Acta Clin Croat 2022; 61:599-604
doi: 10.20471/acc.2022.61.04.05

Original Scientific Paper



# DEPRESSION AND FATIGUE ARE DUE TO OBSTRUCTIVE SLEEP APNEA IN MULTIPLE SCLEROSIS

Mario Mihalj[1,3], Zrinka Janković[3], Eni Jadrijević Kodžoman[1], Gorana Veselica[1], Ana Katić Ćurković[1], Ana Repić Buličić[1] and Meri Matijaca[1,2,3]

[1]Department of Neurology, Split University Hospital Center, Split, Croatia;
[2]Department of Neurology, Division of Neuroimmunology, Split University Hospital Center, Split, Croatia;
[3]School of Medicine, University of Split, Split, Croatia

SUMMARY – To our knowledge, there is no study investigating whether fatigue and depression as the most commonly reported symptoms in multiple sclerosis (MS) and obstructive sleep apnea (OSA) patients have arisen from primary mechanisms of MS or from secondary associated conditions such as OSA in MS patients. The aim of our survey study was to determine whether depression and fatigue in MS patients were associated with clinical features of OSA or with MS. We conducted a self-administered survey using four validated questionnaires (STOP-BANG, Epworth Sleepiness Scale, Fatigue Severity Scale and The Center for Epidemiologic Studies Depression Scale-Revised) in 28 consecutive outpatients with proven MS. The prevalence of MS patients at an increased risk of OSA was 29% and age was positively correlated with this risk (p=0.019). None of the clinical features of MS patients (subtype, disability status, disease duration, modifying therapy, other medication) was correlated with depression and fatigue. On the contrary, excessive daytime sleepiness as a hallmark of OSA was significantly and positively associated with the level of depressive symptoms (p=0.004) and level of fatigue (p=0.015). Also, depression was significantly and positively correlated with the increased risk of OSA (p=0.015) and age of MS patients (p=0.016). Finally, a significant positive correlation was found between fatigue severity and level of depressive symptoms (p=0.003). OSA is a common disorder in MS patients. The clinical features and risk factors for OSA in MS patients are associated with the two most commonly reported symptoms of depression and fatigue, thus supporting the hypothesis that both symptoms are due to a secondary condition in MS.

Key words: *Depression; Fatigue; Multiple sclerosis; Obstructive sleep apnea*

## Introduction

The most commonly reported symptoms of fatigue and depression are features of many diseases, especially chronic ones such as multiple sclerosis (MS) and obstructive sleep apnea (OSA)[1,2]. More recent articles indicate a high prevalence of OSA in MS patients. It is unknown whether fatigue and depression are due to primary pathophysiological mechanisms that have an impact in the development of MS or to secondary mechanisms associated with other conditions such as sleep-disordered breathing (SDB), in this case OSA. Studies on the link between MS and the aforementioned symptoms are controversial and it remains a matter of debate[1-4].

To our knowledge, there is no study investigating whether fatigue and depression have arisen from primary MS mechanisms (immune system or sequels of the central nervous system damage, modifying therapy,

Correspondence to: *Mario Mihalj, MD, PhD,* Department of Neurology, Split University Hospital Center, School of Medicine, University of Split, Spinčićeva 1, HR-21000 Split, Croatia
E-mail: m.mihalj@inet.hr

Received June 4, 2020, accepted June 1, 2021

etc.) or from secondary associated conditions such as OSA in MS patients.

## Subjects and Methods

The study was approved by the appropriate institutional research ethics committee and was performed in accordance with ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. All procedures performed in studies involving human participants were in accordance with ethical standards of the institutional and/or national research committee (Bioethics Committee of the Split University Hospital Center, No. 2181-147-01/06/M.S.-18-2) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All participants in the study provided informed consent prior to inclusion in the study.

