DOI: 10.4274/gulhane.galenos.2021.1471
Gulhane Med J 2021;63:141-6

Sleep disorders in multiple sclerosis

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Date submitted:
21.10.2020
Date accepted:
01.01.2021
Online publication date:
15.06.2021

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Keywords: Multiple sclerosis, sleep disorders, fatigue, depression, pain

ABSTRACT

Aims: Previous studies have reported that sleep disorders are frequently seen in patients with multiple sclerosis (MS). In this study, we aimed to investigate the frequency and related factors of sleep disorders in these patients.

Methods: In this cross-sectional study, sleep disorder was assessed using the Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS). Fatigue, generalized pain, anxiety, depression symptoms, restless legs syndrome (RLS) and urinary dysfunction were evaluated using the Fatigue Severity Scale (FSS), visual analogue scale (VAS), Hospital Anxiety and Depression Scale (HAD), and RLS Rating Scale and Scales for Outcomes in Parkinson's disease-Autonomic. Logistic regression analysis was used to assess the potential associations between a sleep disorder diagnosis and the investigated conditions.

Results: Fifty-six patients [age (mean±standard deviation): 36.2±2.8 years; female: 30.4%] were included. Fifty percent of the patients scored 5 or more according to PSQI. ESS, HADS, FSS and VAS scores of patients with sleep disorder were significantly higher than those of patients with no sleep disorder ($p=0.002$, $p=0.001$, $p<0.001$, and $p<0.001$, respectively). Logistic regression analysis showed significant associations between sleep disorder and fatigue [Odds ratio (OR): 6.54 (95% confidence interval (CI): 1.08-39.57, $p=0.041$)], depression [OR: 9.82 (95% CI: 1.47-65.6), $p=0.018$], and generalized pain disorders [OR: 1.79 (95% CI: 1.23-2.3), $p=0.002$].

Conclusions: Our results show that half of the patients with MS suffer from sleep disorders. Sleep disorders in this group are associated with fatigue, depression, daytime sleepiness, common body pain, and immunomodulatory treatment.

Introduction

Multiple sclerosis (MS) is an autoimmune disease characterized by demyelination and axonal loss in the central nervous system (CNS). The prevalence is 120/100.000 (1). Sleep disorders are frequently seen in patients with MS. It is known that half of the patients have sleep disorders (2,3). The frequent sleep disorders in MS are insomnia, sleep apnea, restless leg syndrome (RLS), narcolepsy, circadian rhythm disorders, and rapid eye movement sleep behavior disorder. These disorders can result in daytime sleepiness, fatigue, depression, and pain (4,5). Factors related to sleep disorders in MS patients have been investigated in previous studies. Demographic characteristics such as age, gender, and socioeconomic status and other factors including MS subtype, disease duration, severity of disability, treatment, especially immunomodulatory drugs, and disease-related factors such as urinary incontinence, body pain, depression, anxiety disorder, and night cramps have been reported to cause sleep disorders (6-8).

Unfortunately, sleep disorders in MS are not sufficiently focused in clinical practice, although they are commonly seen. It is very important to determine the sleep disorders in patients with MS and to arrange their treatments in terms of improving the quality of life of the patients.

Our aim in this study was to investigate the frequency of sleep disorders in patients with MS, and to explore the potential association between a sleep disorder diagnosis and common clinical conditions in these patients.

Methods

Patients

This study was conducted in Ankara University, Department of Neurology between September 2008 and January 2010. Fifty-eight patients who fulfilled the criteria for MS according to the revised McDonald diagnostic criteria were included in this cross-sectional observational study (9). Demographic and disease specific data including disease duration (based on symptom onset), attack frequency, MS subtype (relapsing remitting, primary progressive, secondary progressive) and medications used for MS prophylaxis [interferon-beta (IFN-β) 1a-1b, glatiramer acetate, mitoxantrone] were collected. All patients included in the study were in remission period. None of the patients received steroid treatment in the last three months. Patients with diseases that could be confused with MS, including systemic lupus erythematosus and CNS vasculitis, and patients with systemic diseases that might cause sleep disturbance (psychiatric disorders such as depression and anxiety disorders, prostate diseases such as benign prostatic hyperplasia) were excluded.

