Sleep and stroke

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Introduction

This article includes discussion of sleep and stroke, vascular dementia, and atrial fibrillation. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

In this article, the author highlights the importance of obstructive sleep apnea as a risk factor for stroke. Rehabilitation and recovery are less successful in the presence of sleep apnea. Habitual short and long sleep durations, long-standing night shift work, and periodic leg movements of sleep negatively affect cerebrovascular morbidity and mortality. Vascular dementia may be a complication of uncontrolled sleep apnea with hypoxemia.

Key points

- Obstructive sleep apnea is the most common sleep disorder and is a major risk factor for stroke and transient ischemic attack.
- Central sleep apnea is also a risk factor for ischemic stroke.
- All stroke and transient ischemic attack patients should be screened for sleep disorders and, if appropriate, should be considered for treatment with CPAP.
- Sleep apnea is present in 70% of acute stroke patients.
- Treatment of sleep apnea may lower the incidence of vascular morbidity and mortality.
- Wake-up stroke may be related to severe sleep apnea, right-to-left shunt provoked by long-duration apnea events in patients with patent foramen ovale, or atrial fibrillation in sleep apnea patients.
- Vascular dementia may be a complication of uncontrolled sleep apnea with nocturnal hypoxemia.

Historical note and terminology

The major sleep disorder associated with stroke is sleep apnea (Culebras 2013). Gastaut described obstructive sleep apnea and pointed out its relevance for the pathogenesis of Pickwickian syndrome (Gastaut et al 1966). The Pickwickian syndrome (now termed obesity hypoventilation syndrome) was recognized and named in 1956 (Burwell et al 1956). The association of sleep apnea with stroke was stressed with the discovery of snoring as a risk factor for stroke, the high incidence of sleep apnea in stroke patients (Kapen et al 1991), and a significant peak for stroke incidence in the morning hours (Marshall 1977). In 2008, the American Heart Association highlighted in a scientific statement concepts and evidence important to understanding the interactions between sleep apnea and vascular disease (Somers et al 2008).

Clinical manifestations

Presentation and course

It may be difficult to differentiate the sleepiness and other symptoms associated with obstructive sleep apnea from such acute manifestations of cerebrovascular disease as lethargy, apathy, and neglect, particularly with strokes in specific locations, such as bilateral paramedian thalamic infarctions. The spouse of a stroke victim may describe a lack of energy, falling asleep during activities, and fatigue. Additional questioning may elicit a history of snoring (with repetitive respiratory interruptions), restless sleep, nonrestorative sleep, and weight gain prior to or following the stroke. Weakness of pharyngeal dilator muscles following a stroke may contribute to the elevated resistance in the upper airway that is common in obstructive sleep apnea. Dysphagia and dysarthria in acute stroke patients are generally associated with sleep apnea (Culebras 2012).

Twenty-four hour ambulatory blood pressure monitoring reveals that arterial pressure ordinarily falls during nocturnal sleep 10% to 20% below that of diurnal waking, However, 50% of acute hemispheric ischemic stroke patients are

"nondippers" (a fall of less than 10%), as are 23% of lacunar infarct patients versus 7% of controls (Kukla et al 1998). In general, target organ damage is greater in nondippers than in dippers, even though they may have comparable 24-hour mean blood pressure levels. Interestingly, both "reverse dipping" and "extreme dipping" (greater than 20% nocturnal reduction) are independent risk factors for multiple silent lacunar infarcts in elderly Japanese hypertensive patients (Kario et al 2001).

The incidence of periodic central sleep apnea during sleep (Cheyne-Stokes) in stroke patients has been reported to be as high as 41% (Siccoli et al 2008) (a smaller, earlier study cited 53%). Furthermore, data from the Sleep Heart Health Study reveal that the presence of central sleep apnea is associated with MRI evidence of white matter ischemic changes or frank infarcts (Robbins et al 2005), and central sleep apnea is an independent risk factor for stroke in elderly patients (Muñoz et al 2012).

Sleep disruption and nonrestorative sleep are ubiquitous following hemispheric strokes as is daytime sleepiness, even in the absence of sleep apnea. The presence of sleep continuity disturbances in the acute phase of stroke may represent a risk factor for poor outcome (Vock et al 2002). In a rat model of middle cerebral artery ischemic stroke, sleep deprivation hindered functional recovery and impaired synaptogenesis and cell proliferation (Zunzunegui et al 2011). Lastly, poststroke depression may affect up to one third of hemispheric stroke patients.

