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Et al.

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Brainstem lesions are associated with sleep apnea in multiple sclerosis

Elle Levit, Andrew Bouley, Ursela Baber, Ina Djonlagic and Jacob A Sloane

Abstract

Background: Studies linking MRI findings in MS patients with obstructive sleep apnea severity are limited.

Objective: We conducted a retrospective study to assess MRI abnormalities associated with obstructive sleep apnea (OSA) in patients with multiple sclerosis (MS).

Methods: We performed retrospective chart review of 65 patients with multiple sclerosis who had undergone polysomnography (PSG) for fatigue as well as brain MRI. We measured the number of lesions in the brainstem and calculated the standardized third ventricular width (sTVW) as a measure of brain atrophy, and subsequently performed correlation analyses of the apnea-hypopnea index (AHI) with brainstem lesion location, sTVW, and Expanded Disability Status Scale (EDSS).

Results: MS Patients with OSA were significantly older and had a higher body mass index (BMI) and higher AHI measures than patients without OSA. After adjustment for covariates, significant associations were found between AHI and lesion burden in the midbrain (p < 0.01) and pons (p = 0.05), but not medulla.

Conclusions: Midbrain and pontine lesions burden correlated with AHI, suggesting MS lesion location could contribute to development of OSA.

Keywords: Sleep apnea, brainstem, apnea hypopnea index, atrophy, multiple sclerosis

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Introduction

OSA is a common problem in the general population with an estimated prevalence of 2–16%, while OSA prevalence in MS patients appears to be much higher. OSA causes repeated arousals, which can contribute to neurocognitive complaints, decreased quality of life, and fatigue. Fatigue is a common, multifactorial symptom in MS, affecting up to 90% of MS patients, and OSA may contribute to fatigue given its prevalence in MS patients.

MS patients with radiographic evidence of general brainstem involvement have significantly higher AHI compared to those without, suggesting that regional brainstem dysfunction may contribute to the severity of OSA.

OSA has other cerebral implications such as increased atrophy of gray and white matter. Brain atrophy is also seen in MS and is a marker of disease progression. Anecdotal reports show that patients with both conditions have more brain atrophy than with MS alone.

Our objectives were to refine radiographic localization of MS lesions that associate with OSA in MS patients. Given brainstem control of the upper airway musculature, arousals, and loop gain management, we hypothesize demyelinating lesions in various brainstem regions may predispose MS patients to OSA. Additionally, we have begun to explore the link between OSA and brain atrophy, and whether this could play a role in declining functional status as measured by EDSS.

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Methods

Subjects: 65 patients with MS from the Beth Israel Deaconess Medical Center (BIDMC) MS Clinic who had undergone either in-lab polysomnography (PSG) or home PSG for a chief complaint of fatigue were included in our study. 23 patients had undergone home PSG and 42 had an in-lab PSG. Inclusion criteria were diagnosis of MS, age 18 or older, and presence of a sleep study and brain MRI. Other serious neurological disorders were exclusionary including stroke, brain tumor, or parkinsonism. Baseline characteristics including age at onset of MS, gender, age at sleep study, duration of disease from onset to sleep study, type of MS, EDSS, and BMI at time of sleep study were determined through chart review. Centrally acting medicines were present but balanced between groups. Data collection and analysis was approved by the BIDMC Institutional Review Board.

MRI Variables: An MRI obtained within one year of sleep study was available for all patients included in the study. Two independent neurologists reviewed MRI data and counted the number of cerebral and brainstem lesions and mean values were calculated. Third ventricular width (TVW) was measured from the axial T1-weighted scan on which this structure was maximally visible in its antero-posterior extent. Standardized third ventricular width (sTVW) was then calculated by dividing by total brain width measured at the same level, a validated measure of brain atrophy used for monitoring disease progression in MS. We were unable to use computerized volumetric measurement tools due to diverse MRI practices for the studied patients.