The patients were examined by the same neurologist and severity of disability was assessed by the Kurtzke (10) Expanded Disability Status Scale (EDSS). This scale is applied to eight functional area of the CNS, is graded by 0 to 10. 0 represents normal situation, 10 represents death by MS. The lower score predicts the less disability of the patient.

Clinical Assessments

The patients were interviewed face to face and the information was taken from them. Sleep disorders were evaluated using the Turkish version of the Pittsburgh Sleep Quality Index (PSQI) (11). PSQI includes 24 questions to assess the frequency and severity of information about sleep duration, sleep latency and special problems related to sleep, 19 questions are self-assessment questions, 5 is replied by the spouse of roommate of the patient, used only for clinical information and does not count towards scoring. Based on the previously recommended cut-off value (11), the patients included in the study were categorized into two groups (PSQI score ≥5 “sleep disorder”, and PSQI score <5 “no sleep disorder”).

Daytime sleepiness and sleep status were assessed by using the Epworth Sleepiness Scale (12). In this scale, people are asked about the likelihood of falling asleep during the daily activities and they are required to rate it between 0 and 3 points. The scale has 8 items. The evaluation is done as follows: 0-5: Normal, 6-10: Normal but excessive daytime sleepiness, 10-12: Excessive but mild daytime sleepiness, 12-15: Excessive but moderate daytime sleepiness, 16-24: Excessive daytime sleepiness.

To assess the level of fatigue of the patients, the Turkish version of Fatigue Severity Scale (FSS) was used (13). This scale assesses level of fatigue with 9 questions. All questions are replied and scored as 1 (I don’t agree at all) - 7 (I totally agree). FSS score is the average value of these nine questions. Higher scores indicate increased severity of fatigue.

The items related to urinary dysfunction (8-13) of the Scales for Outcomes in Parkinson’s disease-Autonomic (SCOPA-AUT) scale, which was mainly developed for Parkinson’s patients, were used to question urinary functionality (14). Relevant questions in this scale are scored as “0-Never, 1-Sometimes, 2-Regularly, 3-Recently, 4-catheter is used”. High score indicates severe urinary dysfunction.

The anxiety and depressive status of the patients were evaluated with the Hospital Anxiety and Depression Scale (HADS), which questions the life events of the last few days. HADS is a scale prepared to screen anxiety and depression in people with physical disorders. The scale is a feedback scale and consists of 14 items, 7 of which investigate the symptoms of depression and 7 of anxiety. The patient is required to give an answer that expresses how he has been feeling, considering the last few days. Answers are scored in a four-point Likert scale and between 0 and 3. Depression and anxiety questions are scored separately; 8-10 points borderline, 11 points and above are considered abnormal (15).

The patients were examined in terms of RLS. The International RLS Study Group (IRLSSG) developed “Restless Legs Syndrome Rating Scale”, which has five-questions minimal diagnostic criteria based on the patient’s history and additional criteria supporting the diagnosis were determined (16). Supporting features are not necessary for diagnosis but are helpful in uncertain cases. Those meeting all RLS diagnostic criteria were evaluated as RLS (+).

The visual analog scale (VAS) was used to assess common body pain. The patients were asked to score according to the severity of pain, with 0 points if there was no pain and 10 points for the most severe pain.

All procedures were performed in accordance with the Declaration of Helsinki, an approval was received from the Research Ethics Committee of Medical Faculty Ankara University (protocol number: 135-3915, date: 29.07.2008), and an informed written consent was obtained from all participants or legal representatives.

Statistical Analysis

Descriptive and quantitative data are given as mean and standard deviation. Demographic data and the PSQI scores of the two groups were compared using the Student’s t-test (for continuous variables) or a chi-square test (for categorical variables). A logistic regression analysis was further performed to assess the association between sleep disorders and related

factors. The significance threshold was set to p<0.05. SPSS Statistics 15.0 Software Package (SPSS Ltd., Chicago, IL, US) was used for the analysis.