Prognosis and complications

A brief sleep history should be part of the diagnostic workup for every stroke or transient ischemic attack and should include the following details:

(1) presence of loud snoring
(2) witnessed apneas
(3) frequent arousals, particularly with gasping
(4) nonrestorative sleep
(5) excessive daytime sleepiness
(6) nocturia (Chen et al 2011)

Presence of the above symptoms may alert the clinician to the need for polysomnography, particularly if the patient is overweight or obese because obstructive sleep apnea increases morbidity and mortality in stroke patients (Parra et al 2004; Turkington et al 2004). Sleepiness, fatigue, and poststroke depression are all likely to exert an unfavorable influence on stroke outcome through effects on motivation and performance (Cherkassky et al 2003; Kaneko et al 2003; Park et al 2009). All of these conditions are often associated with reduced sleep quality, which may independently impair performance. Furthermore, the lack of restorative sleep generally leads to impaired sleep hygiene, such as excessive napping during the day, further reducing nocturnal sleep efficiency.

Obstructive sleep apnea independently contributes to cognitive dysfunction in stroke patients through hypoxemia and sleeping discontinuity. The prospective memory test is a simple but sensitive method to detect sleep apnea-induced cognitive impairment in stroke patients (Zhang et al 2017).

Clinical vignette

JT was a 62-year-old male who presented with dysphasia and minimal right hemiparesis. He had a history of hypertension, noninsulin-dependent diabetes mellitus, gout, chronic alcoholism, chronic pancreatitis, and depression. He was on multiple cardiovascular medications, glipizide, and fluoxetine. On examination, his blood pressure was 110/70. He was talking incomprehensibly, and his family said that he had become more forgetful. There was a predominantly Wernicke-type dysphasia and a right visual field cut. Chest x-ray revealed moderate congestive heart failure. CT revealed old lacunae in the left hemisphere along with a new hypodensity in the left temporal-occipital area with obliteration of sulci. There were also periventricular ischemic changes. The echocardiogram revealed enlargement of the left atrium and dysfunction of the left ventricle. He was thought to have embolic stroke and was started on crystalline warfarin sodium and an angiotensin-converting enzyme inhibitor, but these medications were discontinued because of poor tolerance. He was seen in the Sleep Wake Disorder Unit 3 months later. In the interim, with the help of speech therapy, his dysphasia markedly improved. He complained of insomnia and fatigue since his stroke and insisted that he had no sleep complaints previously. He denied abnormal leg movements or breathing problems. At the time of the sleep study he reported that his usual sleeping hours were from 3 A.M. to 6:30 A.M. and that he was not sleepy and unable to fall asleep prior to that time. The polysomnogram revealed a bedtime of 10:47 P.M. and arise

time 5:42 A.M. His sleep efficiency was 85%, with a latency to sleep of 24 minutes and 27 minutes to the first REM period. Stage 1 was 34%, delta sleep was completely absent, and REM sleep was 20%. He had 151 respiratory events, of which 47 were apneas and 104 hypopneas. They were predominantly obstructive in nature. The apnea-hypopnea index was 25.6, and the lowest oxygen saturation was 89% in REM sleep. He spent 68% of his sleep time in a supine position; respiratory events were posture-dependent. There were no periodic leg movements. The multiple sleep latency test revealed a latency of 18 minutes, and there were no sleep-onset REM periods.

Comment. This may be an example of a sleep disorder precipitated by stroke, which seems to be much less common than preexisting obstructive sleep apnea acting as a risk factor for stroke. The complaint of insomnia was only partially confirmed by the polysomnogram, but he did have significant apnea. Of note is his lack of obesity (5 feet 9 inches tall and 135 pounds) and the fact that there was no excessive daytime sleepiness, either subjectively or objectively. Finally, his short REM latency on the polysomnogram was related either to his previous depression (despite fluoxetine), to the presence of brain damage in the left hemisphere, or both factors acting in concert.

Biological basis

Etiology and pathogenesis

Obstructive sleep apnea may act as a risk factor for stroke because of its association with systemic hypertension and other risk factors for stroke, including atrial fibrillation. One study found that the morning surge of blood pressure was the strongest predictor of stroke during an average follow-up period of 41 months in elderly hypertensives (Kario et al 2006); obstructive sleep apnea may contribute to that surge, and nifedipine, administered at bedtime, may reduce the surge (Hermida et al 2009). Additionally, changes in autoregulation of cerebral blood flow in severe obstructive sleep apnea may contribute to the increased morning stroke risk (Urbano et al 2008).

