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,

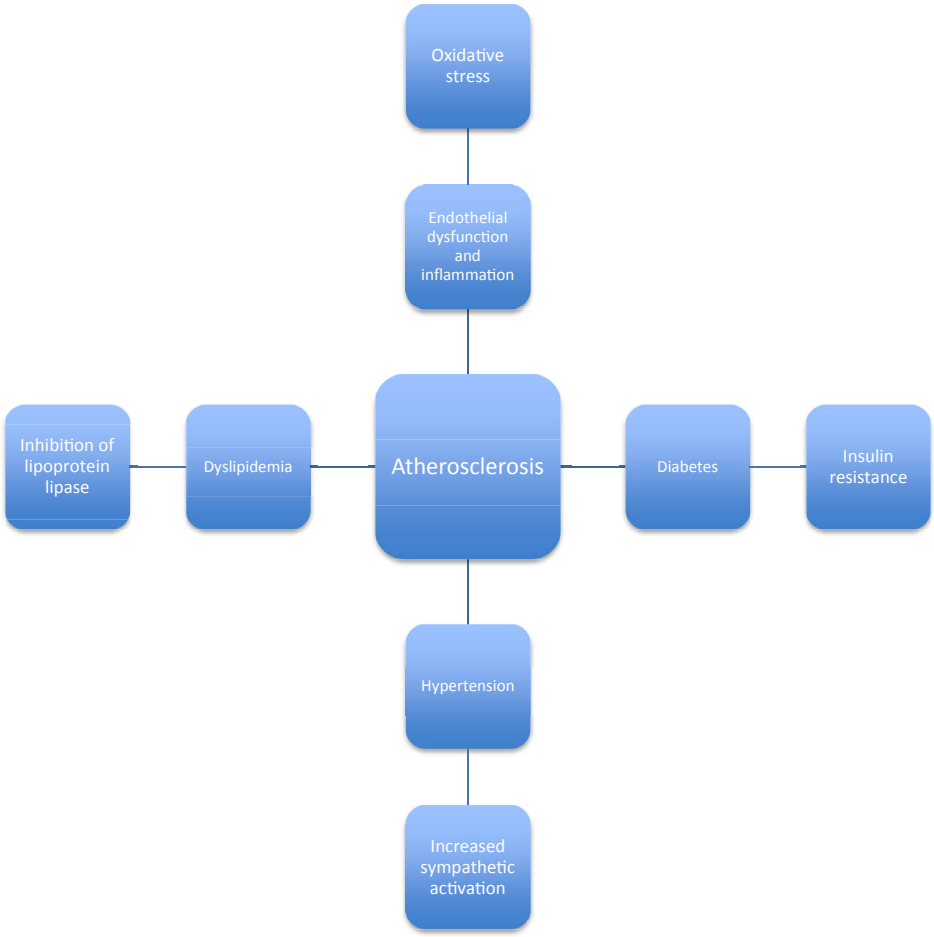

Fig. 1. Intermittent hypoxia during apneic events increases atherosclerosis via multiple mechanisms.

selectins, and vascular cell adhesion molecules, data suggest these markers are significantly elevated in patients with OSA, again associated with influence by age and BMI[21] (**Fig. 2**). In harvested endothelial cells in patients with OSA, the nuclear factor, NF-κB, increased, and nitric oxide synthase expression and activity decreased. These changes reversed after treatment of OSA with continuous positive airway pressure (CPAP) therapy.[24]

Stroke Subtypes

Several investigators questioned whether OSA predisposes to certain ischemic stroke types, that is, large-vessel versus Small-vessel strokes. However, no studies have yet demonstrated a significant difference in type of ischemic stroke seen in patients diagnosed with sleep-disordered breathing (SDB) compared with those without. Although no significant relationship was seen between SDB and size of vessel occluded, a significant increase in cardioembolic strokes was observed in patients with SDB compared with those without.[25] Notably, most studies assessing this question rely on a diagnosis of SDB after stroke occurred.