Following approval of the Bioethics Committee of the Split University Hospital Center and written consent of the patients, we conducted a self-administered survey that comprised of questions on elevated risk of OSA (STOP-BANG)[5], evaluation of excessive daytime sleepiness (Epworth Sleepiness Scale)[5], presence and severity of fatigue (Fatigue Severity Scale)[6], and symptoms of depression (CESD-R-20)[7]. The questionnaires were administered to 28 out of 46 recruited consecutive MS outpatients with clinically and paraclinically (magnetic resonance imaging, visually evoked potentials, somatosensory evoked potentials, motor evoked potentials (MEPs), and analysis of cerebrospinal fluid for oligoclonal banding and IgG-index) proven MS (McDonald criteria, 2017 Revision)[8] at the Split University Hospital Center during routine follow-up visits between April 13 and August 5, 2018. MS patients who had concomitant neurological disorders that could increase OSA risk and who partially completed the questionnaires were excluded from the survey.

The questionnaires were administered by physicians (ZJ, GV, AĆK, ARB) blinded to subject clinical history. Patients had opportunities to discuss questionnaire responses and symptoms with physicians.

Validated Croatian versions of the questionnaires were used in the survey. The STOP-BANG questionnaire consists of 8 (yes/no, score: 1/0) questions and measures that form the acronym (Snoring, Tired, Observed Apnea, Blood Pressure, BMI, Age, Neck circumference, Gender). STOP-Bang scores ≥3 suggest an increased risk of OSA[5].

The Epworth Sleepiness Scale (ESS) is an 8-item questionnaire that uses 4-point Likert scale items to quantify the likelihood of dozing in sedentary situations; scores ≥10 are consistent with excessive daytime sleepiness[5]. The Fatigue Severity Scale (FSS) is a 9-item questionnaire that uses a 7-point Likert scale to assess the severity of fatigue. Average FSS scores ≥36 are suggestive of fatigue[6].

The Center for Epidemiologic Studies Depression Scale-Revised (CESD-R-20) is a 20-item questionnaire that uses 4-point Likert scales (0-3) to quantify the presence and severity of depression symptoms; score ≥16 (0-60) indicates an increased risk of clinical depression[7].

The Expanded Disability Status Scale (EDSS) quantifies disability of MS patients in eight functional systems (pyramidal, cerebellar, etc.) by assigning a Functional System Score (6-point scale) in each of these and monitors changes in MS. EDSS score (0-10) up to 2.5 is considered mild disability, 3-6.5 moderate disability, ≥6.5 very severe disability, and 10 death due to MS[9]. EDSS was evaluated and filled out by an experienced neuroimmunologist (MM).

### *Statistics*

Categorical variables were expressed as numbers and proportions (%) and were examined using the $\chi^2$-test. Continuous variables were expressed as median and interquartile range (IQR). Scores on the questionnaire scales were analyzed as continuous scores and with scores dichotomized into mild and moderate groups according to the diagnostic cut-off value for EDSS questionnaire. Results were presented using nonparametric Mann-Whitney U test. Bivariate associations between continuous variables were examined with Spearman's rank correlation due to ordinal rank values on questionnaires. All tests were 2-tailed, and the level of significance was set at $p<0.05$. All analyses were conducted using the SPSS version 17 computer program (SPSS Inc., Chicago, IL, USA).

## Results

The study included 28 MS patients, 11 (39%) men and 17 (61%) women. There were no gender differences in disease duration ($z=0.945$; $p=0.345$), age ($z=0.283$; $p=0.777$) or disability (rho=0.365; $p=0.056$). The prevalence of MS patients with an increased risk of OSA