Polysomnography Data: We reviewed in-lab and home PSG reports from BIDMC Sleep Clinic and outside sleep centers. For in-lab sleep studies, overnight PSG had been performed with a six-channel electroencephalogram, electrocardiogram (ECG) and oxyhemoglobin saturation by pulse oximetry. For home sleep studies, patients underwent overnight PSG with Alice NightOne type 3 home sleep testing device, with recording of oxyhemoglobin saturation and heart rate by pulse oximetry. Results of both types of sleep studies were interpreted by board certified sleep medicine physicians following the American Academy of Sleep Medicine standards apnea and hypopnea scoring. Diagnosis of obstructive sleep apnea required five or more obstructive respiratory events per hour of sleep with associated fatigue or snoring, or greater than 14 obstructive respiratory events per hour regardless of other symptoms. Apnea was defined as cessation of airflow lasting for at least 10 seconds, while hypopnea was defined as a reduction of airflow of 30% or more lasting for at least 10 seconds. AHI was defined as the sum of apneas and hypopneas and dividing by the sum of total sleep time in hours. The apnea hypopnea 4% index (AHI4%) was defined as the total number of apneas and hypopneas with greater than or equal to 4% SpO2 desaturations plus the number of apneas per hour of sleep, which is the current guideline from Medicare for coverage of CPAP. Variables evaluated from sleep study included AHI, AHI4%, and central apnea index (CAI). Data were collected at time of sleep study, so as to include only patients not treated for OSA.

Statistical Analysis: Statistical tests were performed using R-Studio statistics software. Tests were 2-sided with the level of statistical significance set at 0.05. No mathematical correction was made for multiple comparisons. All of the continuous quantitative variables were presented as mean values with standard deviation reported. The differences in continuous variables between patients with and without OSA were assessed by Student’s t-test. Linear correlations were applied to further evaluate factors that may affect AHI after controlling for independent risk factors for obstructive sleep apnea, including age, male gender and BMI. We also controlled for risk factors for brainstem lesions, including MS disease duration, smoking, and hypertension. Linear correlations were also performed between AHI and sTVW, controlling for age, male gender, BMI, MS disease duration, smoking, and hypertension.

Results

Baseline data: Baseline characteristics for MS patients with OSA and MS patients without OSA are shown in Table 1. Sixty-five subjects with MS with complete PSG data and MRI were identified. Thirty-six patients had OSA diagnosed via PSG, and 29 did not have OSA. No patients were diagnosed with central sleep apnea. Four patients had secondary progressive MS (3 with sleep apnea and 1 without), and the rest had relapsing remitting MS. No significant differences between subjects with and without OSA emerged for female gender, age at onset of MS, the number of years between onset of MS symptoms and initial PSG, smoking status, and depression (Table 1). Restless leg syndrome was virtually absent from this patient population. Significant differences between age and BMI at time of sleep test were identified, with OSA patients being both older and with higher BMIs than those without OSA. There was also a significant positive
The association between the presence of OSA and EDSS as well as hypertension. We also observed a significant correlation between the presence of OSA and sTVW, a measure of brain atrophy. Sleep Measures: The mean AHI was significantly higher in MS patients with OSA compared to those without (p < 0.01), as was the AHI4% (p < 0.01) (Table 2). There was no significant difference found in regard to the number of central apneas and hypopneas in these patient populations. Maximum O2 desaturation was significantly lower in those MS patients with OSA.

Univariate and Multivariate Analyses: Univariate analysis was notable for a significantly higher number of average lesions in the pons when comparing patients with and without OSA. There was no significant difference found in the number of lesions in the midbrain and medulla in patients with and without OSA (Table 3). Linear correlation analyses were performed to determine any associations between AHI and location of brainstem lesions. After controlling for known OSA risk factors of age, gender, BMI, as well as disease duration, hypertension, and smoking status, there were significant positive associations between AHI and average number of lesions measured in the midbrain (p < 0.01), pons (p < 0.01), and infratentorial lesions (p < 0.01) (Table 4). No significant association with number of medullary lesions was seen. We found no correlations with numbers of cerebral lesions,