Respiratory changes are commonly seen acutely after stroke and can be correlated to stroke location. Respiratory apraxia results from strokes in

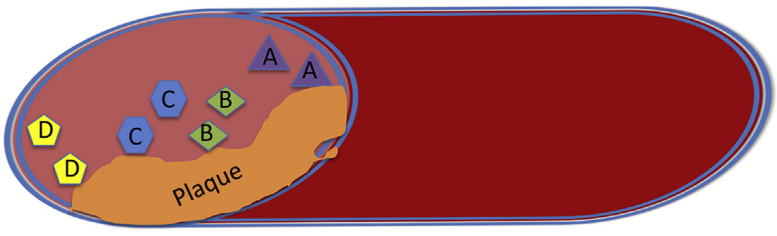

Fig. 2. OSA increases the risk of atherosclerosis and plaque formation by increasing inflammatory mediators, including (A) CRP, (B) IL-6, (C) ICAMs, and (D) tumor necrosis factor-α.

the frontal lobe, basal ganglia, or internal capsule. Neurogenic hyperventilation occurs after pontine strokes; apneustic respirations can result after strokes in the inferior medial posterior area of the pons; central alveolar hypoventilation syndrome (Ondine curse) can occur after medullary stroke, and medullary strokes at the level of C1 can impair voluntary respiration if stroke localizes posteriorly or automatic respiration if localized anteriorly. These respiratory patterns often lack significant prognostic implications, although low carbon dioxide can be associated with poorer prognosis. The mean prevalence of respiratory changes presenting in the acute poststroke period is 59%, with OSA being the most common respiratory disorder.[26]

Central sleep apnea

CSA is defined by a cessation or decrease of ventilatory effort during sleep and is usually associated with an oxygen desaturation. CSA is seen in up to 26% of patients following a stroke, but the CSA often improves as acuity of stroke decreases.[27] CSA is often a result of anterior circulation lesions.[28] In addition, the incidence of CSA increases in patients with larger strokes and strokes associated with significant mass effect.[29] The presence of CSA after stroke portends poorer prognosis despite higher minimum SaO_2 levels observed in patients with central respiratory events compared with those without central respiratory events.[28] Treatment of CSA after stroke includes CPAP therapy and adaptive servoventilation (ASV), although use of ASV is currently controversial in patients with predominant CSA, and moderate to severe congestive heart failure has recently been based on the mortality data from the SERV-HF study.[30]

Functional outcome after stroke

Several studies prove SDB increases incidence and recurrence of stroke as well as lowers mortality.[31] However, a dearth of studies exists detailing functional outcome after stroke in patients with sleep apnea. Recently, Aaronson and colleagues[32] investigated functional outcome of patients admitted to a neurorehabilitation unit. Within 4 weeks of admission, patients received several neuropsychiatric tests assessing vigilance, attention, memory, working memory, executive functioning, language, visuoperception, psychomotor ability, and intelligence. Within the first few weeks, an ambulatory overnight cardiorespiratory polygraphy was performed to generate an oxygen desatuation index (ODI, a surrogate index for sleep apnea severity). The investigators discovered patients with an elevated ODI demonstrate statistically worse impairment in attention, executive functioning, visuoperception, psychomotor ability, and intelligence. These patients also had a significantly increased length of stay in the rehabilitation unit and were less functionally independent on discharge from the unit. There was no significant difference in levels of sleepiness, fatigue, depression, or anxiety between the patients with an elevated ODI and non-SDB patients.

Further sleep apnea and stroke studies

One of the most compelling and as of yet unanswered questions in terms of sleep apnea and stroke is whether treatment of sleep apnea improves neurologic outcome. Although there are several prospective cohort studies available demonstrating improved functional outcome with CPAP treatment of sleep apnea, the control population typically consists of nonadherent patients, thus introducing selection bias. No studies have been performed with sham CPAP treatments in this setting, arguably because of ethical consideration of nontreatment in diagnosed sleep apnea patients. A few studies are underway, most notably TOROS, to provide a reliable answer to whether treating sleep apnea significantly improves functional outcome after stroke.

Further studies are also necessary to assess the causal relationship between several correlative factors seen in stroke and sleep, including dyslipidemia, hypertension, and atrial fibrillation.

