Sleep and Comorbid Neurologic Disorders

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Relationship Disclosure: Dr Watson serves on the Board of Directors for the American Academy of Sleep Medicine and the American Sleep Medicine Foundation. Dr Viola-Saltzman reports no disclosure.

Unlabeled Use of Products/Investigational Use Disclosure: Drs Watson and Viola-Saltzman report no disclosures.

ABSTRACT

Purpose of Review: An understanding of the impact of sleep on neurologic disorders, and the impact of neurologic disorders on sleep, provides fresh opportunities for neurologists to improve the quality of life and functioning of their patients.

Recent Findings: Sleep-disordered breathing (SDB) is a risk factor for cerebrovascular disease and should be considered in all TIA and stroke patients. Sleep disorders can amplify nociception and worsen headache disorders; and some headaches, including those related to SDB and hypnic headache, are sleep specific. REM sleep behavior disorder may be an early sign of neurodegenerative disease. Focal lesions of almost any etiology (eg, multiple sclerosis and CNS malignancies) in the hypothalamus, basal forebrain, or brainstem may result in sleep disturbance, sleepiness, and insomnia. Sleep-related hypoventilation and fatigue are common in neuromuscular disease. SDB and epilepsy are mutually facilitatory, and poor sleep can exacerbate epilepsy.

Summary: Continued surveillance for sleep disorders by neurologists is rewarded by new treatment avenues in their patients with the possibility of improved clinical outcomes.

Continuum (Minneap Minn) 2013;19(1):148–169.

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INTRODUCTION

Sleep medicine is neurology; all sleep disorders emanate from or involve the central or peripheral nervous system. Even sleep-disordered breathing (SDB), considered by many a pulmonary or otolaryngologic disorder, is caused in large part by ineffective maintenance of oropharyngeal muscle tone in sleep. The intersection between sleep and neurologic disorders is broad and deep. Almost every neurologic disorder affects or is affected by sleep.

CEREBROVASCULAR DISEASE AND SLEEP-DISORDERED BREATHING

Multiple well-adjusted, cross-sectional studies show a dose-response relationship between sleep-disordered breathing (SDB) severity and odds of prevalent stroke.[1,2] Longitudinal studies also demonstrate that increased SDB severity increases incident stroke risk.[2–6] Even mild SDB is associated with increased incident stroke[5] and increased risk of composite stroke, TIA, or death.[6] The reverse is also true: incident cardiovascular disease is associated with worsening of SDB over a 5-year period.[7] Incident stroke in particular increases central SDB, which is common following stroke, and may represent silent brain ischemia disturbing central respiratory mechanisms.[8] **Table 8-1** presents a synopsis of epidemiologic studies assessing incident stroke in patients with SDB.

Stroke timing favors a role for SDB. Awakening increases sympathetic nervous system activity and the renin-angiotensin-aldosterone axis, causing a sharp morning rise in arterial blood pressure and heart rate. Both ischemic and hemorrhagic stroke have a peak incidence in the morning hours, with ischemic stroke occurring about the time

TABLE 8-1 Synopsis of Studies Assessing Incident Stroke in Patients With Sleep-Disordered Breathing

Study	N =	Time Followed (Years)	Number of Events (Strokes) Observed	Fully Adjusted Odds Ratio or Hazard Ratio	*P* Value	Comments
Arzt[2]	1189	4	21	OR: 3.08 (95% CI; 0.74–12.81)	.120	Unadjusted OR: 4.31 (1.31–14.15), *P*=.02
Munoz[3]	394	6	20	HR: 2.52 (95% CI; 1.04–6.01)	.040	HR presented for subjects with severe obstructive sleep apnea (apnea-hypopnea index [AHI] ≥30 events/h)
Redline[4]	5422	~8	193	HR: 2.86 (95% CI; 1.10–7.40)	.016	Incident stroke was not associated with AHI quartiles in women
						HR presented for highest AHI quartile (>19 events/h); *P* value is for trend
Valham[5]	392	10	47	HR: 3.56 (95% CI; 1.56–8.16)	.011	HR presented for subjects with moderate to severe obstructive sleep apnea (AHI ≥15 events/h); *P* value is for trend
Yaggi[6]	1022	~3	88	HR: 1.97 (95% CI; 1.12–3.48)	.010	Outcome was incident stroke and death

OR = odds ratio; CI = confidence interval; HR = hazard ratio.

