{+VE}$	10	22.73
PLM +ve	16	36.36%

There was a statistically significant difference between patients with and without different sleep complaint as regard sleep efficiency which is significantly lower in patients with sleep complaints and RDI which was significantly higher in patients with sleep complaints **(Table 4)**.

Table (4): Comparison between patients with sleep complaints and patients without as regard sleep parameters

Complaint / Parameters	+ve sleep complaint(n=36) Mean ± SD	-ve sleep complaint(n=8) Mean ± SD	P-value
Sleep latency	26.62 ± 15.37	24.52 ± 21.37	0.583
Sleep efficiency %	68.67 ± 7.17	82.76 ± 27.35	**0.03**
N1%	10.29 ± 4.36	11.55 ± 7.06	0.759
N2%	55.52 ± 5.85	55.41 ± 5.57	0.720
N3%	17.38 ± 5.75	17.28 ± 6.31	0.380
REM latency (Min)	58.76 ± 43.85	60.79 ± 39.94	0.583
REM%	16.81 ± 5.71	15.52 ± 6.94	0.061
PLMI	6.67 ± 6.89	4.52 ± 4.78	0.795
RDI	8.38 ± 8.03	6.10 ± 9.12	**0.01**

We found that 10 patients have apnea (22.73%), i.e. they have respiratory desaturation index (RDI) above five mainly due to hypopnea. They included 6 patients had mild apnea (60%) (RDI >5), and 4 patients had moderate apnea, i.e. RDI>15 with a percentage of 40%. Patients with apnea tended to have reduced deep sleep percentage (N3), and higher N1 (shallow sleep) **(Table 5)**.

Table (5): Comparison between group with apnea and group without apnea as regard sleep parameter

Apnea / Parameters	Apnea -ve No. = 34	Apnea +ve No. = 10	P-value
Sleep latency	25.41 ± 19.61	25.39 ± 18.23	0.75
Sleep efficiency%	69.31 ± 23.97	60.33 ± 15.35	0.51
N1%	9.25 ± 5.91	14.17 ± 5.07	**0.02**
N2%	54.91 ± 5.49	56.44 ± 5.88	0.47
N3%	19.00 ± 5.51	14.33 ± 5.85	**0.00**
REM latency (Min)	66.75 ± 39.28	47.83 ± 42.84	0.08
REM%	16.63 ± 6.02	15.06 ± 7.14	0.21

16 of the patients were found to have significant, PLMI > 15, and they has associated sleep complaint but the difference was not statistically significant **(Table 6)**.

Table (6): Comparison between group with PLMD +VE and PLMD-VE as regard polysomnographic data

PLMI / Parameters	Negative PLMI No. = 28	Positive PLMI No. = 16	P-value
Sleep latency	25.25 ± 19.26	26.50 ± 17.94	0.329
Sleep efficiency%	65.20 ± 22.73	72.50 ± 6.89	0.087
N1%	11.18 ± 6.36	9.83 ± 3.19	0.893
N2%	55.36 ± 5.29	56.17 ± 8.28	0.843
N3%	17.64 ± 6.07	15.00 ± 5.51	0.073
REM latency (Min)	59.41 ± 40.83	63.83 ± 47.68	0.686
REM%	15.66 ± 6.14	19.00 ± 8.22	0.194
RDI	7.39 ± 8.86	9.50 ± 7.01	0.134

There were 26 patients (59.1%) which has subjective excessive daytime sleepiness (EDTS) assessed by ESS (Epworth sleepiness scale), sleep latency shorter in the EDTS +ve group and sleep efficiency is lower. N1, N2 sleep stage higher in the +ve group, and N3 is reduced, RDI is statistically significant higher and REM latency is shorter in the EDTS +VE group **(Table 7)**.

Table (7): Comparison between patients with EDTS +ve and EDTS –ve as regard polysomnographic data

EDTS / Parameters	EDTS +ve No. = 26	EDTS –ve No. = 18	P-value
Sleep latency	21.29 ± 14.03	28.38 ± 21.57	0.503
Sleep efficiency%	61.10 ± 18.04	69.69 ± 23.40	0.219
N1%	12.62 ± 5.63	9.86 ± 6.19	0.065
N2%	56.86 ± 5.92	55.90 ± 5.47	0.376
N3%	16.52 ± 6.75	17.90 ± 5.48	0.236
REM latency (Min)	37.38 ± 34.67	76.28 ± 38.12	**0.001**
REM%	16.00 ± 6.72	16.10 ± 6.31	0.839
PLMI	7.14 ± 6.52	4.17 ± 4.95	0.178
RDI	12.95 ± 10.31	3.79 ± 4.20	**0.000**

Sleep parameters in RRMS Vs CPMS (Table 8):

Because the small number of PPMS cases, the PPMS and SPMS were grouped as chronic progressive MS (CPMS). No significant changes in sleep parameters between two groups apart from highly significant increase in RDI ($P<0.01$) in CPMS compared to RRMS **(Table 8)**.