INSOMNIA AND STROKE

Insomnia is defined as persistent difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity and circumstances for sleep and results in some form of daytime impairment.[33] It is the most common sleep disorder, affecting up to 22% of adults.[34] Insomnia varies in chronicity, but even in those with remission, 27% experiencing insomnia relapse within 3 years.[35]

Insomnia is associated with all-cause mortality and cardiovascular death, including stroke.[36] Insomnia incidence in patients who have had a stroke approaches 57%, with 38% reporting insomnia as a preceding symptom to the stroke.[37] In patients who have had a stroke, insomnia incidence is higher in women than in men.[38] Living alone and an older age also increase the risk of insomnia associated with stroke.[39]

Short sleep duration is also associated with increased atherosclerosis risk.[40] Postmenopausal women reporting short sleep demonstrated a distinct increased risk for stroke without an increase in clinically apparent cardiovascular disease.[41] A Japanese study demonstrated patients with short sleep time and higher nocturnal systolic

blood pressures had a significant increase in cardiovascular events.[42] In a similar study on hypertensive patients, the presence of both diabetes and short sleep duration also correlated with increased cardiovascular disease than either independently[43] (**Figs. 3** and **4**).

Several studies indicate insomnia plays an important role in the development of cardiovascular disease, including stroke, and insomnia can affect poststroke outcome and quality of life, if left untreated. Insomnia increases the incidence rate of stroke as identified by a retrospective cohort study performed by Wu and colleagues.[44] Across all ages and both genders, patients with insomnia exhibited a higher incidence rate ratio of stroke compared with those without insomnia. The largest incidence rate ratio was identified in 18 to 34 year olds; the ratios then decreased with advancing age, although incidence of ischemic stroke increased with advancing age.[45] Overall, individuals with insomnia demonstrated a 54% increased likelihood of developing stroke compared with patients without insomnia. Wu and colleagues[44] also studied insomnia chronicity and discovered individuals with persistent insomnia had the highest risk of stroke, followed by individuals with relapsing insomnia. Subjects with insomnia in remission had the lowest increased rate of stroke compared with other subjects with insomnia but still demonstrated a hazards ratio exceeding that of those without insomnia.

Insomnia occurrence after stroke is also increased. Patients with right hemispheric strokes reported more insomnia symptoms than those with left hemispheric strokes in one study.[46] One brain area with insomnia as a prominent symptom includes the thalamus and brainstem, specifically the thalamomesencephalic region, pontomesencephalic region, and/or the pontine tegmentum, which can result in inversion of the sleep-wake cycle and nighttime agitation.[47] Insomnia commonly develops acutely after stroke, although usually with multifactorial cause, including complications of hospitalization, stroke, and/or medications.[26]

Poststroke insomnia also can also affect stroke recovery and quality of life. Insomnia increases the risk of subsequent stroke[48] and worsens psychological health with an associated increase in frequency of suicide.[49] Poststroke insomnia increases physical disability, dementia symptoms, and anxiety.[37] One study demonstrated patients with fewer days of insomnia positively correlated with improvement in overall health, energy, family roles, mobility, mood, personality, social roles, thinking, and work/productivity as reported by patients on a quality-of-life questionnaire.[38] The same study also demonstrated the converse: namely, that an increase in sleepless nights resulted in decreasing energy levels, concentration, and memory, similar to that reported in the general population.[50]

Pathology

Proposed mechanisms linking insomnia to stroke focus on the disruption of sleep seen in patients with insomnia. Increased arousals are implicated in increasing sympathetic activity at night compared with the typical lull in sympathetic activity seen during sleep, which results in nocturnal hypertension. In combination with increased activation of the hypothalamic-pituitary-adrenal axis, cortisol levels elevate, increasing the risk for vascular disease.[51]

In short sleep, nonrestorative sleep correlates with elevated levels of inflammatory cytokines, generating a low-grade inflammation state.[52] Gangwisch and colleagues[53] also demonstrated an association between elevation in sympathetic tone and short sleep.