*Table 1. Demographic and clinical findings of multiple sclerosis (MS) patients*

| Variable | All MS patients | STOP-Bang | |
|---|---|---|---|
| | (n=28) | ≥3 (n=8 ) | <3 (n=20) |
| Age (years, median (IQR)) | 47 (39.5-52) | 51 (48.5-52.7) | 43 (38.2-49.5) |
| Female, n (%) | 17 (61%) | 3 (11%) | 14 (50%) |
| Male, n (%) | 11 (39%) | 5 (18%) | 6 (21%) |
| Body mass index (kg/m$^2$) | 25.4 (24.2-29.7) | 31.3 (30.7-32.9 | 25.1 (23.8-25.4) |
| Disease duration | 8.5 (6-12.8) | 9.5 (7-12.7) | 8.5 (4.2-13) |
| **MS subtype** | | | |
| Relapsing-remitting, n (%) | 21 (75%) | 5 (18%) | 16 (57%) |
| Secondary progressive, n (%) | 3 (11%) | - | 3 (11%) |
| Primary progressive, n (%) | 4 (14%) | 3 (11%) | 1 (3%) |
| **Disease modifying therapy** | | | |
| Beta-interferon | 8 (29%) | 5 (18%) | 3 (11%) |
| Glatiramer acetate | 11 (39%) | 3 (11%) | 8 (29%) |
| Natalizumab | 2 (7%) | - | 2 (7%) |
| Other | 7 (25%) | - | 7 (25%) |
| **EDSS** | | | |
| Overall | 2 (1-3.5) | | |
| Mild (0-2.5) | 16 (57%) | 6 (21%) | 10 (36%) |
| Moderate (3-6.5) | 12 (43%) | 3 (11%) | 9 (32%) |
| Severe ≥6.5* | - | - | - |

Data are presented as median (interquartile range, IQR) for age, body mass index, disease duration, overall disability measured by the EDSS and frequency; n (%) for other variables; *EDSS (Expanded Disability Scale Scores) ≥6.5 = those who are unable to walk without constant bilateral assistance (canes, crutches, braces).

was 29% and age was positively correlated with this risk (rho=0.442, p=0.019). We defined two dichotomous groups of MS patients according to cut-off value for EDSS scores, with mild (EDSS ≤2.5; n=16) and moderate (EDSS=3-6.5; n=12) disability (Table 1).

We found no association among the clinical variables of MS (subtype, disability, disease duration, modifying therapy, other medication, demographic features) and excessive daytime sleepiness as the most prominent symptom of OSA (z=0.255, p=0.798), or with the risk of OSA (z=0.186, p=0.853).

Interestingly, no significant correlations among the variables of MS, especially disability status and fatigue severity (z=0.394, p=0.693) and depression (z=0.255, p=0.798) were detected. Moreover, depression and fatigue as common MS symptoms were significantly and positively correlated with excessive daytime sleepiness as a hallmark of OSA (rho=0.529, p=0.004; and rho=0.456, p=0.015, respectively) (Fig. 1).

Also, depression was significantly and positively correlated with the increased risk of OSA (rho=0.453, p=0.015) and age of MS patients (rho=0.450, p=0.016) (Fig. 2).

Finally, a significant positive correlation was found between fatigue severity and level of depressive symptoms (rho=0.545, p=0.003) (Fig. 3).

## Discussion

Despite the fact that SDB is common in MS, as well as fatigue and depression in MS and OSA[1-4], this is the first study to investigate the relationship among fatigue and depression and clinical features of MS and

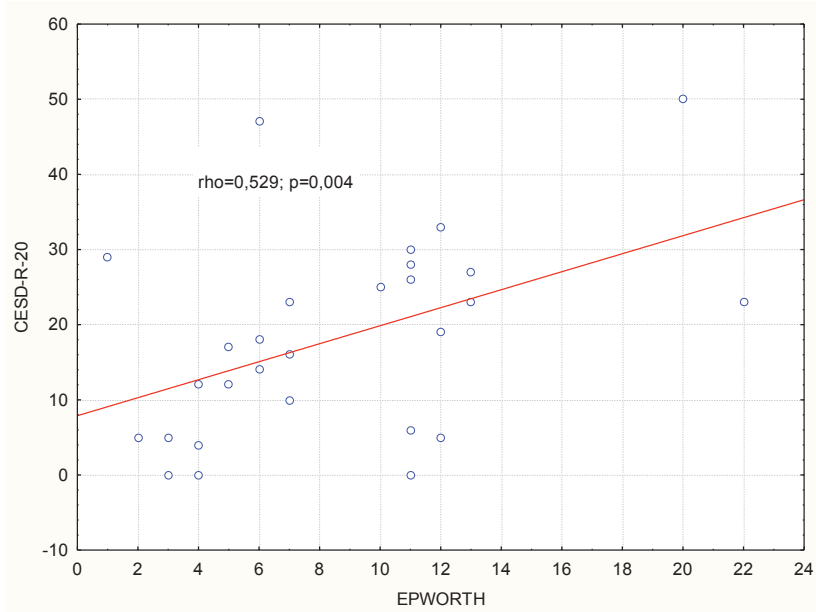


*Fig. 1. Relationship between severity of daytime sleepiness (ESS) and level of depressive symptoms (CESD-R-20) in multiple sclerosis patients (rho = Spearman's rank correlation coefficient, p-value).*