In 2006, the American Heart Association and American Stroke Association, together with other interested groups, issued a guideline on risk factors for stroke in which a recommendation for obtaining a history regarding symptoms of sleep-disordered breathing and referral to a sleep specialist for appropriate patients was considered Class IIb (usefulness/efficacy is less well established by evidence or opinion), Level C (lowest level of evidence – consensus opinion of experts) (Goldstein et al 2006). An update of the guideline has raised the recommendation to Class I (evidence for and/or general agreement that the procedure is useful and effective), Level A (data derived from multiple randomized clinical trials) (Goldstein et al 2011). The effectiveness of sleep apnea treatment to prevent the occurrence of stroke is still unknown according to the guideline (Class IIb, Level of Evidence C).

Atrial fibrillation has been linked to severe, uncontrolled sleep apnea. Atrial fibrillation increases the risk of stroke by 5% to 10% per year (Stroke Risk in Atrial Fibrillation Working Group 2007). Clinical data have shown a strong relationship between sleep apnea and atrial fibrillation, and epidemiologic studies suggest that sleep apnea is a risk factor for new-onset atrial fibrillation. A large study evaluated 3542 patients without atrial fibrillation who underwent polysomnography and were followed for an average of 5 years (Gami et al 2007). In patients less than 65 years old, nocturnal oxygen desaturation predicted new-onset atrial fibrillation. Sleep apnea may confer a poorer prognosis for recovery after atrial fibrillation interventions. In a study of 424 patients undergoing ablation, sleep apnea more than doubled the risk of acute intraprocedural failure (Sauer et al 2006). The effects of sleep apnea therapy on atrial fibrillation outcomes are largely unknown, and prospective randomized controlled trials are necessary to clarify this issue. In 1 study of 47 women and 111 men with subacute ischemic stroke admitted for neurorehabilitation, mean nocturnal desaturation was significantly associated with atrial fibrillation after adjusting for age, neck circumference, Barthel index, and high-density lipoprotein level (odds ratio = 1.19 [95% confidence interval 1.05-1.35], P = .008) (Chen et al 2017). The authors concluded that nocturnal hypoxia due to obstructive sleep apnea is an independent predictor of atrial fibrillation in patients with subacute ischemic stroke. Another study has confirmed the high prevalence of sleep apnea in stroke-affected patients and has identified atrial fibrillation as a major source of stroke in this population, concluding that the strong correlation between age and sleep apnea drives the increased frequency of stroke related to atrial fibrillation (Poli et al 2017).

In severe obstructive sleep apnea, oxygen saturation may fall below 85% for more than half the night and may frequently reach levels below 50%. The consequences of this degree of oxygen desaturation include early onset thickening of the carotid artery wall, even prior to the appearance of other risk factors, such as hypertension (Silvestrini et al 2002). In addition, accelerated carotid atherosclerosis accompanies heavy snoring independent of sleep-disordered breathing (Lee et al 2008). Perhaps this is related to the effects of vibration on the carotid artery.

Inflammation and hypoxia are intertwined at the molecular, cellular, and clinical levels. Repeated hypoxia may damage the endothelium and trigger the release of proinflammatory factors like plasma cytokines, tumor necrosis factor-alpha, and interleukin-6 (Lavie 2004). Chronic intermittent hypoxia causes vascular dysfunction by increasing endothelin, augmenting neurovascular oxidative stress, decreasing vascular neuromuscular reserve, reducing vascular reactivity, and increasing susceptibility to injury (Capone et al 2012).

Wake-up stroke refers to the presence of symptoms and signs of stroke on awakening. Wake-up stroke conjures the notion of some vascular event occurring during the night while the patient is asleep. Clinically significant sleep apnea, nocturnal hypoxemia, atrial fibrillation secondary to hypoxemia, and right-to-left shunt triggered by apnea events in patients with patent foramen ovale should be considered. In a study of 71 patients with mild to moderate stroke, the authors aimed to determine independent variables associated with wake-up stroke (Hsieh et al 2012). Of the 71 patients, 26 (36.6%) had wake-up stroke. Comparing both groups, patients with wake-up stroke had a significantly higher apnea-hypopnea index (23.1 ± 19.4 vs. 12.5 ± 11.9, p = 0.016) and lower mean blood oxygen saturation (95.1 ± 1.5 vs. 95.8 ± 1.3, p = 0.046) than the non-wake-up stroke patients. Severe sleep-disordered breathing (apnea-hypopnea index 30 or higher) was the only independent variable associated with wake-up stroke (OR 6.065, 95% CI 1.451-25.350; p = 0.014). The authors concluded that obstructive sleep apnea is an independent risk factor associated with wake-up stroke.