Poststroke insomnia may localize to specific lesions based on certain symptoms. Supratentorial strokes decrease non-rapid eye movement (NREM) sleep, decrease total sleep time, and reduce sleep efficiency.[54] There is limited

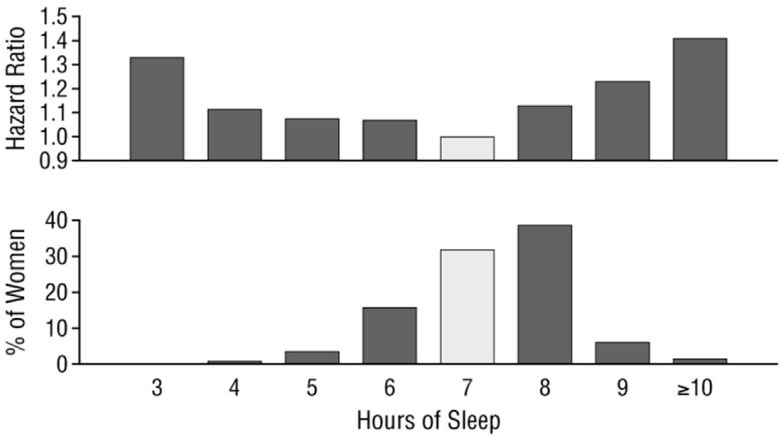

Fig. 3. U-shaped mortality curve for 636,095 women based on self-reported sleep duration. Hazard ratios represent all-cause mortality adjusted for covariates. (*From* Kripke DF, Garfinkel L, Wingard DL, et al. Mortality associated with sleep duration and insomnia. Arch Gen Psychiatry 2002; 59(2):131–6; with permission.)

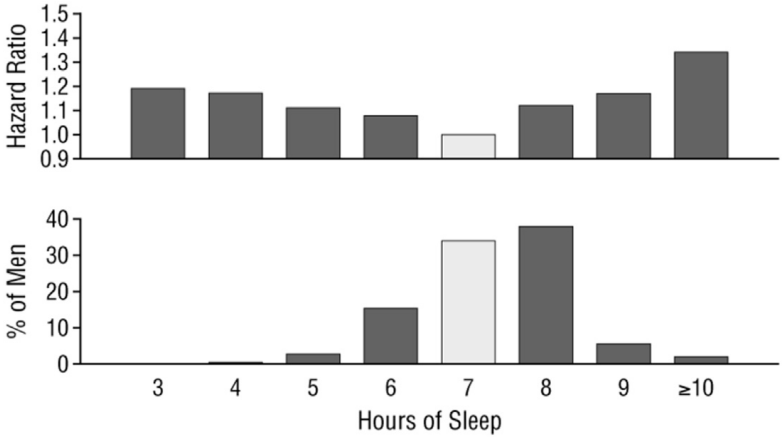

Fig. 4. U-shaped mortality curve for 480,841 men based on self-reported sleep duration. Hazard ratios represent all-cause mortality adjusted for covariates. (*From* Kripke DF, Garfinkel L, Wingard DL, et al. Mortality associated with sleep duration and insomnia. Arch Gen Psychiatry 2002;59(2):131–6; with permission.)

evidence that right hemispheric strokes reduce rapid eye movement (REM) and REM density, whereas left hemispheric strokes decrease NREM stages.[55] Strokes localized to the pontomesencephalic junction and the raphe nucleus may preferentially reduce NREM sleep without affecting REM sleep.[56] Paramedian thalamas strokes and strokes in the lower pons are associated with loss of slow wave sleep but preservation of REM sleep.[26] Conversely, several studies suggest strokes in the lower pons may also reduce REM sleep.[57,58] Finally, some studies suggest infratentorial strokes eliminate sleep spindles, K complexes, and/or vertex waves, thus changing the electroencephalography patterns of NREM sleep.[58] Finally, changes in sleep architecture associated with decreased functional recovery in stroke include decreased sleep efficiency, increased awakenings, decreased stage 2 sleep, decreased sleep spindles and K complexes, and increased stage 3 sleep.[59]