### Table 1. Baseline characteristics of MS patients with and without OSA.

<table>
<thead>
<tr>
<th>Variable</th>
<th>MS patients without OSA (n = 29)</th>
<th>MS patients with OSA (n = 36)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at PSG, mean (standard error)</td>
<td>41.4 (1.9)</td>
<td>48.2 (1.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Age at onset, mean (standard error)</td>
<td>31.7 (1.4)</td>
<td>34.5 (1.6)</td>
<td>0.18</td>
</tr>
<tr>
<td>Years from onset to sleep test, mean (standard error)</td>
<td>9.9 (1.7)</td>
<td>14.0 (1.6)</td>
<td>0.08</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>26 (90%)</td>
<td>25 (69%)</td>
<td>0.07</td>
</tr>
<tr>
<td>BMI, kg/m², mean (standard error)</td>
<td>27.8 (0.8)</td>
<td>32.7 (1.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>2 (6.9%)</td>
<td>10 (27.8%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Depression, n (%)</td>
<td>11 (37.9%)</td>
<td>9 (25.0%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Ever smokers, n (%)</td>
<td>11 (37.9%)</td>
<td>13 (36.1%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>5 (17.2%)</td>
<td>5 (13.9%)</td>
<td>0.74</td>
</tr>
<tr>
<td>EDSS, mean (standard error)</td>
<td>2.2 (0.2)</td>
<td>3.1 (0.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>sTVW, mean (standard error)</td>
<td>0.028 (0.011)</td>
<td>0.040 (0.014)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Legend: Abbreviations: MS = multiple sclerosis; OSA = obstructive sleep apnea; BMI = body mass index; EDSS = Expanded Disability Status Scale; sTVW = standardized third ventricular width. p-values calculated using Student’s T-test or Fisher exact test, p ≤ 0.05.

### Table 2. Sleep study measures for MS patients with and without OSA.

<table>
<thead>
<tr>
<th>Variable</th>
<th>MS patients without OSA (n = 29)</th>
<th>MS patients with OSA (n = 35)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI, mean (standard error)</td>
<td>3.5 (0.6)</td>
<td>28.2 (4.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>AHI4%, mean (standard error)</td>
<td>1.1 (0.9)</td>
<td>11.9 (2.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CAI, mean (standard error)</td>
<td>0.41 (0.22)</td>
<td>0.94 (0.24)</td>
<td>0.11</td>
</tr>
<tr>
<td>Maximum O2 desaturation, mean (standard error)</td>
<td>90.7 (0.5)</td>
<td>84.8 (0.8)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Legend: Abbreviations: MS = multiple sclerosis; OSA = obstructive sleep apnea; AHI = apnea hypopnea index; AHI4% = apnea hypopnea index with 4% or greater desaturation; CAI = central apnea index; O2 nadir = maximum O2 desaturation. p-values calculated using Student’s T-test, p ≤ 0.05.
including lesions in specific lobar distributions, or in periventricular or juxtacortical distributions.

There was no significant correlation between BMI and the average number of brainstem lesions in the midbrain, pons, medulla, and infratentorial lesions. In addition, no association was observed between maximum oxygen desaturation and lesion burden in the midbrain, pons, and medulla (data not shown). After adjusting for covariates, sTVW or EDSS did not correlate with either AHI or maximum oxygen desaturation (Table 4).

**Data availability statement**

Data not provided in the article because of space limitations is stored in de-identified format and is available at the request of any qualified investigators for purposes of replicating procedures and results.

**Discussion**

OSA is frequently seen in MS patients and could contribute to fatigue, a common multifactorial complaint of many MS patients. Currently it is unknown whether OSA develops specifically due to MS disease activity or due to other established factors such as obesity, inactivity, and/or age. Since we do not yet have a prospective analysis of any interplay between OSA and MS, we first wanted to determine correlations between aspects of radiographic MS disease and OSA.

