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Obstructive sleep apnea and stroke: links to health disparities☆,☆☆

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ABSTRACT

Obstructive sleep apnea (OSA) is a novel cardiovascular and cerebrovascular risk factor that presents unique opportunities to understand and reduce seemingly intractable stroke disparity among non-Hispanic blacks and Hispanic/Latinos. Individuals from these 2 groups have up to a 2-fold risk of stroke and greater burden of OSA. Obstructive sleep apnea directly and indirectly increases risk of stroke through a variety of autonomic, chemical, and inflammatory mechanisms and vascular risk factors such as hypertension, obesity, and diabetes mellitus. Untreated OSA exacerbates poststroke prognosis, as it may also influence rehabilitation efforts and functional outcomes such as cognitive function after a stroke. Conversely, treatment of OSA may reduce the risk of stroke and may yield better poststroke prognosis. Unfortunately, in racial/ethnic minority groups, there are limited awareness, knowledge, and screening opportunities for OSA. Increasing awareness and improving screening strategies for OSA in minorities may alleviate stroke risk burden and improve stroke outcomes in these populations. This review article is intended to highlight the epidemiology, clinical characteristics, pathophysiology, diagnosis, and treatment of OSA in relation to stroke risk, with an emphasis on race-ethnic disparities.

Introduction

Stroke remains one of the leading causes of death in the United States. There are approximately 795,000 annual cases and 130,000 stroke related deaths in the United States, making it the fifth leading cause of death. However, stroke remains the second leading cause of adult death worldwide and the leading cause of adult disability.[1,2]

Racial/ethnic minorities, such as non-Hispanic blacks (herein referred to as blacks) and US Hispanics, compared to non-Hispanic whites carry a large burden of the disease.[3,4] Although the burden of stoke is well-documented among blacks, US Hispanic stroke rates are less well documented. Available studies suggest that US Hispanics have over a 2-fold increased stroke risk compared to non-Hispanic whites.[5,6] Treatment of vascular risk factors, such as hypertension, tobacco, and diabetes mellitus, improved the prevention and stroke outcomes.[7] However, the presence of these vascular risk factors explains about half of the strokes, particularly among minority populations. Therefore, it is imperative to focus on novel risk factors for stroke.[8,9]

Obstructive sleep apnea (OSA) is a novel risk factor for stroke and cardiovascular mortality. Long-term follow-up of the Sleep Heart Health Study and the Wisconsin Sleep Cohort shows nearly 3- to 4-fold higher associations between baseline OSA and incident stroke.[10-12]

The Sleep Heart Health Study observed an increased risk of stroke in men with moderate to severe OSA (hazard ratio of 2.9; 95% confidence interval [CI], 1.1-7.4), whereas women with an apnea-hypopnea index (AHI) of 25 or more also had an increased stroke risk after a median of 8.7 years.[13] However, sparse data are available describing sleep and stroke risk in minorities.

Mounting evidence suggests that OSA is also related to subclinical brain infarcts and ischemic white matter hyperintensities by magnetic resonance imaging, markers of cerebral small vessel disease, which predict incident stroke and vascular cognitive impairment.[14-16]

This review article summarizes the relationship between OSA and stroke, with specific emphasis on health disparities among US non-Hispanic blacks and Hispanics/Latinos. We review the association of OSA with vascular risk factors and the mechanisms that may lead to increased stroke risk in OSA. In addition, we discuss the association between intermediate phenotypes associated with stroke, such as subclinical markers of cerebrovascular disease and vascular cognitive impairment.

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Prevalence and risk factors for OSA in race-ethnic minorities

Obstructive sleep apnea is characterized by loud and frequent snoring, witnessed apneas, excessive daytime sleepiness, fatigue, poor concentration, restlessness, and morning headaches. The diagnosis of OSA is confirmed by polysomnography or home-sleep testing. Factors such as being male, increased body mass index ≥30, and hypertension are associated with an increased likelihood of OSA.[16]

Some estimate that the prevalence of OSA in the United States is approximately 17% in adults and, of these, up to 25% are older than 65 years. However, the prevalence could be higher in minorities as few population-based studies indicate that a significant amount of racial/ethnic minorities report OSA-like symptoms.[17,18] In a sample of community-dwelling blacks from the Jackson Heart Study, snoring was reported by 66.3% of men and 58% of women, whereas daytime sleepiness was reported by 68.6% of men and 61.4% of women.[19] The Cleveland Family Study, using polysomnography to confirm OSA, found a higher frequency of OSA among blacks (31%) compared to whites (10%).[20] A meta-analysis of 10 studies showed an increased frequency and severity of sleep apnea among blacks compared to non-Hispanic whites.[21] In addition, in The Hispanic Community Health Study/Study of Latinos (HCHS/SOL), the largest study of Hispanic/Latinos in the United States, 34% of men and 18% of women met criteria for OSA, using the minimal criteria of an AHI ≥5.[22] Some estimates suggest that up to 93% of women and 82% of men with moderate to severe OSA remain untreated.[16]