Table (8): Comparison between RRMS patients and CPMS

Variables \ Groups		CPMS No = 22	RRMS No = 22	P-value
Sleep latency	**Mean ± SD**	28.10 ± 19.09	21.35 ± 18.42	0.127
Sleep efficiency%	**Mean ± SD**	65.23 ± 18.84	67.35 ± 25.54	0.869
N1%	**Mean ± SD**	12.23 ± 5.82	9.20 ± 6.09	0.069
N2%	**Mean ± SD**	56.17 ± 5.58	54.40 ± 5.66	0.074
N3%	**Mean ± SD**	16.27 ± 5.92	18.90 ± 5.96	0.082
REM latency(Min)	**Mean ± SD**	58.37 ± 40.94	62.30 ± 42.52	0.589
REM%	**Mean ± SD**	15.67 ± 6.77	16.65 ± 5.98	0.385
PLMI	**Mean ± SD**	6.37 ± 6.70	4.00 ± 3.81	0.372
RDI	**Mean ± SD**	8.50±7.21	0.92±1.02	**<0.01**

Age of patients and duration of illness did not correlate with sleep profile in our patients (Table 9).

Table (9): Comparison between Patients with and without sleep complaints as regard age, sex and duration of disease

Variables \ Sleep complaint	+ve sleep complaint No 36	-ve sleep complaint No 8	P-value
Age	22.10 ± 8.96	45.07 ± 9.90	0.356
Female	19	6	0.251
Male	17	2	
Duration	7.67 ± 3.40	8.10 ± 4.50	0.915

DISCUSSION

Our study revealed that there are quiet indicatives of significant sleep alternations in patients with multiple sclerosis. They are often associated with disability, pain, leading to impairment of quality of life; the high prevalence of sleep complaint goes with what had been reported by previous investigators *(Ana and Manuel, 2011).*

Motor and sensory symptoms such as leg spasms and paresthesias are common symptoms in MS and which was found in patients in our study.

Insomnia was frequent in our MS patients with a prevalence rating higher than 70%.

Initial insomnia and middle insomnia were the most frequent types of insomnia followed late insomnia. Excessive sleepiness during the day (hypersomnia) was reported in 59.1 % and abnormal leg movement during sleep in 36.36%.

Frequent nocturnal micturation was in 59.1% of patients and sleep-disordered breathing together with PLM disorders that causes transient arousal that may follow, coincide with or even directly precede the limb movement producing fragmentation of nocturnal sleep. Similarly, *Veauthier (2015)* have reported that MS patients had higher rates of insomnia and hypersomnia than healthy controls. They reported different reasons for different types of insomnia in their

study, with anxiety and pain being the commonest causes of initial insomnia and nocturia the commonest cause of middle insomnia.

Regarding sleep profile assessment by polysomnography, significant affection of sleep continuity and poor sleep stability have been observed in MS patients compared to control group as shown by poor sleep efficiency, increased sleep latency, increased number of arousals as well as increased number of awaking after sleep onset. *Nociti et al. (2017)* reported similar findings.

Regarding sleep architectures; our study revealed that MS patients were poor sleep than healthy control. The presence of paraesthesias, nocturia, PLM disorders, and sleep-disordered breathing were associated with decreased depth of sleep *(Tiffany and Eilis, 2016)*. Although, in a study by *Sivaci et al. (2018)* no significant changes in sleep stages were reported compared to the control group, the presence of higher rates of pain, nocturia, PLM disorders and sleep disordered breathing in our study than the previous study could explain the difference.

RDI was significantly higher in MS patients compared to control group. Six patients had mild sleep apnea and hypopnea and four patients had moderate sleep apnea and hypopnea.

The total PLM index was significantly increased in MS patients. Its prevalence in our patients by PSG was 36.36%. PLMD has a potential to disrupt sleep by causing frequent arousals resulting in non-refreshing sleep, day time fatigue, and hypersomnia.

Bjorvatn et al. (2012) reported that PLMD is a common cause of poor sleep.

Also, *Sivaci et al. (2018)* reported that PLM symptoms are very common in MS patients (36.58%), higher disability and cervical cord damage represent a significant risk factor for RLS in MS patients in their study. RLS and PLMD are closely linked sleep movement disorders *(Brass et al., 2014)*. The majority of patients with RLS also have PLMD when a sleep. Similarly, *Nociti et al. (2017)* performed polysomnographic studies in 25 patients with multiple sclerosis and in an age and sex matched control group. The prevalence of PLM was significantly higher in the multiple sclerosis groups.

