






Sleep-Related Breathing Disorders in Multiple Sclerosis: Prevalence, Features and Associated Factors

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Background: Multiple sclerosis (MS) represents a risk factor for sleep disorders, but there are conflicting results about the prevalence and severity of sleep-related breathing disorders (SRBD) in MS. Most available data come from self-administered questionnaires.

Objective: To conduct a polysomnographic study in MS focused on SRBD, compared to a group of healthy controls (HC), also considering the neuroimaging findings. To evaluate the impact of SRBD on vigilance, fatigue and depression in MS.

Methods: In this cross-sectional, observational, instrumental study, 67 MS patients (men/women: 20/47; mean age: 50.6±8.2 years) underwent PSG and maintenance of wakefulness test. Findings were compared to 67 age-, sex-, BMI-matched HC, by using parametric (Student's *t*-test) and nonparametric statistics (chi-squared test). A subgroup analysis was then performed, evaluating the influence of brainstem (mesencephalic, pontine and medullary) lesions at neuroimaging on instrumental and clinical data: MS patients with at least one brainstem lesion vs MS patients without vs HC.

Results: The frequency of SRBD was comparable in MS patients and HC. No MS patient had a central apnea index $\geq 2/h$. The respiratory disturbance index (RDI) did not correlate to clinical parameters such as fatigue and depression. Patients with MS were drowsier than HC (47% vs 26%, $p = 0.019$) and showed a worse sleep pattern, in terms of duration, efficiency and architecture.

Conclusion: Our study does not provide evidence of an association between MS-specific symptoms such as fatigue, sleepiness, depression and central or obstructive apneas, even in the presence of brainstem lesions.

Keywords: sleep-related breathing disorders, multiple sclerosis, sleep quality, polysomnography

Introduction

Multiple sclerosis (MS) is an immune-mediated demyelinating and neurodegenerative disease of the central nervous system, which represents the leading cause of nontraumatic neurological disability in young adults. Up to 50% of patients with multiple sclerosis (MS) are at increased risk for sleep disorders.^{1,2} Insomnia and restless legs syndrome (RLS) represent the most common sleep complaints³ in MS, with significant impact on quality of life and critical symptoms, such as fatigue.⁴ Despite this, sleep is yet underinvestigated in patients with MS. Although a growing amount of literature on sleep and MS has become available in the past decade, only a few studies have evaluated prospectively sleep by polysomnography (PSG).⁵

MS and sleep-related breathing disorders (SRBD) have shared consequences, such as fatigue, sleepiness, cognitive impairment and depression, which may contribute to increased morbidity. Although some contend that the prevalence and severity of SRBD are higher in persons with MS, the current literature reports conflicting results,⁵ and most of the available data come from self-administered questionnaires studies.

Little is known about the pathophysiological mechanisms that contribute to SRBD in people with MS and vice versa. Some speculate that obstructive sleep apnoea syndrome (OSAS) could worsen MS-related disability or progression through its association with local/systemic inflammation.⁶ On the other hand, MS-related central nervous system lesions, in particular in areas critical for respiration, like the brainstem, might contribute to both obstructive and central sleep apnoea.⁷

The primary aim of the current study was to compare prevalence, severity and PSG features of SRBD in patients with MS and healthy controls and their correlations with neuroimaging findings. Secondary aims were to look for clinical determinants of SRBD in MS and to evaluate the impact of SRBD on vigilance, fatigue and depression in MS.

Materials and Methods

Participants

A cross-sectional, observational study in a sample of patients older than 18 years old and affected by MS according to McDonald criteria⁸ or clinically isolated syndromes (CIS)⁹ was carried out. Additional inclusion criteria were an Expanded Disability Status Scale (EDSS) score <7.0 (range 0–10),¹⁰ and a brain magnetic resonance imaging (MRI) performed within the 12 months preceding the evaluation. MRI exams were performed using 3T Magnetom “Skyra” (Siemens, Erlangen, Germany) scanner with a 20-channel head coil. All participants were examined with a conventional protocol before and after contrast administration (0.1 mmol/Kg of Gadobutrolum). Sagittal 1-mm fluid-attenuated-inversion-recovery (FLAIR) 3D T2-weighted and axial 3 mm dual echo (T2/proton-density weighted) images were acquired and employed to assess the number of T2-visible lesions in the brainstem, subdivided in mesencephalic, pontine and medullary. All images were reviewed by a neuroradiologist (D.D.), blinded to clinical data.