Results

Of the 58 patients recruited in the study, two patients were excluded due to missing PSQI scores. The remaining 56 patients [39 women (69.6%)] were divided into two groups: patients with PSQI score ≥5, "with sleep disorder", (n=28) and PSQI score <5, "no sleep disorder", (n=28). Age, gender, marital status, education level and occupational status, presence of additional diseases (diabetes mellitus, systemic Behçet's disease, lumbar disk hernia, urticaria, varicosis, allergy, etc.), MS duration and average attack number, EDSS scores, presence of RLS and urinary dysfunction of two groups were similar. (Table 1). The subtype of MS was relapsing remitting in 96.4% (n=54), primary progressive in 1.8% (n=1) and secondary progressive in 1.8% (n=1) of the patients. Due to the small number of groups except for the relapsing remitting MS subgroup, statistical evaluation was not done between these subgroups.

Twenty-four of the patients (42.9%) did not use any medication for MS prophylaxis. Thirty-two patients (57.1%) were receiving disease modifying therapy (DMT). The most commonly used DMT was IFN-β (n=25). Being under DMT was statistically higher in patients with sleep disorders (p=0.03).

ESS, HADS, FSS and VAS scores of patients with sleep disorder were significantly higher than those of patients with no sleep disorder diagnosis (p=0.002, p=0.001, p<0.001, and p<0.001, respectively).

Risk factors for sleep disorders in patients with MS were investigated by the logistic regression analysis. Gender, number of MS attacks, medication, FSS, anxiety and depression according to HADS, urinary dysfunction according to SCOPA-AUT test, and common body pains according to VAS were evaluated. Independent association was found between fatigue, depression, generalized body pain and sleep disorders (Table 2).

Discussion

In this study, half of the MS patients had sleep disorders. In patients with sleep disorders, the frequency of being under DMT, daytime sleepiness, anxiety, depression, fatigue, and common body pain were higher than in the patients without sleep disorders. In addition, fatigue, depression and common body pain were found to be independent variables for sleep disorders in MS.

Sleep disorders are higher in MS patients than in the healthy population. In several studies, it has been reported that 42-65% of patients with MS describe sleep disorders (17). In the review published by Čarnická et al. (18), it was stated that the

Table 2. The association between fatigue, depression, generalized body pain and sleep disorders

	OR (95% CI)	p value
Common body pain	1.79 (1.23-2.6)	0.002*
Fatigue	6.54 (1.08-39.57)	0.041*
Depression	9.82 (1.47-65.6)	0.018*

OR: Odds ratio, CI: Confidence interval
*p value <0.05.

Table 1. Demographic and disease-related characteristics of groups with and without sleep disorders

	No sleep disorder (n=28)	With sleep disorders (n=28)	p value
Age (year), mean (±SD)	37.3 (±2.97)	35.28 (±3.72)	0.53
Gender male n, (%)	11 (19.7)	6 (10.7)	0.14
Marital status (married) n, (%)	15 (26.8)	17 (30.3)	0.58
Education (15 year and above) n, (%)	11 (19.6)	8 (14.3)	0.44
Current working status n, (%)	17 (30.3)	16 (28.6)	0.78
Additional disease n, (%)	10 (55.5%)	8 (44.4%)	0.57
MS duration (year), mean (±SD)	8.2 (±6.6)	6.8 (±5.1)	0.5
MS attack number mean (±SD)	3.4 (±3.6)	4.9 (±5)	0.17
EDSS score mean (±SD)	2.1 (±1.7)	1.4 (±1.2)	0.34
DMT n, (%)	12 (37.5)	20 (62.5)	**0.03***
Prevalence of RLS n,(%)	0 (0)	2 (3.6)	0.5
ESS score mean (±SD)	2.3 (±2.7)	5.6 (±4.4)	**0.002***
HADS-A score mean (±SD)	5.5 (±3.7)	9.6 (±4.5)	**0.001***
HADS-D score mean (±SD)	4.3 (±3.5)	8.5 (±3.8)	**0.000***
FSS score mean (±SD)	3.3 (±1.8)	5.2 (±1.2)	**0.000***
SCOPA-AUT score mean (±SD)	5 (±5.9)	5.4 (±3.3)	0.12
VAS score mean (±SD)	2.7 (±2.6)	5.7 (±2.5)	**0.000***