Diagnosis and Treatment of Insomnia

Diagnosis of insomnia is primarily clinical and often includes a detailed history, a 2-week sleep diary, identification of potential confounding medical and psychiatric illnesses, and occasionally, quality-of-life and daytime functioning questionnaires. Polysomnography is only indicated for patients with insomnia in instances of insomnia refractory to pharmacologic or cognitive treatment or if another sleep disorder is suspected. Actigraphy may be used to delineate sleep patterns, especially if the patient's sleep perception is difficult to discern.[60]

The simplest and perhaps most important treatment of insomnia after stroke involves encouraging appropriate sleep hygiene, including limiting exposure to nighttime stimulation and increasing exposure to daylight. Other important practices of appropriate sleep hygiene include limiting exposure to "smart" devices (smartphone, tablet) and backlit screens in the bedroom, avoiding work or thinking about work in the bedroom, and maintaining a dark, quiet environment in the bedroom.

Psychological and behavioral modifications are indicated as first-line therapy for insomnia in all adults, either independently or coupled with other therapies including medications.[60] Cognitive behavioral therapy, including stimulus control therapy, sleep restriction therapy, and/or relaxation therapy, are recommended as standard of care for insomnia treatment.

Pharmacotherapy may supplement cognitive behavioral therapy but is recommended to be restricted to short-term use. The consensus statement of use of pharmacotherapy recommends choosing pharmacologic agents based on symptom pattern, treatment goals, past treatment responses, patient preference, cost, availability of other treatments, comorbid conditions, contraindications, concurrent medication interactions, and side effects.[60] In stroke patients, sedative hypnotics should generally be avoided if possible because of the risk of increased memory impairment, disorientation, and falls.

Other treatments specifically evaluated in stroke patients include acupuncture and problem-solving therapy. A double-blinded randomized control trial demonstrated utility of intradermal acupuncture in reducing insomnia in poststroke patients.[61] Problem-solving therapy with or without cognitive behavioral therapy also demonstrated efficacy in improving insomnia symptoms in stroke patients.[62] However, cognitive behavioral therapy remains the recognized standard of treatment for insomnia.

HYPERSOMNIA AND STROKE

Hypersomnia is defined as an "inability to stay awake and alert during the major waking episodes

of the day, resulting in periods of irrepressible need for sleep or unintended lapses into drowsiness or sleep."[33] The prevalence of hypersomnia in the adult population is estimated at 20%.[63] In the stroke population, hypersomnia affects up to 27% of patients.[64] Studies investigating the association between short sleep duration and stroke abound, but studies addressing the relationship between long sleep duration and stroke are less prevalent. However, recent investigations reveal a U-shaped curve demonstrating increased mortality in both short and long sleepers, and a recent American Academy of Sleep Medicine consensus statement recommends at least 7 hours of sleep per night for adults, with a qualifier identifying unclear risk of increased mortality with sleep exceeding 9 hours.[65]

Several studies indicate that sleep exceeding 9 hours increases cardiovascular risk. The NOMAS study revealed an increased risk of cardiovascular outcomes but not myocardial infarction or nonvascular causes of death in patients with increased daytime sleepiness as measured by a modified Epworth sleepiness scale. This increased risk in cardiovascular events persisted after adjustment for covariates such as obesity, hypertension, and diabetes. The study further demonstrated a greater risk of mortality in excessively sleepy women compared with men but no significant difference when evaluating race or ethnicity.[66] Long sleepers demonstrated that increased mortality correlated strongly with socioeconomic status.[67] However, a study using data from the Nurses' Health Study failed to identify an independent relationship between daytime sleepiness and long sleep time and increased cardiovascular morbidity and mortality when controlling for confounding factors.[68]

The abnormality underlying the association between hypersomnia and stroke is not well understood, although several theories exist. The most prominent hypothesis focuses on demonstrable increased incidence in obesity and diabetes seen in patients with hypersomnia. A study investigating sleep in older women demonstrated decreased physical activity in patients with increased sleepiness and fatigue.[69] Long sleep is associated with increased development of diabetes also, although the underlying abnormality is unclear.[68] Metabolic syndrome, often seen in patients with obesity and diabetes, results in increased proinflammatory cytokines.[70] Proinflammatory cytokines induce sleep as an evolutionary response to promote rest and recovery from illness.[71] Another confounder often associated with hypersomnia is depression, which increases mortality and risk of heart disease.[72] A study investigating the relationship between hypersomnia and mortality discovered that depression attenuated the relationship between hypersomnia and increased mortality.[73]