Exclusion criteria were: Mini Mental Status Examination (MMSE) score lower than 24; clinical MS relapse within the last 3 months; radiologically isolated syndrome (RIS); history of drug and/or alcohol abuse; any serious general medical condition such as decompensated cardiopulmonary disease, cancer or decompensated renal failure, as well as any major neurological condition other than MS that could interfere with the correct execution of the study design. MS was classified as primary progressive, secondary progressive, or relapsing-remitting.

A group of healthy controls (HC), age-, sex- and body mass index (BMI)-matched with MS patients, was randomly selected by the HypnoLaus Sleep Cohort,¹¹ which is a large population-based cohort recruited in Lausanne (Switzerland). They had to be in general good health and were excluded if any of the following was present: a diagnosis of any significant sleep disorder(s) other than SRBD, major mental illness including any indications of cognitive problems as determined by history. A full-night home PSG had been previously recorded in the group of controls, in the same standard way adopted for MS patients.¹²

All procedures performed in this study were in accordance with the Helsinki declaration and the protocol was approved by the Ethics Committee: Comitato etico cantonale (Ufficio di Sanità, 6501 Bellinzona, Switzerland), Trial No.: EOC.NSI.13.02. All participants signed an informed consent.

Questionnaires

Patients were interviewed concerning their medical history; received a complete clinical and neurological examination, including the Expanded Disability Status Scale (EDSS) score assessment. All participants filled in the following questionnaires: Epworth Sleepiness Scale (ESS) (range: 0–24; cutoff for normality: ≤10), Beck Depression Inventory (BDI) (range: 0–21; cutoff for normality: <9), Multiple Sclerosis Quality of Life (MSQoL) (range: 0–84; cutoff for normality: <38), Pittsburgh Sleep Quality Index (PSQI) (range: 0–21; cutoff for normality: <5), Fatigue Severity Scale (FSS) (range: 9–63; cutoff for normality: 36), Modified Fatigue Impact Scale (MFIS) (range: 0–84; cutoff for normality: 38).

Polysomnography and Maintenance of Wakefulness Test

Within one week from the screening visit, participants underwent a full night PSG by a portable device (Embletta ST + Proxy), and a maintenance of wakefulness test (MWT) the following day (the latter not available for the controls).

The PSG montage included the following: EEG, electrooculogram, electromyogram (EMG) of chin and both tibialis anterior muscles, electrocardiogram, body position; oro-nasal airflow (nasal pressure cannula), thoracic and abdominal movements, and oxygen saturation.

Apnea was scored in the presence of a drop in the nasal pressure signal peak amplitude by $\geq 90\%$ of the pre-event baseline, lasting ≥ 10 s, while hypopnea when it drop by $\geq 30\%$ of the pre-event baseline, in association with either $\geq 3\%$ arterial oxygen desaturation or an arousal.¹³ The diagnosis of OSAS was established in the presence of: 1) complaints of diurnal sleepiness (ESS ≥ 10) and an apnea/hypopnea index (AHI) $> 5/h$; or 2) AHI $\geq 15/h$.¹⁴

The MWT quantify, under PSG recording, the ability to stay awake in sleep-promoting environmental conditions.¹⁵ Patients were instructed to stay awake during the four sessions, each of 40 min of recording. Sleep latency was assessed in each of the four recordings and then the average of latencies was calculated.¹⁶

Statistical Analysis

Descriptive statistics were used, followed by between-group comparisons by means of the Student's *t*-test. Frequency data were analyzed by means of the chi-squared test. Correlations were assessed by means of the Pearson's correlation coefficient; following the indications by Cohen,¹⁷ we considered correlations 0.10, 0.30, and 0.50 as corresponding to small, medium, and large sizes, respectively. One-way between-groups analysis of variance (ANOVA) was conducted to explore the impact of brainstem lesions on instrumental and clinical parameters.

Results

Sixty-seven patients with MS (56 (86.3%) relapsing-remitting), whom 47 women (70.1%), with a mean age of 50.6 ± 8.2 years and a mean BMI of 25.4 ± 5.3 kg/m², completed the study. Sixty-seven healthy subjects matched for sex, age and BMI served as a control group (Table 1).