most people are waking up to start their day.[9] Interestingly, none of the more common vascular risk factors or other etiologic factors for stroke (including patient demographics, vascular distribution, ischemic heart disease, previous myocardial infarction, diabetes mellitus, hypertension, smoking, hyperlipidemia, stroke severity and recurrence, stroke subtype, and other clinical features) vary in a statistically significant manner according to the clock time of stroke onset.[10] The temporal pattern of stroke points to the impact of circadian factors on vascular tone, coagulative balance, and blood pressure. Perhaps most compellingly, a case-control study comparing subjects with wake-up stroke to those without wake-up stroke found the wake-up stroke group had higher apnea-hypopnea and obstructive apnea indices and lower mean oxygen saturation levels. The presence of severe sleep apnea (apnea-hypopnea index [AHI] greater than 30 events/h) was independently associated with wake-up stroke.[11]

During healthy nocturnal sleep, both systolic and diastolic blood pressures drop by 10% to 20% from respective daytime mean levels. Some patients, referred to as nondippers, have less than a 10% decline in blood pressure relative to respective daytime means. Nondipping, over time, likely contributes to left ventricular hypertrophy, renal pathology, and deleterious effects on brain vasculature such as atheromatous narrowing or occlusion of larger cerebral vessels, thickening of cerebral arteries by lipohyalinosis, and increased blood coagulability. Nondipping blood pressure

KEY POINTS

- Sleep-disordered breathing is a term that encompasses all breathing disturbances in sleep, including obstructive sleep apnea, central sleep apnea, Cheyne-Stokes respirations, and upper airway resistance syndrome.
- Sleep-disordered breathing is an independent risk factor for stroke.

pattern is associated with stroke independent of sex and race.[12] Stroke risk is increased by 80% for every 5 mm Hg increase in sleep-time blood pressure.[13] Obstructive sleep apnea (OSA) is one of the most common causes of nondipping nocturnal blood pressure.

The effect of SDB on blood pressure is not confined only to the sleep period. Approximately 50% to 60% of patients with OSA are hypertensive, while about 30% to 40% of hypertensive patients have OSA.[14] Peppard and colleagues[15] performed a 4-year, population-based, prospective cohort study of OSA and hypertension. After adjusting for multiple confounders, they found that even people with few episodes of apnea or hypopnea (0.1 events/h to 4.9 events/h) at baseline had 42% greater odds of having hypertension at follow-up than people with no episodes. They also found those with mild SDB (AHI of 5.0 events/h to 14.9 events/h) and those with more severe SDB (AHI of 15.0 or more events/h) had approximately 2 and 3 times, respectively, the odds of having hypertension at follow-up than those with no episodes of apnea or hypopnea.[15] Resistant hypertension is defined as blood pressure that requires four or more antihypertensive medications. Stunningly, 80% to 90% of these patients have OSA. Pathophysiologic mechanisms include activation of the renin-angiotensin-aldosterone system by intermittent hypoxia and aldosterone-related fluid retention causing parapharyngeal edema.[14] Thus, OSA is a risk factor for hypertension and a major risk factor for stroke.

Treatment of Obstructive Sleep Apnea to Improve Blood Pressure

In two meta-analyses reporting changes in blood pressure levels, patients randomized to continuous positive airway pressure (CPAP) therapy compared with controls reduced systolic blood pressure by approximately 1.5 mm Hg to 2.5 mm Hg and diastolic blood pressure by 1.5 mm Hg to 2.0 mm Hg.[16,17] In another two meta-analyses reporting changes in blood pressure obtained by ambulatory monitoring, CPAP use was associated with an approximately 1.0 mm Hg to 1.5 mm Hg reduction in both 24-hour systolic and diastolic blood pressure.[18,19] In subgroup analyses, severe OSA (more than 30 events per hour), higher blood pressure levels, and greater CPAP adherence were associated with larger reductions in blood pressure.[16–19]

Additional Obstructive Sleep Apnea–Related Factors That Increase Stroke Risk

OSA increases systemic sympathetic nervous system activity and atrial size (through left ventricular hypertrophy and increased transmural pressure), which increases the risk of atrial fibrillation, a major stroke risk factor.[20] In addition, cardioverted atrial fibrillation is more likely to recur in untreated versus treated OSA patients.[21] Sleep disruption and chronic intermittent hypoxia in OSA increase oxidative stress and vascular inflammation, which results in endothelial dysfunction characterized by reduced vasodilatation and enhanced vasoconstriction, including chronic prothrombotic and procoagulant activity.[22] Apneas are associated with reduced cerebral perfusion and delayed cerebrovascular compensatory response to changes in blood pressure.[23,24] CPAP therapy has beneficial effects on vascular function and inflammatory and oxidative stress in these patients.[25] OSA is associated with patent foramen ovale (PFO), an important cause of cryptogenic stroke. During an obstructive apnea, large intrathoracic pressure swings and hypoxic pulmonary vasoconstriction act in concert to alter the interatrial pressure balance in favor of right to left

PFO shunting,[26] which may be preventable with CPAP therapy.[27] The presence of sleep apnea, including the duration and severity of disease, is associated with carotid intima-media thickness,[28] some of which is reversible with the application of CPAP therapy.[29] SDB is also associated with diabetes mellitus and insulin resistance, with the strength of association increasing as a function of OSA severity.[30] The effect of CPAP therapy on glucose metabolism in patients with OSA has yet to be established. **Figure 8-1** displays the complicated risk-factor relationship between SDB and stroke.