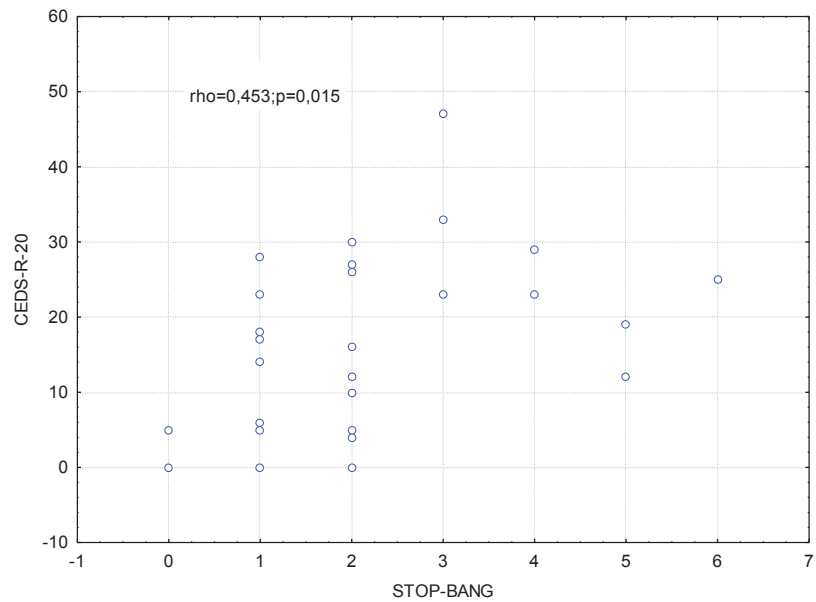


*Fig. 2. Relationship between the risk of OSA (STOP-BANG) and level of depressive symptoms (CESD-R-20) in multiple sclerosis patients (rho = Spearman's rank correlation coefficient, p-value).*

OSA in MS patients. It is unknown whether fatigue and depression are due to primary pathophysiological mechanisms that have an impact in the development of MS or to secondary mechanisms associated with other conditions such as SDB, in this case OSA[1-4].

In our study, the prevalence of OSA in MS was 29%, mainly in older males with greater body mass index, which is consistent with previously published studies[3,4].