Among patients with MS, 64.2% were fatigued, with a mean FSS and MFIS score of, respectively, 41.7 ± 16.9 and 42.7 ± 22.4 points. 11.9% of patients had a severe disability with an EDSS ≥ 4 , and 63.5% of all patients were depressed, according to the BDI score.

MS Vs Control Group

As illustrated in Figure 1, the proportion of MS with a RDI $> 5/h$, $> 15/h$, $> 30/h$ was 40.3%, 16.4% and 4.5%, respectively, while corresponding figures were 58.2% ($p = 0.057$), 29.9% ($p = 0.100$), 11.9% ($p = 0.210$) in healthy controls.

The diagnosis of OSAS was more frequent in healthy controls than in the MS group, without reaching statistical significance (35.9% vs 25.4%, $p = 0.262$). The percentage of patients with an AHI $> 15/h$ in the supine position was 22.4% in the MS group. AHI during REM sleep (AHI-REM) did not differ between healthy subjects and patients ($p = 0.35$). All subjects with an AHI $> 5/h$ had obstructive sleep apnea, no patient had a central or mixed AHI $> 2/h$.

Patients had a higher sleep onset latency ($p = 0.001$), awakening index ($p < 0.001$), and a lower sleep efficiency ($p < 0.001$), total sleep time ($p < 0.001$), percentage of slow wave sleep ($p = 0.07$) and REM sleep ($p < 0.001$), when compared to controls (Table 2). Sleep quality impairment was also reflected by PSQI scores ($p < 0.001$, $t = 7.465$).

Forty-seven percent of patients reported an ESS score higher than 10, of whom 16.7% and 40% had a pathological MWT, when considering the threshold of 20 and 30 minutes, respectively. The level of drowsiness was significantly lower in the control group: 25.8% had an ESS score > 10 ($p = 0.019$, $\Phi = 0.23$), for which MWT was not available (Table 3).

Correlation of SRBD with Clinical/Instrumental Variables in MS Group

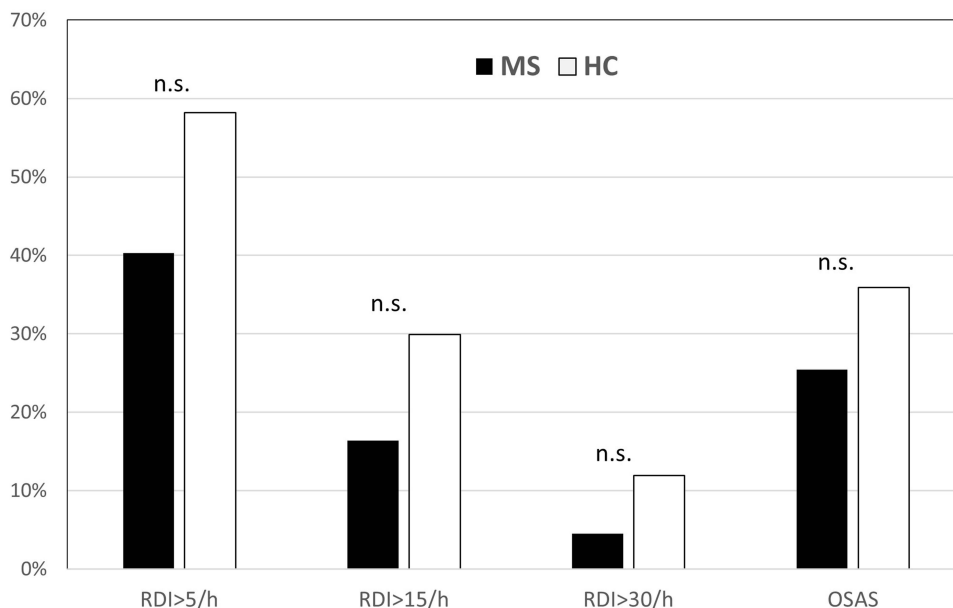
In the MS group, RDI was positively correlated with age ($r = 0.39$, moderate-to-large size, $p < 0.001$), BMI ($r = 0.47$, large size, $p < 0.001$), and negatively with sleep efficiency ($r = -0.30$, moderate size, $p = 0.014$) and MSQoL54 ($r = -0.27$, moderate size, $p = 0.042$). No correlation was found with the disability status (EDSS), fatigue (FSS and MFIS), depression