In this study, we aimed to determine if brainstem lesion location could predict severity of OSA. We found that MS patients with obstructive sleep apnea had an increasing AHI in relation to brainstem lesion number when controlled for age, gender, and BMI. Specifically, we found a correlation with AHI and lesions in the midbrain and pons, but not the medulla. This expands upon previous data that MS patients with brainstem involvement have significantly higher AHI,8 highlighting the importance of specific lesion location in modulating sleep apnea.

OSA is a heterogeneous disorder influenced by upper airway patency but also other factors, including genioglossus responsiveness, arousal threshold, and loop gain.15 Therefore, brainstem dysfunction could play a role in OSA development and severity. Our findings may shed light on neuroanatomic mechanisms and possible dysfunction contributing to OSA in MS. Sleep is promoted by the ventrolateral preoptic nucleus (VLPO) and median preoptic nucleus (MnPO) in the hypothalamus, as well as the parafacial zone in the medulla.19 Wakefulness in OSA may be mediated by the parabrachial (PB) complex in the dorsolateral pons, which receives signals from the medullary nuclei, including nucleus of the solitary tract (NTS), pre-Bötzingger Complex and the...
retrotrapezoid nucleus (RTN)/parafacial respiratory group (pFRG), which generate rhythm and respond to hypercarbia.\textsuperscript{20–22} Output from the external lateral PB subnuclei feeds back to the medulla, driving increased respiratory rate in hypercapnia. The lateral crescent PB subnuclei projects to more rostral targets involved in wakefulness through the midbrain.\textsuperscript{19} It is clear that a complex interplay of various brainstem nuclei coordinate maintenance of sleep or the transition to wakefulness.

Interruption of these pathways, which could occur through demyelination in MS, could in turn alter the physiologic response to rising CO\textsubscript{2} and re-establishment of the airway through awakening, manifesting clinically as an increase in AHI. As observed in our study, lesions in the midbrain and pons were associated with an increase in AHI. We hypothesize this observation could be due to damage of nuclei such as the PBlc and its projections, effectively reducing the normal physiologic ventilatory response to hypercapnia, thereby increasing AHI. It is also possible that midbrain and pontine lesions lower arousal threshold resulting in recurrent awakenings to reestablish the compromised upper airway, and an increase in AHI.\textsuperscript{14–16}

Brain atrophy has been described in OSA and is also seen as a result of longstanding MS.\textsuperscript{10,11} In our study, standardized third ventricular width was used as a surrogate for overall brain atrophy and did not have a significant relationship with AHI after correcting for covariates. We feel this result is inconclusive for many reasons, including small study size and brain volume measurement methodology, and are aiming to conduct another study with more sophisticated tools.

Among potential study limitations, the small sample size, low lesion frequency, and retrospective and observational, cross-sectional design preclude conclusions on causation. Our overall MRI related methodology was not automated both in terms of lesion counts and volumetric measurements. Computerized metrics of MRI data were not possible since MRIs were generated by different sites and at different times. We used a mix of home sleep studies and in-lab PSGs, and home sleep studies are less sensitive to detect milder forms of OSA. However, we found no differences between groups in study types performed. Finally, we were surprised to have only 4 progressive MS patients in our study. This reduced EDSS averages, and may have made statistical analyses with this metric less robust.

Our work suggests that brainstem lesion location in MS patients could contribute to increased AHI and the development of clinical OSA. Testing for OSA is encouraged, since OSA is common in MS an may develop in MS patients without classic risk factors for OSA. Although unproven here, it is also possible that aggressive treatment of MS may help avoid development of OSA as a comorbidity. Further work will be needed to prospectively determine the effect of MS on OSA development, the role of OSA in MS worsening and MS relapses, as well as to determine possible interplay between OSA treatment with MS outcomes.

Conflict of Interests
The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Sloane served of advisory boards for Biogen, Genentech, Celgene, EMD Serono, Genzyme. Other authors have no disclosures.

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