Sleep and Stroke

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KEYWORDS

• Stroke • Sleep • Obstructive sleep apnea • RLS/PLMS • Parasomnias • Cerebrovascular accident • Central sleep apnea • Insomnia • Sleep duration

KEY POINTS

- Growing evidence suggests that sleep amount and sleep disorders may impact risk for stroke; conversely, the cerebrovascular events may change sleep drive and affect breathing patterns during sleep.
- Treatment of sleep disorders, whether causative of stroke or caused by stroke, will likely improve sleep-related symptoms and may improve further stroke risk and long-term outcomes.
- Sleep apnea, both obstructive and central, is strongly associated with increased cerebrovascular events.
- Other sleep disorders, including insomnia, RLS/PLMS, and parasomnias may also result in increased incidence of stroke.
- Short and long sleep duration increase cardiovascular events by increasing sympathetic tone and low-grade inflammation.
- Treatment of sleep disorders reduces sleep disruption and can improve functional stroke outcome as well as decrease stroke risk.

Strokes are one of the most common causes of death in the United States.[1] Growing evidence suggests that sleep amount and sleep disorders may impact risk for stroke; conversely, the cerebrovascular events may change sleep drive and affect breathing patterns during sleep. This article describes the most up-to-date information on the linkage between sleep and stroke and attempts to demonstrate how some physicians may use changes in sleep to limit the risk of stroke in some patients.

SLEEP APNEA AND STROKE

Sleep apnea is defined by decreased airflow occurring during sleep. Two main types of sleep apnea exist: obstructive and central. Obstructive sleep apnea (OSA) is the most common type of sleep apnea and consists of complete or partial occlusion of the airway, usually accompanied by an associated oxygen desaturation or arousal. Central sleep apnea (CSA) occurs when respiratory effort is decreased or absent and is commonly associated with conditions such as heart failure. The most widely accepted epidemiologic data project that 4% of men and 2% of women suffer from OSA,[2] although more recent data suggest that the incidence of sleep apnea in highly developed countries could be as high as 20% in men and 10% in women.[3]

In patients with a history of stroke or transient ischemic attack, sleep apnea incidence is significantly higher than the general population, with estimates suggesting 72% for apnea-hypopnea index (AHI) >5/h and 38% for AHI >20/h.[4] In a small study evaluating sleep-disordered breathing (SDB) incidence in an inpatient stroke rehabilitation unit, 91% demonstrated AHI >10/h with a mean AHI of 32/h.[5] Furthermore, several prospective cohort studies indicate increased risk of cardiovascular events in patients with OSA; OSA serves as an independent risk factor for cardiovascular events.[6–9]

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The American Heart Association recommends screening for OSA for stroke prevention and suggests treatment is reasonable, although its effectiveness for primary prevention of stroke remains unknown.[10]

The 2014 recommendations by the American Heart Association include stratification of antithrombotic therapy based on CHA_2DS_2-VASc score, which does not incorporate the presence of sleep apnea. A retrospective cohort study by Yaranov and colleagues[11] revealed that patients who had atrial fibrillation and OSA developed stroke more commonly than atrial fibrillation patients without OSA (odds ratio 3.84).

Pathology of Obstructive Sleep Apnea and Stroke

Although the specific causal mechanism linking sleep apnea to increased stroke risk has yet to be identified, several direct and indirect relationships contributing to atherosclerosis are known. Atherosclerosis, traditionally viewed as solely a disease of lipid storage, is now thought to be multifactorial, with several processes contributing to plaque development. Factors contributing to atherosclerotic development include hypertension, metabolic syndrome (diabetes, dyslipidemia), and smoking. Inflammatory mediators of atherosclerosis include markers of systemic inflammation (eg, interleukin [IL]-6, C-reactive protein [CRP], intracellular adhesion molecules [ICAMs]), fibrinogen, and lipoprotein (a).

OSA causes repetitive episodes of decreased oxygenation mimicking asphyxia and results in negative intrathoracic pressure. Increased arousals from sleep occur in response to decreased oxygen levels and increased circulating carbon dioxide levels. Arousals during sleep increase sympathetic activation, resulting in brief increases in blood pressure. Patients with OSA demonstrate increased incidence of refractory hypertension, perhaps as a result of the changed nocturnal blood pressure.[12] OSA may also cause insulin resistance resulting in diabetes mellitus type 2,[13] thought to be secondary to an increase in circulating cortisol. Leptin, a hormone released by adipocytes in response to food, is decreased in patients with OSA, lowering their metabolic rate, decreasing the sensation of fullness, and contributing to metabolic syndrome and increased weight gain.[14]

The predominant abnormality of OSA stems from intermittent hypoxia occurring during apnea and hypopnea events. In several mice models, intermittent hypoxia resulted in increased formation of fatty streaks in the aortic arch and acceleration in development of disease in those genetically prone to atherosclerosis.[15,16] Intermittent hypoxia has been implicated in worsening dyslipidemia, oxidative stress, and endothelial dysfunction and inflammation. In addition, OSA is associated with a significant increase in carotid intima-media thickness and arterial stiffness evidenced as an early indication of atherosclerosis.

Intermittent hypoxia contributes to dyslipidemia by increasing levels of very low-density lipoprotein (VLDL) secretion. This increased secretion is mediated by upregulation of stearoyl coenzyme A desaturase 1, which increases in direct proportion to severity of nocturnal hypoxia.[17] Decreased lipoprotein clearance also contributes to an increase in circulating VLDL. Lipoprotein lipase contributes to clearing circulating lipoproteins, and intermittent hypoxia inhibits its activation. Patients with OSA who used positive pressure therapy as treatment had increased lipoprotein lipase activity.[18] However, several other studies contradict a relationship between OSA and dyslipidemia, and additional studies have been suggested to further investigate the relationship.[19]

Intermittent hypoxia resulting from OSA is highly associated with oxidative stress. Oxygen free radicals lead to lipid peroxidation, which are acquired more easily by macrophages; this causes macrophage foaming and provides a substrate for the progression of the atherosclerotic plaque.[17] Although most studies verify an increase in lipid peroxidation and oxidized low-density lipoprotein in patients with OSA, the lack of benefit seen with antioxidant therapy raises the question of whether oxidative stress is a result of vascular inflammation instead of atherosclerosis[20] (**Fig. 1**).

OSA is also correlated with an increase in inflammatory mediators and cytokines thought to contribute to endothelial dysfunction. A direct proportional relationship is observed with elevation of inflammatory markers in patients with increased AHI, resulting in increased serum levels of markers, including CRP and IL-6. Several studies indicated an increase in CRP was independently associated with OSA and nocturnal hypoxemia, although contradictory studies found increased CRP to be more independently associated with body mass index (BMI) than OSA severity. IL-6, responsible for CRP production by the liver, also increases in patients diagnosed with OSA compared with those without, although contradictory studies exist linking this mediator to BMI as well.[21] Intracellular adhesion molecules, which facilitate leukocyte adhesion to vascular endothelium, increase in OSA patients compared with controls, and they increase in direct proportion to nocturnal hypoxemia.[22] OSA and nocturnal hypoxemia severity also increase tumor necrosis factor-α with additional influence by age and BMI.[23] Although data are limited on IL-8,