SD: Standard deviation, MS: Multiple sclerosis, EDSS: Expanded Disability Status Scale, DMT: Disease modifying therapy RLS, Restless legs syndrome, ESS: Epworth Sleepiness Scale, HADS-A: Hospital Anxiety and Depression Scale Anxiety score, HADS-A: Hospital Anxiety and Depression Scale Depression score, FSS: Fatigue Severity Scale, SCOPA-AUT: Scales for Outcomes in Parkinson's disease-Autonomic, VAS: Visual analogue scale.
*p value <0.05.

prevalence of sleep disorders was between 25% and 54%. In a broad-based cross-sectional study conducted with 1,063 patients, 13.3% of MS patients had mild sleep problems, 21.5% had moderate sleep problems, and 30% had severe sleep problems (3). Similarly, in another study, 47.5% of 120 patients with definite MS were classified as patients with sleep problems, scoring 5 or more points from the PSQI (19). The most common sleep problems in MS patients can be listed as difficulty falling asleep, frequent and/or early awakenings, breathing-related sleep disorders such as insomnia, snoring and sleep apnea, and RLS (2,20). In our study, in accordance with the literature, sleep disorders were found in 50% of MS patients according to PSQI.

It is known that sleep disorders in MS patients are associated with disease severity, depression, and fatigue. Sleep problems are the most frequent variable affecting MS-related fatigue (21). There are other studies showing the relationship between fatigue and sleep disorders (22-24). While the prevalence of insomnia is much lower in MS without depression, those with insomnia are at a high risk for depression (25). Depression worsens sleep disorders and there is a strong relationship between the two (20,26). Similarly, patients with MS with high anxiety levels are more likely to have sleep disorders than those without anxiety (27,28). In addition, it has been shown that patients who describe sleep disorders have more daytime sleepiness and that the treatment of sleep disorders will improve fatigue and daytime sleepiness (29,30). The results of our study also showed that depression, anxiety, daytime sleepiness, and fatigue were more common in the group with sleep problems, in line with the previous studies.

It is thought that sleep disorders in MS can be affected by sociodemographic and disease characteristics such as disease severity, duration, gender, age, and occupation, and urinary dysfunction (3,19). Urinary dysfunction, especially nocturia, can cause sleep disturbance and indirectly MS-related fatigue (22). In our study, unlike previous studies, no significant relationship was found between age, gender, occupation, disease severity, disease duration, urinary dysfunction and sleep disorders.

The prevalence of RLS in MS patients is reported between 4.2% and 19% (31). In a study from Turkey, RLS in patients with MS was found to be 2.55 times more than in the healthy population, and there was a relationship with depression and fatigue (32). RLS in MS patients causes sleep disorders and increases fatigue (17,20). In our study, the frequency of RLS was 3.6%, and this rate is lower than in other studies. Again, unlike the literature, we could not find a significant relationship between sleep disturbance and RLS. The reason for this may be the low number of patients.

Sixty-six % of MS patients describe common body pain, and 25% of them indicate that their pain is severe. It has been found that body pain is associated with disease severity, depression, and sleep disturbance (33). Chronic pain increases insomnia and leads to the impairment of sleep quality (34,35). The results of our study also confirm this finding.

IFN-β therapy modulates proinflammatory cytokines, changes the sleep patterns and impairs sleep structure. Sleep quality disturbance may be observed, especially on days of IFN injection (36,37). In our study, the medications used by the patients were determined as IFN-β1a (40.6%), IFN-β1b (37.6%), glatiramer acetate (18.7%) and mitoxantrone (3.1%), and a significant relationship was found between the medications and sleep disorders.