There was a significant decrease in the Percentage of REM sleep and highly significant decrease in REM latency in MS patients compared to control group.

Our study revealed 18.2% with narcolepsy diagnosed by narcoleptic symptoms. Narcoleptic symptoms have long been recognized in patient with MS. A genetic link between narcolepsy and MS has also been suspected for many years *(Lunde et al., 2012)*.

Hypothalamic MS plaques have been shown to cause hypersomnia and narcoleptic symptoms in the context of low CSF hypocretin-Level *(Kiziria et al., 2013)*.

Our study revealed 22.73 % with apnea. This was not consisting with the results of *Braley et al. (2014)* who investigated 30 MS patients and 30 healthy controls (HC) by PSG using an AHI-cut-off of 5/h and they found OSA in 80 % of MS patients and 63 % of controls.

The main problem of the variability of these results is the use of different scoring instruments, classification systems, and cutoff values, especially different AHI cutoffs *(Giuseppe et al., 2016).*

Our study revealed no significant difference in sleep parameters in RRMS compared to CPMS type except for increased RDI in CPMS type than remitting type *Kiziria et al. (2013)* reported similar results.

Age of patients, gender and duration of illness did not correlate with sleep profile in our patients, which is similar to finding in general populations *(Giuseppe et al., 2016).*

Our study revealed twenty six patients with excessive day time sleepiness (EDTS) as measured by ESS score, sleep latency shorter in the EDTS +ve group and sleep efficiency is lower. N1, N2 sleep stage higher in the +ve group, and N3 is reduced, RDI is statistically significant higher and REM latency is shorter in the EDTS +VE group.

Recurrent episodes of apnea hypopnea in some of our patients may lead to nocturnal hypoxemia and day time somnolence. Also, PLMD causing frequent arousals resulting in non-refreshing sleep and day time somnolence.

CONCLUSION

Sleep disturbances are very frequent in MS patients and can interact with pain and fatigue. Appropriate treatment of sleep disorders may improve quality of life which is usually impaired in MS patients with sleep disorders.

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إضطرابات النوم فى عينة من المرضى المصريين المصابين بالتصلب المتناثر (دراسة إكلينيكية ومعملية)

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خلفيـــة البحـــث: إضـــطرابات النـــوم هـــي أعـــراض شـــائعة لمرضـــي التصـــلب المتعـــدد. ويعـــاني مرضـــي التصـــلب المتعـــدد مـــن إضـــطرابات النـــوم بنســـبة أعلـــي مـــن العامـــة مثـــل الأرق و إضـــطراب التـــنفس اثنـــاء النـــوم وإضـــطراب إيقـــاع الســـاعة البيولوجيـــة ومتلازمة تململ الساقين.

الهـــدف مـــن البحـــث: تقيـــيم إضـــطرابات النـــوم لـــدي مرضـــي التصـــلب المتعـــدد مـــن اجـــل من أجل ضمان التشخيص المبكر والعلاج المناسب لهؤلاء المرضى.

المرضـــى وطـــرق البحـــث: تـــم تضـــمين جميـــع المرضـــى مـــن وحـــدة التصـــلب العصـــبي المتعـــدد بقســـم الأمـــراض العصـــبية بمستشـــفيات جامعـــة الأزهـــر الـــذين يعـــانون مـــن مـــرض التصـــلب العصـــبي المتعـــدد المؤكـــد ســـريريا فـــي الدراســـة الحاليـــة. وقـــد تـــم تصنيف هؤلاء المرضى إستنادًا إلى معايير ماكدونالدز 2017.

نتـــائج البحـــث: تـــم تســـجيل 44 مريضـــا مـــن مـــرض التصـــلب المتعـــدد، و تـــم تصـــنيف أكثـــر مـــن نصـــف مرضـــي التصـــلب المتعـــدد علـــي أنهـــم يعـــانون مـــن الأرق، وقلـــة كفـــاءة النوم، وإنخفاض نسبة النوم المصحوب بحركة العين السريعة.

الاســـتنتاج: إضـــطرابات النـــوم شـــائعة عنـــد مرضـــي التصـــلب المتعـــدد، ونظـــرا للتـــأثير المحتمـــل لهـــذه الحـــالات علـــي النتـــائج الصـــحية والوظيفيـــة لهـــؤلاء المرضـــي فـــان التعـــرف الفـــوري والعـــلاج المصـــمم خصيصـــا لهـــذه المشـــكلات ضـــروريان لتحســـين الحالة الصحية لمرضي التصلب المتعدد.

الكلمات الدالة: التصلب المتعدد، معمل النوم، إضطرابات النوم.