In a study of 335 patients (mean age 64 years) with wake-up stroke or transient ischemic attack, 202 (60%) had at least 1 long obstructive sleep apnea (greater than 20 seconds) and 116 (35%) a right-to-left shunt; 69 (21%) had both (Ciccone et al 2013). There were significantly more wake-up strokes and transient ischemic attacks in subjects with right-to-left shunt plus long obstructive sleep apnea than those without this association (27/69 vs. 70/266; OR 1.91, 95% CI 1.08 to 3.38; p=0.03). The authors concluded that the combination of long obstructive sleep apnea and right-to-left shunt could be a potentially treatable risk factor for cerebrovascular ischemic events. The authors hypothesized that long obstructive sleep apnea can lead to right-to-left shunting and propitiate paradoxical embolism.

To investigate the relationship between nocturnal atrial fibrillation and wake-up stroke, Riccio and colleagues prospectively assessed every acute ischemic stroke and transient ischemic attack patient admitted to hospital over a 3-year period (Riccio et al 2013). They studied 356 patients, 274 (77.0%) with a diagnosis of acute ischemic stroke and 82 (23.0%) with transient ischemic attack. A total of 41 (11.5%) events occurred during night sleep. Newly diagnosed atrial fibrillation was detected in 27 patients of 272 without known atrial fibrillation (9.9%). The authors found an independent association between newly diagnosed atrial fibrillation and wake-up ischemic stroke and transient ischemic attack (odds ratio 3.6, 95% confidence interval 1.2-7.7, p = 0.019) and concluded that the odds of detecting newly diagnosed atrial fibrillation were 3-fold higher among wake-up cerebrovascular events than among non-wake-up events.

Epidemiology"

Most surveys have reported a 75% incidence of obstructive sleep apnea in stroke patients based on an apnea-hypopnea index of 10 and approximately 50% based on an index of 20 or more (Bassetti and Aldrich 1999). In a 10-year follow-up of subjects enrolled in a large, community-based epidemiologic survey, the relative risk for stroke was significantly greater in those individuals who reported excessive daytime sleepiness, a symptom that may be associated with sleep apnea syndrome (Empana et al 2009). More importantly, the ongoing multicenter Sleep Heart Health Study found that even mild degrees of sleep-disordered breathing posed a modest but significant risk factor for stroke with an odds ratio of 1.58 (Shahar et al 2001). Finally, a number of longitudinal studies have shown that obstructive sleep apnea is a risk factor for stroke. Two studies reported that even after adjustment, the presence of sleep apnea was associated with a greater odds ratio (1.97) for stroke and death compared with a control group after an average follow-up interval of 3.3 years (Yaggi et al 2005) and after 10 years (hazard ratio 1.76) (Sahlin et al 2008). The MESA study (Multiethnic Study of Atherosclerosis) reported a higher incidence of cardiovascular events, including stroke, in patients with a diagnosis of obstructive sleep apnea (Yeboah et al 2011).

The association of stroke with sleep apnea may change with time. Parra and colleagues described polysomnographic findings during the first 3 days after a first-ever stroke and compared them with the findings 3 months later (Parra et al 2000). The apnea-hypopnea index declined from 71.4 to 61.6 at the later time-point, primarily due to a drop in central events (including Cheyne-Strokes respiration), whereas the number of obstructive events remained stable. This suggests that obstructive apneas usually predate an acute stroke, whereas central apneas may arise from the stroke itself.

Stroke may be more prevalent in women with sleep apnea. In 1 large study, 71,779 female nurses 40 through 65 years of age without previously diagnosed vascular disease were followed for 8 years, and frequency of snoring was assessed using mailed questionnaires; 398 women suffered a stroke (Hu et al 2000). The age-adjusted relative risk of stroke was 1.60 (95% CI 1.21 to 2.12) for occasional snorers and 1.88 (95% CI 1.29 to 2.74) for habitual snorers. After further adjustments, the association between snoring and vascular disease remained positive at 1.33 (95% CI 1.06 to 1.67) for regular snorers. Although the study did not identify patients with sleep apnea, the assumption was made that habitual snoring was a marker of obstructive sleep apnea and likely the background risk factor for vascular disease.