This study has some limitations. Although the presence of sleep disorders in MS patients and related patients and disease characteristics were examined in detail, it was not compared with healthy individuals in terms of sleep disorders. The small number of our sample is another limitation.

Conclusion

In conclusion, sleep disorders are frequent in MS patients and are associated with fatigue, depression, daytime sleepiness, common body pain and immunomodulatory treatment. It may be possible to increase sleep quality and reduce other symptoms with appropriate treatment of sleep disorders. Therefore, sleep disorders should be questioned in clinical evaluations of MS patients. Prospective randomized controlled studies with larger samples are needed to determine the related factors affecting sleep disorders.

Ethics

Ethics Committee Approval: All procedures were performed in accordance with the Declaration of Helsinki, an approval was received from the Research Ethics Committee of Medical Faculty Ankara University (protocol number: 135-3915, date: 29.07.2008).

Informed Consent: Informed written consent was obtained from all participants or legal representatives.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Y.A.A., Design: Y.A.A., B.S.A.P., Data Collection or Processing: Y.A.A., Analysis or Interpretation: Y.A.A., B.S.A.P., Literature Search: B.S.A.P., Writing: YAA, B.S.A.P.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Coles A. Multiple sclerosis. Pract Neurol. 2009;9:118-126.
2. Tachibana N, Howard RS, Hirsch NP, Miller DH, Moseley IF, Fish D. Sleep problems in multiple sclerosis. Eur Neurol. 1994;34:320-323.