Table I Demographic and Clinical Parameters

	MS (n=67)		HC (n=67)		
Age, mean, SD	50.6	±8.2	51.8	±6.9	n.s.
Male, n, %	20	29.9%	20	70.1%	n.s.
Female, n, %	47	70.1%	47	29.9%	n.s.
BMI (kg/m²), mean, SD	25.4	±5.3	25.3	±4.8	n.s.
CIS, n, %	4	6.0%			
RR-MS, n, %	56	83.6%			
SP-MS, n, %	3	4.5%			
PP-MS, n, %	4	6.0%			
EDSS, mean, SD	2.7	±1.4			
Patients with:					
Mesencephalic lesions, n, %	12	17.8%			
Pontine lesions, n, %	21	31.3%			
Medullary lesions, n, %	15	22.4%			
DMTs:					
None, n, %	7	10.5%			
Injectables, n, %	29	43.3%			
Orals, n, %	16	23.9%			
Antibodies, n, %	15	22.3%			

Abbreviations: MS, multiple sclerosis; HC, healthy controls; BMI, body mass index; CIS, clinical isolated syndrome; RR-MS, relapsing-remitting multiple sclerosis; SP-MS, secondary progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; EDSS, expanded disability status scale; DMTs, disease modifying treatments; n.s., not significant.

(BDI), and sleep quality (PSQI). AHI_{REM} was higher in patients with $EDSS \geq 4$ ($t = 2.30$; $p = 0.025$). The oxygen desaturation index (ODI), but not the RDI, correlated with subjective sleepiness ($r = 0.27$, moderate size, $p = 0.034$) (Figure 2). There was no correlation between mean sleep latency at MWT and respiratory parameters.

**Figure 1** Frequency of sleep-related breathing disorders in patients with multiple sclerosis and in healthy controls.

Abbreviations: MS, multiple sclerosis; HC, healthy controls; RDI, respiratory disturbance index; OSAS, obstructive sleep apnea syndrome; n.s., not significant.

Table 2 Polysomnographic Parameters

	MS + BS Lesions¹ (n = 31)	MS – BS Lesions² (n = 36)	MS (n = 67)³	HC (n = 67)⁴	P Values	
Total sleep time, min	351.3±63.3	368.3±59.9	360.3±61.5	406.1±66.4	p < 0.001	1,2,3 vs 4
Sleep latency, min	40.5±33.6	26.3±33.4	32.9±34.0	16.6±22.4	p = 0.001	1,3 vs 4
Awakenings/hour	7.1±5.6	6.5±2.9	6.7±4.4	18.4±9.3	p < 0.001	1,2,3 vs.4
Sleep efficiency, %	76.0±11.0	81.9±10.7	79.1±11.2	87.6±9.8	p = 0.032	1 vs 2; 3 vs.4
Stage N1, %	10.1±4.2	10.3±4.7	10.2±4.5	10.2±6.0	n.s.	
Stage N2, %	44.5±10.6	40.7±9.1	42.5±10.0	44.3±9.5	n.s.	
Stage N3, %	17.8±8.0	19.1±8.8	18.5±8.4	22.7±9.3	p = 0.022	1,3 vs 4
Stage REM, %	16.3±7.4	18.0±6.4	17.2±6.9	22.9±5.7	p < 0.001	1,2,3 vs 4
WASO, min	54.8±45.2	51.1±37.3	52.8±40.9	59.3±48.6	n.s.	
PLMSI	14.1±19.2	15.5±29.3	14.8±25.0	10.0±14.8	n.s.	
AHI	10.3±16.7	5.8±6.7	7.9±12.5	11.4±14.8	n.s.	
RDI	10.9±16.7	5.8±6.7	7.9±12.5	12.6±15.0	n.s.	
Supine AHI	13.8±20.1	9.9±17.3	11.7±18.6	n.a.	n.s.	
REM AHI	9.8±18.4	13.5±16.8	11.8±17.5	17.3±17.9	n.s.	
ODI	4.9±11.1	3.0±5.0	3.5±8.3	6.5±14.8	n.s.	
T90	1.9±7.2	1.2±3.8	1.6±5.6	2.3±8.5	n.s.	

Abbreviations: MS, multiple sclerosis; BS, brainstem; HC, healthy controls; min, minutes; WASO, wakefulness after sleep onset; PLMSI, periodic limb movements during sleep index; AHI, apnea-hypopnea index; RDI, respiratory disturbance index; ODI, oxygen desaturation index; T90, percentage of sleep time with an SpO₂ <90%; n.s, not significant; P values <0.05.

