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COMMENTARY

The Role of Obstructive Sleep Apnea in Cognitive Dysfunction in Multiple Sclerosis

Commentary on Braley et al. Sleep and cognitive function in multiple sclerosis. *SLEEP* 2016;39(8):1525–1533.

Raman K. Malhotra, MD

SLUCare Sleep Disorders Center, Department of Neurology, Saint Louis University School of Medicine, St. Louis, MO

Cognitive dysfunction is one of the most common symptoms of multiple sclerosis (MS). In this issue of *SLEEP*, Braley and colleagues[1] demonstrate a relationship between polysomnographic measures of obstructive sleep apnea (OSA) and sleep disturbance in multiple sclerosis patients and various standardized tests of neurocognitive function. I am hopeful that the findings of this study will fuel further research establishing identification and treatment of OSA and other sleep disorders as a new opportunity for treatment of cognitive dysfunction in multiple sclerosis.

It is estimated that the majority of multiple sclerosis patients suffer from impairments in cognition, including processing speed, working memory, learning, executive function, visuospatial processing, and language dysfunction.[2] These findings can occur early in the disease, and can affect adults and even children with multiple sclerosis.[3] There have been studies suggesting that the cognitive dysfunction may occur in patients with "subclinical" multiple sclerosis and be apparent at the time of discovery.[4] The significance of this symptom is the effect it has on quality of life, employment, and school performance of multiple sclerosis patients. These patients, some early in the course with otherwise good baseline functioning, may appear "well," though suffer from deficits in thinking and cognition which are crucial for functioning in life.

Proven, safe, effective treatments for cognitive dysfunction have fallen short thus far. Wake-promoting agents such as methylphenidate and armodafinil have shown improvement in some measures of neurocognitive dysfunction and also hold some promise in treatment of multiple sclerosis patients. A recent small, double-blind placebo-controlled study supported use of extended release amphetamine as a possible treatment option.[5] The outcome measures in this study were similar to the neuropsychological tests and endpoints utilized by Braley, et al.[1] Cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists have also been evaluated for this purpose with mixed results. Despite some promising studies, evidence from a Cochrane Review did not support pharmacotherapy for cognitive dysfunction in multiple sclerosis patients.[6] Besides insufficient evidence, there are concerns about the controlled nature of some of these medications and potential side effects. Furthermore, these medications likely do not address the underlying process or factors that are contributing to the cognitive deficits. The pathophysiology of the cognitive dysfunction is thought to be related to demyelinating lesions in the cortex and throughout the brain of multiple sclerosis patients. Supporting this mechanism is the fact that cognitive impairment correlates with cortical atrophy and axonal loss.[7]

Multiple sclerosis patients have numerous sleep complaints and suffer from primary sleep disorders such as obstructive sleep apnea, insomnia, and restless legs syndrome, that frequently go unrecognized.[8] Undiagnosed and untreated obstructive sleep apnea could be an explanation for some of the cognitive dysfunction that is seen in this population. The intermittent hypoxia and sleep fragmentation resulting from obstructive sleep apnea create decrements in neurocognitive function in the general population, and likely have the similar or even greater effect in patients with multiple sclerosis. Obstructive sleep apnea has also been shown to cause some of the same neuroimaging and neuropathological abnormalities in the cortex and axons as seen in patients with multiple sclerosis.[9,10]