Hypersomnia may present as a result of stroke as well. Lesions affecting the reticular activating system (RAS) often result in hypersomnia. These lesions include bilateral thalamic lesions, thalamo-mesencephalic lesions, upper and medial pontomedullary regions where RAS fibers are highly concentrated.[26] Lesions in the cerebral hemispheres tend to be less associated with hypersomnia because the RAS fibers are more diffuse, but large cerebral lesions, lesions affecting the left more than the right hemisphere, and lesions affecting the anterior more than the posterior regions result in increased hypersomnia.[74] Paramedian thalamic infarcts result in the most severe hypersomnia cases and typically present with sudden-onset stupor with preservation of responses to stimuli.[75]

Hypersomnia treatment is important especially during rehabilitation. A recent study demonstrated patients exhibiting hypersomnia symptoms in an acute rehabilitation unit were 10 times more likely to be discharged to a nursing facility and had significantly worse functional outcomes.[76] Treatment of hypersomnia in stroke patients differs little from standard treatment of hypersomnia. Mainstays of treatment involve use of amphetamines, modafinil, methylphenidate, and in some cases, levodopa therapy. One study demonstrated that levodopa and methylphenidate treatment improved arousal levels and poststroke outcome when administered in an acute rehabilitation center over a 3-week period.[77,78] Care should be taken when using amphetamines and their derivatives in patients with strokes given the potential for elevation of blood pressure and heart rate (**Table 1**).

OTHER SLEEP DISORDERS AND STROKE (RESTLESS LEG SYNDROME, PERIODIC LIMB MOVEMENTS IN SLEEP, PARASOMNIAS)

Among the sleep disorders, there are 2 types of leg movements that are regularly diagnosed. Restless leg syndrome (RLS) presents as a desire to move the legs that worsens at night and at rest, is partially relieved with movement, and worsens without movement.[33] Periodic limb movements in sleep (PLMS) are defined as leg movements seen during polysomnography that last 0.5 to 10 seconds and occur every 5 to 90 seconds, and at least 4 movements occur consecutively with at least an 8 uV increase in amplitude from baseline as seen in the limb movement leads.[79] Recent studies suggest a relationship between sleep-related leg movements and cardiovascular disease, including

Table 1
Stroke lesions and sleep disorders

	Stroke Lesions Associated with Sleep Disorder
Sleep apnea	Frontal lobe (respiratory apraxia), pontine stroke (neurogenic hypoventilation), inferomedial posterior pons (apneustic respirations), medullary stroke (Ondine curse)
Insomnia	Supratentorial stroke (decreased NREM, TST, SE), right hemisphere decreased REM, left hemisphere decreased NREM, paramedian thalamus strokes decreased NREM, infratentorial strokes eliminate sleep spindles, K complexes, and/or vertex waves
Hypersomnia	Reticular activating system, bilateral thalamic lesions, lesions affecting left more than right and anterior more than posterior, paramedian thalamic infarcts (present with sudden onset stupor)
RBD	Brainstem infarcts

Abbreviations: SE, sleep efficiency; TST, total sleep time.

stroke, although the association of the leg movements with possible vascular phenomena started with Ekbom in the 1940s.[80]

Several cohort studies, including the Wisconsin Sleep Cohort Study, demonstrated significantly increased incidence of hypertension and heart disease in those patients also reporting symptoms of RLS. The Sleep Heart Health Study also reported an increase in cardiovascular disease and coronary artery disease in patients with RLS, but only in RLS sufferers experiencing symptoms at least 16 times per month and with severe symptoms.[81] In a cohort study on older men, a PLMS arousal index exceeding 5 events per hour resulted in an increased risk for cardiovascular disease even after controlling for several comorbid conditions, including age and BMI.[82] According to a study performed by Siddiqui and colleagues,[83] elevated blood pressure following PLMS occurred in increasing and predictable ways based on type of PLMS. However, a few studies failed to find a correlation between hypertension and RLS, and the MEMO study demonstrated an inverse relationship between blood pressure and RLS.[84–86]