Table 3 Clinical Parameters and MWT

	MS + BS Lesions¹ (n = 31)	MS – BS Lesions² (n = 36)	MS (n = 67)³	HC (n = 67)⁴	P Values	
ESS	9.3±5.2	9.5±4.6*	9.4±4.8	7.0±3.7*	p = 0.011	2,3 vs 4
MWT, sleep latency	33.9±9.6	33.5±8.8	33.7±9.1	n.a.	n.s.	
FSS	37.2±19.7	45.7±13.2	41.7±16.9	n.a.	n.s.	
MSQoL54 Ph	60.5±23.4	58.9±18.8	59.6±21.0	n.a.	n.s.	
PSQI	16.8±8.2	17.0±7.9	16.9±8.0	4.7±2.6	p < 0.001	1,2,3 vs 4
BDI	13.9±11.0	14.7±12.2	14.3±11.6	n.a.	n.s.	

Abbreviations: MS, multiple sclerosis; BS, brainstem; HC, healthy controls; ESS, Epworth sleepiness scale; MWT, maintenance of wakefulness test; FSS, fatigue severity scale; MSQoL54 M/Ph, multiple sclerosis quality of life – mental/physical; PSQI, Pittsburgh sleep quality index; BDI, Beck depression inventory; n.a., not available; n.s., not significant.

Influence of the Symptomatic Treatment

Excessive daytime sleepiness (EDS) was associated with regular therapy with anti-depressants: 58.7% of patients with EDS received anti-depressants vs 27.3% of those without EDS (χ^2 6.2, $p = 0.025$). A similar association was found with benzodiazepines ($t = 2.18$, $p = 0.03$). There was no correlation between anti-depressant/benzodiazepine consumption and respiratory parameters.

SRBD and MRI Findings in MS

Fifteen (22.4%) MS patients had lesions in the medulla, 21 (31.3%) in the pons and 12 (17.8%) in the midbrain. Sleep efficiency was significantly lower in MS with brainstem lesions than in MS without ($t = -2.196$, $p = 0.032$), while the respiratory variables (RDI, AHI-REM, central apnea index, ODI, percentage of sleep time with an SpO₂ <90%) did not differ between MS patients with and without brainstem lesions, as well as between healthy controls and MS patients with brainstem plaques (Table 2). The number of lesions in the medulla, pons and midbrain (considered both together and individually) did not correlate with RDI.

Discussion

This is the largest PSG study focused on sleep-related breathing disorders in MS carried out so far. We did not find a higher RDI and OSAS frequency in MS patients compared to healthy controls and the percentages of subjects with RDI >5/h or >15/h were slightly, but not significantly, higher in the control group. No MS patient had a central apnea index ≥ 2 /h, neither in the subgroup with brainstem lesions. As expected, sleep quality in MS was significantly lower than in healthy controls. However, in the MS group, RDI was not correlated with PSG markers of sleep quality, with the exception of sleep efficiency, neither with clinical parameters such as fatigue, depression, sleepiness, subjective sleep quality, and disability status. The presence of lesions in the brainstem was not correlated with any of the sleep-related parameters.

According to ESS, patients with MS were drowsier than healthy subjects. Only ODI and pharmacotherapy (benzodiazepines and anti-depressants) were correlated with drowsiness.

The current literature reports conflicting results concerning the prevalence and severity of SRBD in MS.^{5,18} Studies based on self-reported questionnaires suggested an elevated risk of OSA in MS patients.^{19,20} Nevertheless, the STOP-BANG test may not be an accurate tool to identify OSA patients in comorbidity with MS, where the high prevalence of fatigue might represent a confounding factor.²¹ According to a recent review (2020),⁵ there are only five instrumental case-control studies taking into account RDI or AHI, of which only one involved more than 50 patients (sample size = 62). AHI values varied considerably between studies, ranging from normal to moderately increased. Among these five studies, only Braley et al⁷ found that the AHI and central apnea index (but not obstructive apnea index) were higher in MS patients than in controls, while the others did not find any differences.^{22–25} However, compared to our sample, the