In another study, the authors provided evidence that stroke has a higher incidence in Chinese women 35 years old or younger, with a sleep apnea/hypopnea index of 5/hour or higher (Chang et al 2014). The authors used a universal insurance claims database and identified a large cohort of sleep apnea patients using polysomnography. They identified 29,961 patients with sleep apnea and compared the sex- and age-specific stroke risk with a control group. The sleep apnea cohort had a higher stroke incidence in women with an adjusted hazard ratio between males and females of 1.21 (95% CI 1.01 to 1.24; $p < 0.05$) and 1.44 (95% CI 1.20 to 1.72; $p < 0.05$), respectively. Stratified by age, the effects of sleep apnea on stroke risk in women decreased with advancing age (adjusted HR 4.90, 95% CI 1.93 to 12.4 for subgroup aged 20 to 35 years; adjusted HR 1.64, 95% CI 1.01 to 2.65 for subgroup aged 36 to 50 years; adjusted HR 1.38, 95% CI 1.01 to 1.89 for subgroup aged 51 to 65 years). The authors concluded that young Chinese women with sleep apnea are at higher risk of stroke and hypothesized that structural and hormonal differences in young women might have increased the risk of stroke.

In a study of 394 old males aged 70 to 100 years, the authors concluded that severe obstructive sleep apnea/hypopnea (AHI [apnea/hypopnea index]=30/hour or higher) increases the risk of ischemic stroke in an elderly male non-institutionalized population, independently of known confounding factors (Muñoz et al 2006).

In a cross-sectional analysis of 1475 individuals, the authors found that subjects with an apnea-hypopnea index of 20/hour or greater had increased odds for stroke (odds ratio 4.33; 95% CI 1.32 to 14.24; $p = 0.02$) compared with those without sleep-disordered breathing (AHI < 5) after adjustment for known confounding factors (Arzt et al 2005). They concluded that there is a strong association between moderate to severe sleep-disordered breathing and prevalent stroke, independent of confounding factors.

There is growing evidence that small vessel disease and leukoaraiosis are worse in subjects with sleep apnea disorder. White matter disease in the form of leukoaraiosis is associated with sleep-disordered breathing in acute stroke patients (Harbison et al 2003), and there is a greater risk of silent strokes in high-risk individuals who have nocturnal oxygen desaturation (Eguchi et al 2005). A study found that obstructive sleep apnea with an AHI of more than 15/hour is a risk factor for cerebral white matter changes in middle-aged and older patients (OR 2.08; 95% CI 1.05 to 4.13) (Kim et al 2013). Also, it has been shown that obstructive sleep apnea with an AHI of more than 15 is a risk factor for silent cerebral infarction in patients older than 65 (OR 2.44; 95% CI1.03 to 5.80) (Cho et al 2013). In another study, moderate-to-severe obstructive sleep apnea was associated with multiple indicators of cerebral small vessel disease, including white matter hyperintensities, cerebral microbleeds, and enhanced perivascular spaces as seen in MRI (Song et al 2017). It has also been suggested that moderate-to-severe obstructive sleep apnea can be 1 of the independent predictors of cerebral microbleeds, which are considered a surrogate marker of overt stroke (Koo et al 2017).

These observations support the hypothesis that brain regions with poor hemodynamic reserve are preferentially affected in sleep apnea and coincide with reports of permanent alteration of auditory event-related potentials in these patients. In fact, obstructive sleep apnea may be a risk factor for subcortical ischemic vascular dementia, a notion supported by the observation that older women (mean age 82.3 years) with obstructive sleep apnea more than 15/hour were more likely to develop mild cognitive impairment or dementia (adjusted odds ratio [AOR] 1.85; 95% CI 1.11 to 3.08) (Yaffe et al 2011; Román 2013). In a home polygraphic study of 2636 men (median age 76.0 ± 5.3 years), it was found that nocturnal hypoxemia was associated with cognitive mental decline as measured by the Modified Mini-Mental (MMM) scores (Blackwell et al 2015). For each 5 points of increment in desaturation index there was an annualized decline in MMM of 0.36 points (P=0.01.