One theory suggests the relationship between sleep-related leg movements and cardiovascular disease including stroke relates to increased sympathetic activation seen with arousals associated with PLMS. Increased sympathetic activation is suggested by changes in pulse rate associated with PLMS. Interestingly, the pulse rate increase precedes the PLMS movement. A study by Winkelman[87] identified an increase in heart rate occurring 3 cardiac cycles before PLMS onset with peak at 4 cardiac cycles after PLMS onset. A study by Sforza and colleagues[88] found accelerations in heart rate were highest when PLMS induced a noticeable electroencephalogram (EEG) microarousal.

Published case studies describe increased PLMS and RLS incidence after stroke.[89,90] Lee and colleagues[91] identified an incidence of 12% of stroke patients presenting with RLS. Most patients develop bilateral symptoms of RLS, but a third complain of RLS affecting the contralateral side to the stroke. Conversely, a relationship has been identified suggesting PLMS can increase the risk for stroke. A study done in 26 subjects with RLS control-matched to 241 patients without RLS demonstrated a greater volume of subcortical lesions and cortical atrophy seen in the RLS group.[92] The above studies provide anecdotal evidence that RLS/PLMS may increase the risk of stroke, especially in the basal ganglia, internal capsule, or corona radiata.

Pathophysiology

The pathophysiology resulting in correlation between sleep-related leg movements and cardiovascular consequences such as stroke has yet to be identified definitively, but several theories exist. The most prominent theory linking leg movements to cardiovascular risks revolves around hypofunction of the A11 diencephalospinal pathway, which leads to increased sympathetic output to the periphery via somatic muscle fibers.[93] Typically, increased sympathetic activity results in heightened spinal sensory signaling via afferents from the muscle fibers back to the spinal cord, but this activity is dampened by A11 innervation at the dorsal horn. Theoretically, in RLS, the dopaminergic hypofunctioning of the A11 innervation results in a positive feedback loop, causing increased signaling of afferents back to the spinal cord, which also causes heightened sympathetic activation leading to increased RLS symptoms. This theory is supported by lesion creation in this

pathway in rats that results in a restlessness that responds to pramipexole.[94] The A11 diencephalospinal pathway also links sympathetic activation to hypertension and increased risk of cardiovascular consequences like heart disease and stroke.

Comorbid conditions are also posited as a potential pathophysiology linking sleep-related leg movements to increased cardiovascular morbidity and mortality. Winkelman and colleagues[81] suggests that conditions such as anemia and renal failure may contribute to the association between cardiovascular risk and sleep-related leg movement. Many studies identified an association between sleep-related leg movements and OSA, a disorder that more clearly demonstrates increased cardiovascular risks, as described in an earlier section. Conversely, cardiovascular disease may increase the risk of sleep-related leg movements as seen in case studies.

Ferritin level and an iron panel should be a standard part of an RLS evaluation, and iron supplementation in patients with low ferritin with or without low total iron-binding capacity saturation can result in resolution of RLS symptoms. The standard pharmacologic treatment for sleep-related leg movements continues to be dopamine agonists, with the highest level of recommendation encouraging the use of pramipexole 0.5 to 1.5 mg and ropinirole 1 to 4 mg. Levodopa can be used for patients with intermittent and predictable instigating factors exacerbating RLS symptoms. However, levodopa is not recommended for use in patients needing chronic therapy due to the increased risk of augmentation. Gabapentin is increasingly used for RLS and PLMS with success, especially in those with painful RLS or RLS related to diabetic neuropathy. Opioids can also be used for painful RLS. Newer therapy like rotigotine delivered over a 24-hour period via a transdermal patch has been shown to be more effective than pramipexole and ropinirole but also increases the risk of side effects and had a higher discontinuation rate.[95] Gabapentin enacarbil, essentially a prodrug of gabapentin, is approved for use for RLS. Other off-label treatments for RLS and PLMS include pregabalin, carbamazepine, and clonidine, although the level of evidence is low.[96]