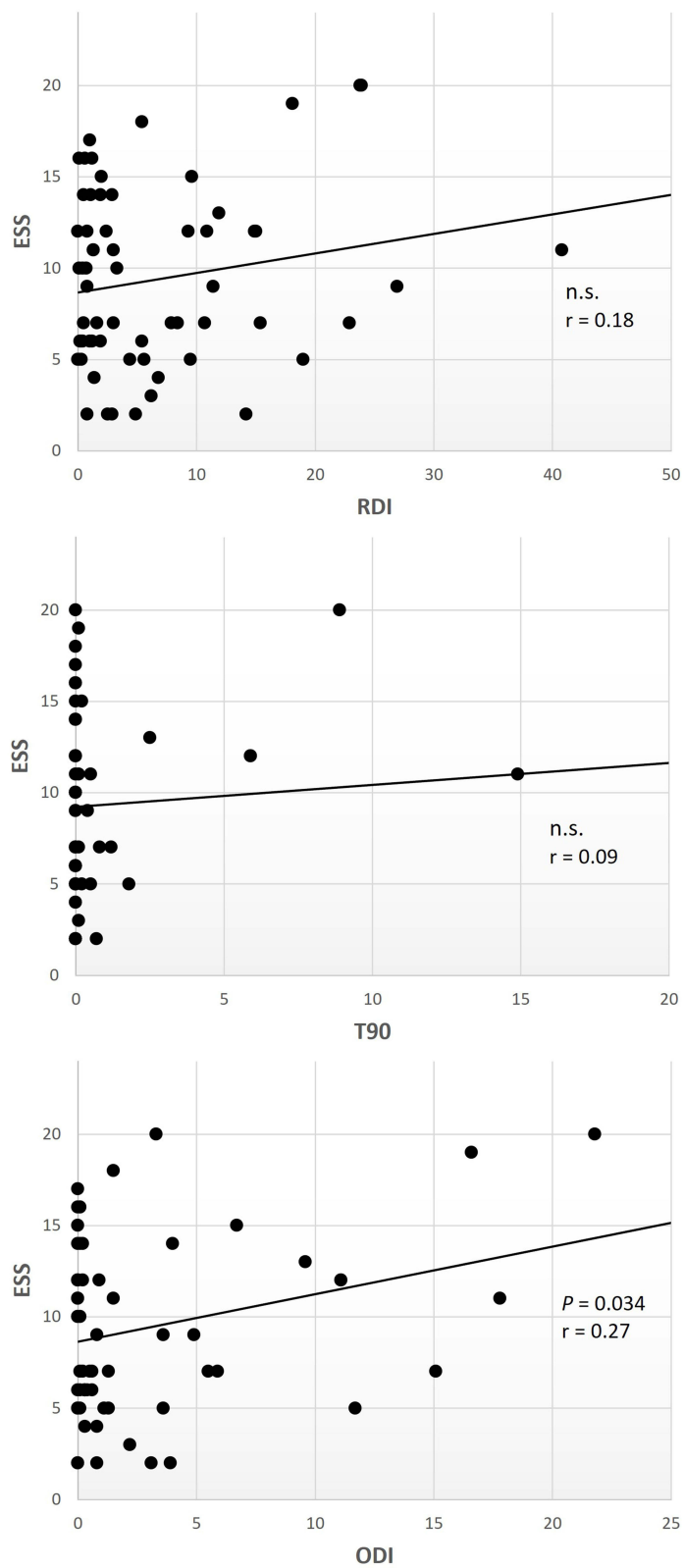


Figure 2 Correlations between sleepiness and respiratory parameters in patients with multiple sclerosis.

Abbreviations: ESS, Epworth sleepiness scale; RDI, respiratory disturbance index; ODI, oxygen desaturation index; T90, percentage of sleep time with an SpO₂ <90%; n.s., not significant.

patients studied by Braley et al⁷ had a higher disease severity, with 30% of patients having progressive MS with an EDSS ≥ 6 , and with brainstem lesions in more than half of the group. A further study considered only obstructive apnea index, finding no difference between MS patients and controls.²³

Another study²⁶ showed a higher AHI, AHI-REM and ODI in patients compared to controls. However, the sample differed from ours in terms of mean age (38.3 years) and sex (56% females). Moreover, the control group consisted of individuals (not affected by MS) who underwent PSG because of sleep complaints.

Two non-controlled studies partially addressed the relationship between SRBD and fatigue in MS, suggesting a positive correlation that diverge from the findings of our study. Nevertheless, the study by Veauthier et al²⁷ lacks of statistics due to the small sample size. The second study by Côté et al²⁸ only focused on the effect of treatment for OSAS (CPAP, positioning devices, weight loss) on fatigue, finding an improvement of fatigue after a successful intervention.