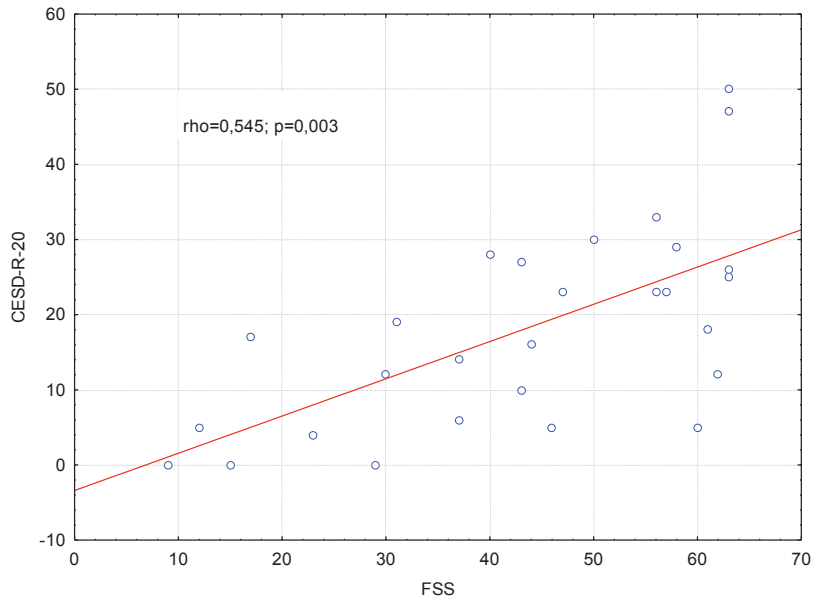


*Fig. 3. Relationship between the severity of fatigue (FSS) and level of depressive symptoms (CESD-R-20) in multiple sclerosis patients (rho = Spearman's rank correlation coefficient, p-value).*

We did not find correlation among any clinical features of MS (subtype, disability status, disease duration, modifying therapy, localization of lesions) with excessive daytime sleepiness as the hallmark of OSA, or with the risk of OSA, which is inconsistent with recently published studies[3,4].

In accordance with the results of published studies[1,3], we found no correlation among disability status and fatigue and depression; however, a recent study suggests a positive correlation[4]. It could be partially explained by the absence of severely disabled/immobile MS patients with comorbidities who were excluded according to exclusion criteria.

A relationship between fatigue and sleepiness is still controversial and unclear. Despite the fact that fatigue and excessive daytime sleepiness are distinct symptoms, we found a significant positive correlation.

Moreover, depression as a common MS symptom was positively correlated with excessive daytime sleepiness as a hallmark of OSA and with age as an independent risk factor for OSA. Depression and fatigue have various and multiple biological mechanisms and risk factors with mutual effect, suggesting a potential multidirectional association among them[10]. In our study, as expected, fatigue and depression were significantly and positively correlated, probably due to partially overlapping symptoms.

These findings highlight that only the clinical feature and risk factor for OSA in MS patients are associated with the two most commonly reported symptoms such as fatigue and depression, favoring the hypothesis that both symptoms are due to a secondary mechanism.

Limitations of the study included the lack of regression analysis due to the small sample and absence of MS patients with severe disability (those who are unable to walk without constant bilateral assistance). It is well known that severely impaired and/or immobile patients are more prone to develop depression and fatigue even with mild physical and mental exertion. We hypothesize that in such MS patients, the prevalence of OSA would be similar, if not higher. In this study, MS patients with comorbidities (stroke, extrapyramidal and neuromuscular diseases) that may cause OSA were excluded. Among the limitations of our study, OSA in MS patients was excluded only based on negative personal and family history and validated questionnaires. Polysomnography was not performed because of additional costs, so it is possible that milder forms of OSA and other SDB that could be associated with depression and fatigue in MS patients were not detected. Therefore, further studies are needed to confirm these preliminary results.

## Conclusion

In conclusion, these findings emphasize the need and importance of screening for OSA and other SDB in MS patients and their treatment with continuous positive airway pressure[11], which would alleviate the severity of these symptoms. Prospective studies have to evaluate whether consequent treatment of OSA and other SDB will beneficially influence these symptoms in MS. And the last but not the least, it would significantly reduce drug consumption in the treatment of depression and fatigue.