In this study, the authors investigated associations between objective measures of obstructive sleep apnea using in-lab, attended polysomnography and objective measures of neurocognitive function in patients with multiple sclerosis. Patients were recruited from a Multiple Sclerosis Center and evaluated by a neurologist, neuropsychologist, and polysomnography. Neuropsychological testing was performed using a validated, 90-minute battery, the Minimal Assessment of Cognitive Function in MS (MACFIMS), which tests a variety of cognitive functions. In-lab, attended polysomnography, the gold standard of diagnosis of obstructive sleep apnea, was performed on all study participants. Polysomnography was able to provide investigators valuable information on respiratory events (i.e., respiratory disturbance index, oxygen desaturation index, minimum oxygen saturation) as well as sleep architecture and arousals (i.e. sleep efficiency, arousal index). Of note, a very high percentage of patients in this study were found to have obstructive sleep apnea (33 of 38 patients), with over a third of them having severe obstructive sleep apnea. Regression models demonstrated relationships between a variety of neuropsychological functions (attention, working memory) and oxygen desaturation index, minimum oxygen saturation, and respiratory disturbance index. Strong associations between verbal memory and response inhibition were also noted with sleep quality measures such as arousal index and total sleep time. This is the first study to demonstrate these findings in multiple sclerosis patients. However, these findings of an association between nocturnal hypoxia and sleep fragmentation and impaired memory and attention have previously been demonstrated in the general population with obstructive sleep apnea.[11–13]

The authors highlight a proposed mechanism to explain their findings. Involved regions of the brain in obstructive sleep apnea are identical to the areas involved with cognitive impairment in multiple sclerosis, such as the hippocampus, cingulate cortex, frontal, and parietal lobes. In obstructive sleep apnea

patients (without multiple sclerosis), treatment with positive airway pressure has shown improvements in hippocampal volume and white matter integrity, and normalize brain processes during cognitive tasks.[10] This implies that treatment of obstructive sleep apnea in multiple sclerosis patients may also lead to improvement in cognitive dysfunction symptoms along with improvement in some central nervous system destruction seen in these patients.

One major strength of the study is the use of in-lab, attended polysomnography to evaluate for sleep-disordered breathing. Many studies, likely due to cost and availability, utilize portable or home sleep apnea tests, which lack electroencephalogram (EEG) important to recognize arousal based respiratory events, sleep fragmentation, and sleep architecture. It is interesting that there were stronger correlations between measures of intermittent hypoxia and oxygen desaturation (oxygen desaturation index and minimum oxygen saturation) as compared to markers of sleep fragmentation or sleep architecture, similar to what the Apnea Positive Pressure Long Term Efficacy Study (APPLES) demonstrated.[14] Further studies using in lab, attended polysomnography with more subjects may help further clarify the different roles intermittent hypoxia or sleep fragmentation play in the development of cognitive dysfunction in this population. It will also be necessary to use a more representative sample of multiple sclerosis patients, as the group recruited for this study had specifically mentioned sleep complaints as part of the recruitment process, likely leading to the very high rates of obstructive sleep apnea diagnosed. Risk stratifying based upon MRI lesion burden and disease-modifying therapy would also be helpful, as the authors state there is evidence that disease modifying therapy may have an effect on not only multiple sclerosis related cognitive dysfunction, but also a positive effect on sleep apnea severity.

I congratulate the authors for bringing attention to the presence of sleep disorders in this population. Most importantly, we look forward to clinical trials on the effects treatment with continuous positive airway pressure (CPAP) or other treatment modalities can have on improving neuropsychological function in patients with multiple sclerosis and obstructive sleep apnea. Clinicians must improve on the identification and treatment of sleep disorders, which are found at a higher rate in multiple sclerosis patients, as disorders such as obstructive sleep apnea, insomnia, and restless legs syndrome significantly affect alertness, cognition, pain, mood, and overall quality of life. Though diagnosing and treating obstructive sleep apnea may not explain all of the cognitive dysfunction in multiple sclerosis patients, this study does make the case that obstructive sleep apnea's role is more prominent that previously recognized.

CITATION

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Address correspondence to: Raman K. Malhotra, MD, Monteleone Hall, 1438 South Grand Boulevard, St. Louis, MO 63104; Tel: (314) 977-4830; Fax: (314) 977-4876; Email: Rmalhot1@slu.edu

DISCLOSURE STATEMENT

Dr. Malhotra has indicated no financial conflicts of interest.