According to our findings, Veauthier et al²⁹ showed poor health-related QoL in MS patients with OSA, even if QoL was assessed with a different questionnaire (Nottingham Health Profile). Finally, no instrumental study provides information on the relationship between SRBD and depression in MS patients.⁵

Our findings indicate that MS is not associated to an increased risk of SRBD, it seems therefore reasonable considering instrumental screening for SRBD only in MS patients with suspicious symptoms. Notably, RDI and AHI in this study do not account for drowsiness, fatigue and depression in MS patients. This suggests physicians should consider treating depression, MS-related fatigue and other sleep complaints, before assessing a possible underlying SRBD. Patients with an elevated ODI represent an exception, since this correlated to subjective sleepiness. However, it is known that in OSAS oxygen desaturations are more associated to drowsiness than AHI.³⁰

Patients with MS showed a worse sleep quality, in terms of duration, efficiency, and architecture compared to healthy subjects. As shown by Buratti et al,³¹ the course of MS may be influenced by sleep quality, possibly because of the role of sleep in some oligodendrocyte functions, such as myelination. Of consequence, sleep quality assessment could be used to obtain prognostic information. In our study, sleep disruption was not imputable to the respiratory pattern during sleep but likely due to other factors, such as insomnia, RLS, periodic limb movements during sleep,³² disease modifying treatments.³³

The presence of lesions within the brainstem, which harbors structures playing a critical role in breathing regulation, was not associated with a greater risk of SRBD or central apneas, but with a worse sleep quality. According to our results, the sole presence of either mesencephalic, pontine or medullary lesions in a patient with MS without SRBD-related symptoms should not per se justify the cost of an instrumental screening for SRBD, at least in the range of MS severity considered in our sample. Our results differ from those of another recent study, with a similar sample size ($n = 65$), which found an association between AHI and the number of lesions in the midbrain and pons, but not medulla.³⁴

Sleep latency at MWT did not correlate to any sleep respiratory parameter. The discrepancy between MWT and ESS is not surprising and has been described also in other disorders, such as OSAS and narcolepsy.³⁵

Limitations

This study has limitations. The exclusion of subjects with an EDSS ≥ 7 and the relatively low median EDSS (2.7) in this MS population limits the generalizability of our results to highly disabled MS. Spinal and cerebral magnetic resonance images were not fully evaluated and were used only for the assessment of the presence of brainstem lesions. Additionally, precise brainstem lesion extension and location were not considered. Cervico-thoracic spine dysfunction due to MS might also contribute to both obstructive and central sleep apnea severity.⁶ Finally, the lack of data on oropharyngeal anatomy prevented us from assessing other causes of OSAS not linked to neuroinflammation and obesity.

Conclusions

Our study did not find evidence of an association between MS and central or obstructive apneas, even in the presence of brainstem lesions. In light of the so far small number of studies on this topic and their limitations, it seems currently reasonable not to screen the MS as well as the general population with PSG for central/obstructive apneas, and limit its use to suspicious cases.

Abbreviations

AHI, apnea/hypopnea index; BDI, Beck Depression Inventory; BMI, body mass index; CIS, clinically isolated syndrome; CPAP, continuous positive airways pressure; EDS, excessive daytime sleepiness; EDSS, Expanded Disability Status Scale; EMG, electromyogram; ESS, Epworth Sleepiness Scale; FSS, Fatigue Severity Scale; HC, healthy controls; MFIS, Modified Fatigue Impact Scale; MMSE, Mini Mental Status Examination; MRI, magnetic resonance imaging; MS, multiple sclerosis; MSQoL, Multiple Sclerosis Quality of Life; MWT, maintenance of wakefulness test; NS, not significant; ODI, oxygen desaturation index; OSAS, obstructive sleep apnea syndrome; PLMS, periodic limb movements during sleep; PLMSI, periodic limb movements during sleep index; PPMS, primary progressive multiple sclerosis; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; RDI, respiratory disturbance index; RIS, radiologically isolated syndrome; RLS, restless legs syndrome; RR-MS, relapsing-remitting multiple sclerosis; SD, standard deviation; SP-MS, secondary progressive multiple sclerosis; SRBD, sleep-related breathing disorders; T90, percentage of sleep time with an SpO₂ <90%; WASO, wake after sleep onset.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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Disclosure

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