Obstructive Sleep Apnea is Linked to Depression and Cognitive Impairment: Evidence and Potential Mechanisms

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Obstructive sleep apnea (OSA) is highly prevalent but very frequently undiagnosed. OSA is an independent risk factor for depression and cognitive impairment/dementia. Herein the authors review studies in the literature pertinent to the effects of OSA on the cerebral microvascular and neurovascular systems and present a model to describe the key pathophysiologic mechanisms that may underlie the associations, including hypoperfusion, endothelial dysfunction, and neuroinflammation. Intermittent hypoxia plays a critical role in initiating and amplifying these pathologic processes. Hypoperfusion and impaired cerebral vasomotor reactivity lead to the development or progression of cerebral small vessel disease (C-SVD). Hypoxemia exacerbates these processes, resulting in white matter lesions, white matter integrity abnormalities, and gray matter loss. Blood–brain barrier (BBB) hyperpermeability and neuroinflammation lead to altered synaptic plasticity, neuronal damage, and worsening C-SVD. Thus, OSA may initiate or amplify the pathologic processes of C-SVD and BBB dysfunction, resulting in the development or exacerbation of depressive symptoms and cognitive deficits. Given the evidence that adequate treatment of OSA with continuous positive airway pressure improves depression and neurocognitive functions, it is important to identify OSA when assessing patients with depression or cognitive impairment. Whether treatment of OSA changes the deteriorating trajectory of elderly patients with already-diagnosed vascular depression and cognitive impairment/dementia remains to be determined in randomized controlled trials. (Am J Geriatr Psychiatry 2016; ■■:■■–■■)

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INTRODUCTION

By the year 2040, 82.3 million Americans, or 21.7% of the U.S. population, will be over 65 years of age, and those aged 85 and older will triple from 6 million in 2013 to 14.6 million in 2040.[1] Consequently, late-life illnesses that cause significant morbidity and mortality will become an increasing public health problem. Such illnesses are frequently comorbid and may have a complex effect on disease progression, prognosis, and response to treatment. For example, epidemiologic studies and clinical trials have frequently illuminated the complex relationship between vascular disease, depression, and cognitive impairment. However, certain comorbidities are just now being recognized as clinically significant, such as the relationship between obstructive sleep apnea (OSA), depression, and dementia.

Currently, 22 million Americans suffer from sleep apnea, but estimates suggest that 80% of men and 93% of women with moderate to severe OSA have not been diagnosed.[2] Although the relationships between OSA and depression or cognitive impairment/dementia are increasingly recognized as a serious public health concern, our understanding of the mechanisms that underlie these associations remains incomplete. It remains unclear how OSA is linked to depression and whether common pathways link OSA to depression and cognitive impairment/dementia.

Herein, we reviewed the literature pertinent to the effects of OSA on the cerebral microvascular and neurovascular systems and present a model describing the key pathophysiologic mechanisms that may underlie these associations, including hypoperfusion, endothelial dysfunction, and neuroinflammation. Further, we also discuss recommendations on how to identify OSA in patients with neuropsychiatric comorbidities and considerations for future research on OSA.

OBSTRUCTIVE SLEEP APNEA

Diagnosis

OSA is defined as repeated complete or partial collapse of the upper airway despite an effort to breathe during sleep. Polysomnography is the gold standard diagnostic test for OSA. Home testing with a portable monitor may be used to diagnose OSA in patients at high risk for moderate to severe OSA as part of a comprehensive sleep evaluation. According to the American Academy of Sleep Medicine criteria[3] for scoring respiratory events, an apneic episode is defined as complete cessation of oronasal airflow for at least 10 seconds with a 90% drop from baseline in oronasal airflow. A hypopneic episode is defined as incomplete airway obstruction for 10 seconds with a 30% drop from baseline in oronasal airflow and a 4% decrease in oxyhemoglobin saturation, or a 50% drop of oronasal airflow and 3% decrease in oxyhemoglobin saturation. The frequency of apneas and hypopneas per hour of sleep defines the apnea-hypopnea index (AHI) and determines the severity of OSA: mild (AHI of 5–15), moderate (AHI of 15–30), or severe (AHI ≥ 30).

Epidemiology

OSA affects 24% of men and 9% of women of ages 30–60 years[4] and 40%–60% of older adults (65+ years).[5] The prevalence of moderate to severe OSA (AHI ≥ 15) is highest[6] and the sex difference lowest in older adults. The prevalence of OSA in postmenopausal women not on hormonal replacement therapy is markedly increased, resulting in the reduced sex difference.[6,7]

Risk Factors

Risk factors for OSA include older age, male sex, a family history of OSA, and upper airway structural abnormalities (e.g., large neck girth and craniofacial abnormalities). OSA is also associated with vascular risk factors including obesity, hyperlipidemia, glucose intolerance, alcohol, and smoking. The impact of body mass index (BMI) on OSA severity decreases with age and is negligible by age 60.[8] Hormone (especially progesterone) decreases in postmenopausal women lead to reduced ventilatory drive and a greater risk of developing OSA.[9]

Clinical Presentations

OSA presents with snoring, frequent awakening or gasping/choking during sleep, waking in the morning with headaches, and dry mouth. Some individuals experience excessive daytime sleepiness and fatigue, which impair cognitive functioning. Individuals with untreated OSA have triple the risk of a motor vehicle