3. Bamer AM, Johnson KL, Amtmann D, Kraft GH. Prevalence of sleep problems in individuals with multiple sclerosis. Mult Scler. 2008;14:1127-1130.
4. Fleming WE, Pollak CP. Sleep disorders in multiple sclerosis. Semin Neurol. 2005;25:64-68.
5. Pokryszko-Dragan A, Bilinska M, Gruszka E, Biel L, Kaminska K, Konieczna K. Sleep disturbances in patients with multiple sclerosis. Neurol Sci. 2013;34:1291-1296.
6. Bamer AM, Johnson KL, Amtmann DA, Kraft GH. Beyond fatigue: Assessing variables associated with sleep problems and use of sleep medications in multiple sclerosis. Clin Epidemiol. 2010;2010:99-106.
7. Kaynak H, Altintaş A, Kaynak D, et al. Fatigue and sleep disturbance in multiple sclerosis. Eur J Neurol. 2006;13:1333-1339.
8. Moreira NC, Damasceno RS, Medeiros CA, et al. Restless leg syndrome, sleep quality and fatigue in multiple sclerosis patients. Braz J Med Biol Res. 2008;41:932-937.
9. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018:17;162-173.
10. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33:1444-1452.
11. Ağargün MY, Kara H, Anlar Ö. The Validity and reliability of the pittsburgh sleep quality index. Turkish Journal of Psychiatry. 1996;7:107-115.
12. Izci B, Ardic S, Firat H, Sahin A, Altinors M, Karacan I. Reliability and validity studies of the Turkish version of the Epworth Sleepiness Scale. Sleep Breath. 2008;12:161-168.
13. Gencay-Can A, Can SS. Validation of the Turkish version of the fatigue severity scale in patients with fibromyalgia. Rheumatol Int. 2012;32:27-31.
14. Visser M, Marinus J, Stiggelbout AM, Van Hilten JJ. Assessment of autonomic dysfunction in Parkinson's disease: the SCOPA-AUT. Mov Disord. 2004;19:1306-1312.
15. Aydemir Ö. Reliability and Validity of the Turkish version of hospital anxiety and depression scale. Turkish Journal of Psychiatry. 1997;8:280-287.
16. Allen RP, Picchietti DL, Garcia-Borreguero D, et al. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria--history, rationale, description, and significance. Sleep Med. 2014;15:860-873.
17. Sakkas GK, Giannaki CD, Karatzaferi C, Manconi M. Sleep abnormalities in multiple sclerosis. Curr Treat Options Neurol. 2019;31;21:4.
18. Čarnická Z, Kollár B, Šiarnik P, Krížová L, Klobučníková K, Turčáni P. Sleep disorders in patients with multiple sclerosis. J Clin Sleep Med. 2015;11:553-557.
19. Merlino G, Fratticci L, Lenchig C, et al. Prevalence of 'poor sleep' among patients with multiple sclerosis: an independent predictor of mental and physical status. Sleep Med. 2009;10:26-34.
20. Braley TJ. Overview: a framework for the discussion of sleep in multiple sclerosis. Curr Sleep Med Rep. 2017;3:263-271.
21. Strober LB, Arnett PA. An examination of four models predicting fatigue in multiple sclerosis. Arch Clin Neuropsychol. 2005;20:631-646.
22. Veauthier C, Paul F. Sleep disorders in multiple sclerosis and their relationship to fatigue. Sleep Med. 2014;15:5-14.
23. Veauthier C, Radbruch H, Gaede G, et al. Fatigue in multiple sclerosis is closely related to sleep disorders: a polysomnographic cross-sectional study. Mult Scler. 2011;17:613-622.
24. Kotterba S, Neusser T, Norenberg C, et al. Sleep quality, daytime sleepiness, fatigue, and quality of life in patients with multiple sclerosis treated with interferon beta-1b: results from a prospective 68 observational cohort study. BMC Neurol. 2018;18:123.
25. Alhazzani AA, Alshahrani A, Alqahtani M, et al. Insomnia among nondepressed multiple sclerosis patients: a cross-sectional study. Egypt J Neurol Psychiatr Neurosurg. 2018;54:17.
26. Clancy M, Drerup M, Sullivan AB. Outcomes of cognitive-behavioral treatment for insomnia on insomnia, depression, and fatigue for individuals with multiple sclerosis: a case series. Int J MS Care. 2015;17:261-267.
27. Garland SN, Scurrey SRM, Ploughman M, Health L, Aging with MSCC. Factors associated with poor sleep in older adults with multiple sclerosis. Int J Behav Med. 2017;24:937-945.
28. Bruce JM, Arnett P. Clinical correlates of generalized worry in multiple sclerosis. J Clin Exp Neuropsychol. 2009;31:698-705.
29. Côté I, Trojan DA, Kaminska M, et al. Impact of sleep disorder treatment on fatigue in multiple sclerosis. Clinical Trial Mult Scler. 2013;19:480-489.
30. Saunders J, Whitham R, Schaumann B. Sleep disturbance, fatigue and depression in multiple sclerosis. Neurology. 1991;41(Suppl 1):320.
31. Hogl B, Kiechl S, Willeit J, et al. Restless legs syndrome: a community-based study of prevalence, severity, and risk factors. Neurology. 2005;14;64:1920-1924.
32. Aydar G, Kurt S, Karaer Unaldi H, Erkorkmaz U. Restless legs syndrome in multiple sclerosis. Eur Neurol. 2011;65:302-306.
33. Ehde DM, Osborne TL, Hanley MA, Jensen MP, Kraft GH. The scope and nature of pain in persons with multiple sclerosis. Mult Scler. 2006;12:629-638.

34. Amtmann D, Askew RL, Kim J, et al. Pain affects depression through anxiety, fatigue, and sleep in multiple sclerosis. Rehabil Psychol. 2015;60:81-90.

35. Neau JP, Paquereau J, Auche V, et al. Sleep disorders and multiple sclerosis: a clinical and polysomnography study. Eur Neurol. 2012;68:8-15.

36. Patel SR, Zhu X, Storfer-Isser A, et al. Sleep duration and biomarkers of inflammation. Sleep. 2009;32:200-204.

37. Rocchi C, Pulcini A, Vesprini C, et al. Sleep in multiple sclerosis patients treated with interferon beta: an actigraphic study. Neurol Res. 2020;42:744-748.