Parasomnias

Parasomnias are undesirable physical events or experiences that occur during entry into sleep, within sleep, or during arousal from sleep.[33] Parasomnias include dream enactment behaviors, sleepwalking, night terrors, and confusional arousals, among others. Most parasomnias present in children and adolescents and resolve by adulthood, but estimated incidence of parasomnias remains approximately 4% in the adult population.[97] Parasomnias may occur secondary to precipitating factors like medications (hypnotics like zolpidem), stress, underlying sleep disorders, or sleep deprivation. Sleepwalking exhibits a strong predilection in first-degree family members with a 10-fold increase in incidence compared with the general population.[98] Parasomnias may also be correlated with stroke.

Parasomnia pathophysiology consists of interruption in sleep stages. Sleep stage shifting occurs as a reorganization and transition of various neuronal centers until one exerts prominence and declares itself, and an arousal during this reorganization is hypothesized to increase complex motor and sensory behavior during sleep.[99]

In REM sleep behavior disorder (RBD) specifically, brainstem lesions are strongly correlated with the development of dream enactment behaviors. In the study by Schenk and Mahowald[100] described in later discussion, one patient developed RBD in response to an acute brainstem stroke and subsequently fractured her hip in the intensive care unit (ICU) during hospitalization. Bilateral pontine tegmental lesions create RBD in animal models. In a study performed in Hong Kong, 22% of patients with a brainstem stroke exhibited associated RBD and demonstrated lower brain volume involved in stroke compared with patients with stroke without RBD. Damage to pontine glutaminergic and medullary GABAergic neurons was implicated as the main abnormality resulting in RBD in this study.[101]

In one of the earliest published studies investigating the relationship of parasomnia behavior in ICU patients, parasomnias resulted from an acute neurologic disorder in 28.5% (4/14) patients. Only 3 of 20 patients identified in the study exhibited symptoms suggestive of NREM parasomnias; the remaining parasomnias consisted of RBD.[100] Of the 4 parasomnia patients in this study who previously had a stroke, all were diagnosed with RBD.

Although RBD is the most commonly associated parasomnia associated with stroke, other parasomnias have been described in association with strokes. Case studies described visual hallucinations especially at sleep onset associated with infarcts in the pontine tegmentum, midbrain, or paramedial thalamus.[47] Increased dreaming or nightmares and a syndrome resembling confusional arousal has been described following strokes in the thalamus, temporal, parietal, and occipital lobes.[102]

No clear evidence exists linking pre-existing parasomnias to the development of stroke; however, as mentioned previously in several sections, sleep disruption itself can result in increased

sympathetic output during sleep, thereby increasing cardiovascular stress.

For definitive diagnosis of parasomnias, polysomnography may be required to distinguish between REM and NREM parasomnias and to evaluate for nocturnal seizures (which may require a full EEG montage).

Treatment of RBD typically consists of optimizing the bedroom environment to reduce risk of injury and treating underlying sleep disorders, such as OSA. Medication therapy for RBD includes clonazepam at 0.5 mg to 2 mg an hour before bedtime. If clonazepam is not well-tolerated or contraindicated, such as in patients with dementia or gait disorders, melatonin is indicated. Melatonin is a safe alternative to benzodiazepines that may also be effective for RBD treatment.[103]

Pramipexole may also be used in this population and has demonstrated effectiveness in some studies, although contradictory studies exist as well. Case studies demonstrated effective treatment with the following medications, although evidence is limited: zopiclone, benzodiazepines other than clonazepam, Yi-gan san, desipramine, clozapine, carbamazepine, and sodium oxybate.[104] Treatment of parasomnias other than RBD is similar, with clonazepam as the suggested initial treatment.

SUMMARY

Over the past decade, the importance of sleep disorders has grown within the medical community, increasingly recognized as being related to many medical conditions. This review has elucidated the bidirectional relationship of stroke with certain sleep disorders, with further research necessary to better understand these correlations. 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.

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