## References


1. Koch M, Mostert J, Heerings M, Uyttenboogaart M, De Keyser J. Fatigue, depression and disability accumulation in multiple sclerosis: a cross-sectional study. Eur J Neurol. 2009;16(3):348-52. doi: 10.1111/j.1468-1331.2008.02432.x.
2. Jackson ML, Stough C, Howard ME, Spong J, Downey LA, Thompson B. The contribution of fatigue and sleepiness to depression in patients attending the sleep laboratory for evaluation of obstructive sleep apnea. Sleep Breath. 2011;15(3):439-45. doi: 10.1007/s11325-010-0355-2.
3. Braley TJ, Segal BM, Chervin RD. Sleep-disordered breathing in multiple sclerosis. Neurology. 2012;79 (9):929-36. doi: 10.1212/wnl.0b013e318266fa9d.
4. Abdel Salam OA, Ghonimi NAM, Ismail MH. Risk of obstructive sleep apnea in multiple sclerosis: frequency, clinical and radiological correlates. Mult Scler Relat Disord. 2019;28:184-8. doi: 10.1016/j.msard.2018.12.015.
5. Pecotic R, Dodig IP, Valic M, Ivkovic N, Dogas Z. The evaluation of the Croatian version of the Epworth sleepiness scale and STOP questionnaire as screening tools for obstructive sleep apnea syndrome. Sleep Breath. 2012;16:793-802. doi: 10.1007/s11325-011-0578-x.
6. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 1989;46:1121-3. doi: 10.1001/archneur.1989.00520460115022.
7. Eaton WW, Muntaner C, Smith C, Tien A, Ybarra M. Center for Epidemiologic Studies Depression Scale: Review and revision (CESD and CESD-R). In: Maruish ME, editor. The Use of Psychological Testing for Treatment Planning and Outcomes Assessment, 3rd edn. Mahwah, NJ: Lawrence Erlbaum, 2004; p. 363-77.
8. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, *et al*. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162-73. doi: 10.1016/s1474-4422(17)30470-2.
9. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33(11):1444-52. doi: 10.1212/wnl.33.11.1444.
10. Bhat S, Gupta D, Akel O, *et al*. The relationships between improvements in daytime sleepiness, fatigue and depression and psychomotor vigilance task testing with CPAP use in patients with obstructive sleep apnea. Sleep Med. 2018;49:81-9. doi: 10.1016/j.sleep.2018.06.012.
11. Corfield EC, Martin NG, Nyholt DR. Co-occurrence and symptomatology of fatigue and depression. Compr Psychiatry. 2016;71:1-10. doi: 10.1016/j.comppsych.2016.08.004.


Sažetak

## DEPRESIJA I UMOR UZROKOVANI OPSTRUKCIJSKOM APNEJOM TIJEKOM SPAVANJA U MULTIPLOJ SKLEROZI

*M. Mihalj, Z. Janković, E. Jadrijević Kodžoman, G. Veselica, A. Katić Ćurković, A. Repić Bulićić* i *M. Matijaca*

Sukladno našim saznanjima nema studije koja je istraživala nastaju li umor i depresija kao najučestaliji simptomi kod bolesnika s multiplom sklerozom (MS) i opstrukcijskom apnejom tijekom spavanja (OSA) primarnim mehanizmima MS ili iz sekundarnih povezanih stanja kao što je OSA kod bolesnika s MS. Cilj naše anketne studije bio je utvrditi jesu li depresija i umor u bolesnika s MS povezani s kliničkim obilježjima OSA ili MS. Proveli smo anketu pomoću četiri validirana upitnika (STOP-BANG, Epworthova ljestvica pospanosti, ljestvica težine umora i revidirana ljestvica depresije Centra za epidemiološke studije) u 28 uzastopnih ambulantnih bolesnika s klinički i paraklinički dokazanom MS. Učestalost bolesnika s MS s povećanim rizikom od nastanka OSA bila je 29%, a dob je bila u pozitivnoj korelaciji s tim rizikom (p=0,019). Nijedna od kliničkih značajka bolesnika s MS (podtip, status invaliditeta, trajanje bolesti, modificirajuća terapija, drugi lijekovi) nije bila u korelaciji s depresijom i umorom. Naprotiv, pretjerana pospanost tijekom dana kao obilježje OSA bila je značajno i pozitivno povezana s razinom simptoma depresije (p=0,004) i razinom umora (p=0,015). Također, depresija je značajno i pozitivno korelirala s povećanim rizikom od OSA (p=0,015) i dobi bolesnika s MS (p=0,016). Konačno, utvrđena je značajna pozitivna korelacija između težine umora i simptoma depresije (p=0,003). OSA je čest poremećaj kod bolesnika s MS. Kliničke značajke i čimbenici rizika za OSA u bolesnika s MS povezani su s dva najčešće prijavljivana simptoma depresije i umora, podupirući tako hipotezu da su oba simptoma posljedica sekundarnog stanja u MS.

Ključne riječi: *Depresija; Umor; Multipla skleroza; Opstrukcijska apneja tijekom spavanja*