In a study of patients with minimal cognitive impairment or with Alzheimer disease, the results showed that in patients with sleep apnea, mental decline started at an earlier age (MC, group 1: 72.63 vs. 83.67; MC, group 2: 72.15 vs. 83.45; MC, group 3: 77.40 vs. 89.89; $p < 0.01$) (AC, group 3: 83.46 vs. 88.13; $p < 0.05$) (Osorio et al 2015).

These studies further suggest that early therapeutic intervention in sleep apnea is desirable.

Prevention

The treatment of severe obstructive sleep apnea patients with CPAP during an average 10.1-year period reduced fatal and nonfatal events, including stroke, compared with untreated sleep apnea patients (Marín et al 2005). Another study demonstrated the efficacy of CPAP treatment for the prevention of vascular events (ie, myocardial infarction, stroke, acute coronary syndrome, and vascular death) in patients with mild to moderate obstructive sleep apnea (AHI 30.9 +/- 21.8) versus untreated controls (AHI 15.3+/-13.0). Over a 6-year follow-up period, treated patients had a 28.5% risk reduction compared with the control group, independent of other possible confounding risk factors (Buchner et al 2007). Another small study found that administration of auto-titrating CPAP to transient ischemic attack patients with obstructive sleep apnea nonsignificantly reduced the incidence of vascular events during a 90-day period following the transient ischemic attack compared with a non-treated control group (2% [1 of 45 patients] versus 12% [3 of 25]) (Bravata et al 2010). Timely diagnosis and treatment of obstructive sleep apnea may also alleviate the worsened functional outcome of stroke patients who have sleep apnea (Cherkassky et al 2003; Kaneko et al 2003; Ryan et al 2011). Another important modifiable risk factor may be insufficient or excessive sleep. The relative risk for ischemic stroke in postmenopausal women followed for 7.5 years was 1.22 in those women who reported sleeping less than or equal to 6 hours per night and who had no cardiovascular disease at baseline (Chen et al 2008). In the same group of women, longer sleep (more than or equal to 9 hours per night) was also an independent risk factor for stroke. Similar findings in the general population were reported by Grandner and colleagues (Grandner et al 2012). Analysis of data from the very large Nurses' Health Study has also revealed a slightly enhanced stroke risk (hazard ratio 1.04) from cumulative lifetime rotating night-shifts, suggesting circadian rhythm disruption along with sleep deprivation as causative factors (Brown et al 2009). Finally, a meta-analysis has confirmed the deleterious effect of short sleep on ischemic stroke incidence in 15 studies comprising 474,684 individuals (relative risk 1.15); in this meta-analysis, long sleep was also significant (RR 1.65) (Cappuccio et al 2011).

Differential diagnosis

Vigilance and attention span can be affected in acute stroke patients by conditions other than excessive sleepiness. Lesions of the right parietal lobe or deep white matter may induce neglect of the opposite side and may present as lethargy. Frontal lobe damage can be associated with apathy or, in more severe cases, with abulia in which patients show no motor or cognitive initiative. Cerebral edema during the first several weeks after a large ischemic lesion or hemorrhage impairs attention span and alertness. Psychomotor retardation can be a feature of poststroke depression, which can be seen in up to 30% of stroke patients. Metabolic and toxic conditions need to be ruled out along with other causes of daytime sleepiness, such as narcolepsy and periodic leg movements of sleep.

Finally, congestive heart failure must be ruled out as a cause of periodic respiration during sleep.

Diagnostic workup

Polysomnography, the most valuable diagnostic test, should be performed in any stroke patient with loud snoring, restless sleep with or without involuntary leg movements, or excessive daytime sleepiness, particularly if the patient is obese. Ten or more respiratory events (apneas and hypopneas) per hour of sleep is a commonly used threshold for the diagnosis of obstructive sleep apnea, but 20 or more respiratory events per hour of sleep may be more significant in predicting morbidity and mortality. A decision regarding management should not just take into account the number of respiratory events, however, but should also be based on the severity of nocturnal hypoxemia, cardiac arrhythmias, and sleepiness. Sleepiness can be quantified objectively by the multiple sleep latency test and subjectively by the Epworth Sleepiness Scale.

Polysomnography may also reveal the presence of periodic movements of sleep, the clinical significance of which is based on association with arousals and complaints of insomnia or hypersomnolence. Indeed, in patients with renal failure, the presence of periodic limb movements of sleep is itself a risk factor for stroke (Lindner et al 2012).