Because blacks and Hispanics have an increased risk of medical conditions that are related to OSA, it is likely that the prevalence of OSA may be greater. Blacks and Hispanic/Latinos compared to whites have higher obesity, hypertension, and cardiometabolic abnormalities (metabolic syndrome and diabetes mellitus) frequencies, which should prompt physicians to evaluate and risk-stratify for OSA among these groups.[23-25] In a cross-sectional analysis of 280 patients with OSA, blacks were more likely to be obese and hypertensive, compared to non-Hispanic whites,[26] whereas participants with moderate to severe OSA (AHI ≥15) from HCHS/SOL had a 90% higher chance of diabetes mellitus and 44% higher chance of hypertension.[22]

There are risk prediction tools, such as the Berlin, the STOP-BANG, and the ARES questionnaire, used in clinical samples and community-based populations that risk-stratify the likelihood of OSA,[27-29] before polysomnography. Although these risk prediction tools are helpful, there are little data in poststroke populations and minorities. Of these, the Berlin questionnaire had moderate diagnostic utility in stroke patients, with a sensitivity of 60% to 70% and specificity of 15% to 55%.[13,30] Despite these high rates and considerable progress in diagnostic tools, most racial/ethnic minorities with OSA remain undiagnosed.

Several studies used OSA predicting tools in stroke and minorities with mixed results. For example, in patients with acute strokes admitted to a tertiary stroke center, Hispanic/Latinos (mostly from Cuban descent) had a higher risk of sleep apnea (based on the Berlin questionnaire) than either black or white participants.[31] These findings were not reproduced by the Brain Attack Surveillance in Corpus Christi sleep apnea study, where prestroke sleep apnea risk did not differ between Hispanic/Latinos of Mexican descent and white participants,[32] but further studies are needed in other Hispanic groups and black patients.

Vascular mechanisms between OSA and stroke

Obstructive sleep apnea may causally lead to stroke through its associations with potent vascular risk factors, such as hypertension, diabetes mellitus, obesity, and atrial fibrillation. Of aforementioned factors, hypertension is considered the strongest predictor and the main modifiable risk factor for stroke. Sleep apnea is independently associated with hypertension and increases the risk of hypertension in a dose-response pattern. Mild OSA, AHI of 5 to 14, was associated with a 2-fold risk of hypertension, whereas those with moderate to severe OSA (AHI ≥15) had a 3-fold risk at 4 years of follow-up. Obesity is a known risk factor for OSA and has been associated with a host of inflammatory and metabolic abnormalities that promote insulin resistance.[25,33] Conversely, physiological perturbations associated with intermittent hypoxemia and increased sympathetic tone also increase risk of obesity and diabetes mellitus in OSA.[34,35] Obstructive sleep apnea leads to altered levels of leptin, a hormone secreted by adipocytes, which promotes the sensation of satiety and increases the metabolic rate. Untreated OSA causes resistance to the metabolic effects of leptin, promoting weight gain and obesity.

Obstructive sleep apnea is associated with a host of cardiac arrhythmias, but relevant to stroke risk is the association between OSA and atrial fibrillation (AF).[36-38] Patients with severe sleep apnea have a 4-fold increased risk of AF, an established risk factor for cardioembolic strokes.[36] Some suggest that OSA may trigger AF by stretching the atrial chamber secondary to swings in the intrathoracic pressure, increasing the left ventricular end-diastolic pressure and possibly increased systemic inflammation. It is hypothesized that vascular strain may lead to cardiac remodeling, which contribute to AF.[36-38]

Obstructive sleep apnea may also promote cerebrovascular disease through increased sympathetic tone, reduction in cerebral blood flow, altered cerebral autoregulation, impaired endothelial function, increased platelet activation, inflammation, and oxidative stress related to the intermittent hypoxemia-reoxygenation.[39] Obstructive sleep apnea can lead to reductions in cerebral blood flow and impaired cerebral autoregulation, possibly damaging the small vessels in the brain.

Few cross-sectional studies show associations between OSA and large vessel subclinical atherosclerosis, such as increased carotid intima-media thickness and carotid plaques, with vibratory trauma from loud snoring potentially playing a role of carotid endothelial function.[40-42] Hypoxemia and reoxygenation leads to oxidant-mediated endothelial dysfunction, which contributes to the atherosclerotic process and may be reversed by treatment with continuous positive airway pressure.[21,43,44]

Treatment of OSA in stroke

Initial treatment of OSA includes avoiding or minimizing factors that may exacerbate OSA (ie, benzodiazepines). Continuous positive airway pressure (CPAP) is the first-line therapy for patients with moderate to severe OSA. Aside from improving sleep quality and daytime symptoms (ie, sleepiness), CPAP could decrease cardiovascular events and has modest effects on blood pressure. Interestingly, in a 5-year prospective observational study of patients with OSA and stroke, individuals with moderate or severe OSA who were nonadherent to CPAP had increased risk of cardiovascular disease or stroke mortality (hazard ratio, 1.6; 95% CI, 1.0-2.5), compared to those adherent to CPAP.[8,40] However, data on OSA and stroke-specific outcomes are limited. An observational study of 96 patients with ischemic strokes and OSA treated if the AHI was ≥20 showed lower mortality at 5 years and fewer nonfatal cardiovascular events at 7 years among patients who complied with CPAP compared to those who did not.[45,46]

Sleep and vascular cognitive impairment

Cognitive impairment is 1 functional area that is often affected by comorbid OSA and stroke. Vascular cognitive impairment is caused