Management

Obstructive sleep apnea adversely affects the length of hospitalization and functional capacity after ischemic strokes (Cherkassky et al 2003; Kaneko et al 2003). In patients with acute stroke, altered vasomotor reactivity may be aggravated by sleep apnea (Alexandrov et al 2009). The authors reported the occurrence of intracranial blood flow

steal in response to changing vasodilatory stimuli like carbon dioxide elevations in patients with sleep apnea and stroke. This phenomenon has been termed the “reversed Robin Hood syndrome.” It might play a pivotal role in clinical deterioration after an acute stroke and has led to the notion that noninvasive ventilatory correction in select acute stroke patients might have a beneficial effect on sleep apnea and brain perfusion.

Continuous positive airway pressure reduced the incidence of recurrent strokes during a 5-year follow-up period in sleep apnea patients compared with patients who did not tolerate the treatment (Martínez-García et al 2009). One study reported a reduction of deaths from cardiovascular events (cardiac and cerebrovascular) in patients with severe sleep apnea treated with CPAP over an average period of 10.1 years (Marín et al 2005), and another study described a 28.5% reduction in vascular morbidity and mortality even in cases of less severe obstructive sleep apnea (apnea-hypopnea index 30.9 +/- 21.8) compared with nontreated patients (average follow-up 6 years) (Buchner et al 2007). For patients who do not tolerate continuous positive airway pressure, alternative therapies include various modes of surgery or dental devices. Weight reduction for obese patients and treatment for alcoholism should be encouraged. One study, however, showed that therapy with CPAP plus usual care, as compared with usual care alone, did not prevent cardiovascular events in patients with moderate-to-severe obstructive sleep apnea and established cardiovascular disease (McEvoy et al 2016).

Patients with cerebrovascular disease and hypertension have a high prevalence of obstructive sleep apnea. The use of portable polysomnography and autotitrating CPAP in the patients' homes improved both the diagnosis and the treatment for sleep apnea compared with usual care but did not lower blood pressure (Bravata et al 2017).

Results in the study by Osorio and colleagues showed that treatment with CPAP slowed onset and progression of mental decline (CMC, group 1: 72.63 vs. 82.10; CMC group 2: 72.11 vs. 82.10; $p < 0.01$) (Osorio et al 2015).

Besides CPAP, intravenous theophylline and oxygen inhalation are the most effective therapies available for stroke patients with periodic breathing. Temazepam 15 mg modestly improved sleep architecture but had no effect on Cheyne-Stokes breathing (Biberdorf et al 1993).

Subcortical lesions can induce periodic leg movements of sleep (Lee et al 2009). If periodic leg movements of sleep are a significant problem, ropinirole .25 to .75 mg or pramipexole up to 0.75 mg prior to sleep is recommended.

Nortriptyline has been used successfully for the treatment of poststroke depression.

Special considerations

Anesthesia

Airway difficulties in sleep apnea patients have been frequently reported in the anesthesiology literature. Careful monitoring and early provision of an airway are necessary and prophylactic tracheostomy should be considered in particularly serious cases.

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**References especially recommended by the author or editor for general reading.

Former authors

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ICD and OMIM codes

ICD codes

ICD-9:
Obstructive sleep apnea: 327.23
Primary central sleep apnea: 327.21
Unspecified sleep apnea with sleep disturbance: 780.57
Mood disorders: 296-301
Sleep-related movement disorder, unspecified: 780.58
Acute but ill-defined cerebrovascular disease: 436

ICD-10:
Sleep apnoea: G47.3
Mood (affective) disorders: F30-F39
Other specified extrapyramidal and movement disorders: G25.8
Cerebrovascular accident NOS: I64

Profile

Age range of presentation

19-44 years
45-64 years
65+ years

Sex preponderance

male=female

Family history

none

Heredity

none

Population groups selectively affected

none selectively affected

Occupation groups selectively affected

none selectively affected

Differential diagnosis list

lesions of the right parietal lobe
lesions of deep white matter
frontal lobe damage
cerebral edema
poststroke depression
metabolic conditions
toxic conditions
narcolepsy
periodic limb movements
congestive heart failure

Associated disorders

Sleep apnea associated with stroke

Other topics to consider

Central sleep apnea
Depression after stroke
Medical complications of stroke
Obstructive sleep apnea
Sleep disorders
Sleep disorders associated with cardiac disorders
Sleep disorders associated with medical disorders