Treatment of Sleep-Disordered Breathing to Prevent Stroke

In patients with previous cardiovascular events and moderate to severe OSA, those noncompliant with CPAP therapy had an increased incidence of new ischemic stroke compared to the compliant group.[31] Long-term CPAP treatment in moderate to severe OSA and ischemic stroke is associated with a reduction in excess risk of mortality.[32] Treatment of OSA by CPAP in stroke patients undergoing rehabilitation improved functional and motor, but not neurocognitive, outcomes.[33] Randomized controlled trials are ongoing with the goal of determining whether CPAP therapy for OSA can prevent incident cardiovascular disease and death.

Sleep-Disordered Breathing Following Stroke

Acutely poststroke, over two-thirds of 161 stroke patients had an AHI of more than 10 events/h. After 3 months, both the AHI and central apnea index were significantly lower than in the acute phase, predominantly because of reductions in central apneas, since the obstructive apnea index remained unchanged. Interestingly, stroke location, type, or vascular

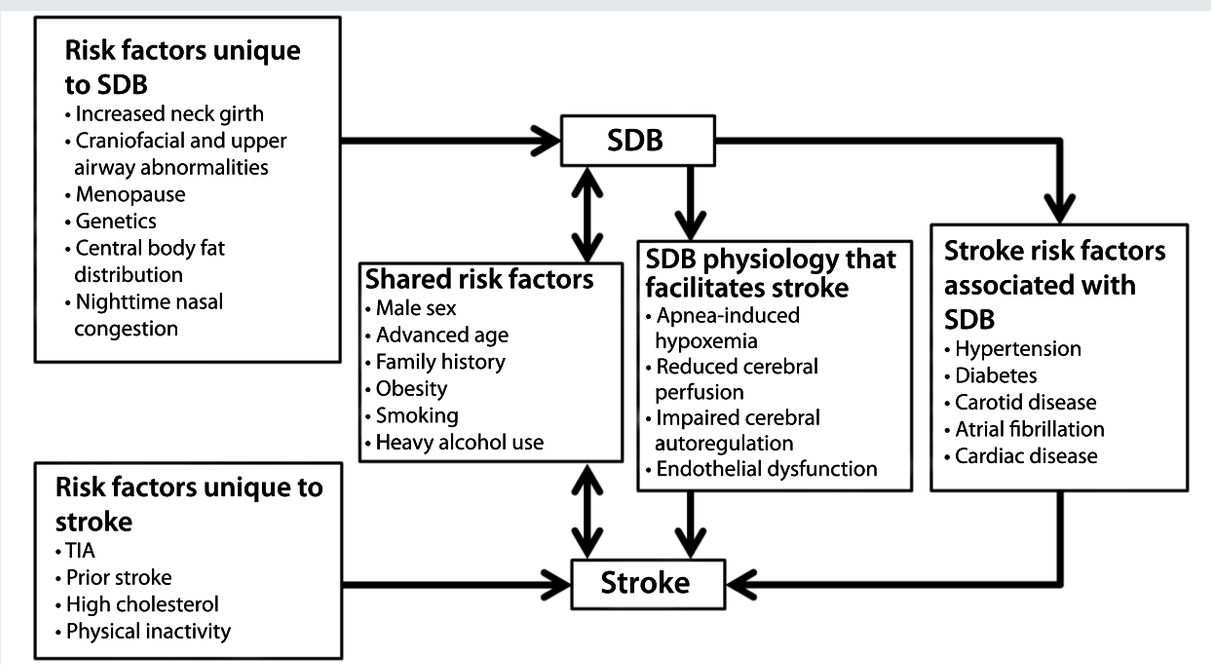

FIGURE 8-1 Interplay of risk factors for sleep-disordered breathing (SDB) and stroke. SDB influences stroke through shared risk factors, facilitation of traditional stroke risk factors, and physiology unique to SDB. The latter likely explains why SDB is associated with incident stroke after adjustment for many of these other risk factors.

KEY POINTS

- Sleep-disordered breathing should be considered in all stroke and TIA patients.
- Cervical dystonia is associated with reduced sleep quality and sleepiness, even when compared to patients with other focal movement disorders.

territory was not associated with SDB in this study.[34] This, along with the fact that SDB frequency and severity are the same for stroke and TIA patients,[35] suggests that although stroke itself can worsen SDB through effects on oropharyngeal musculature and brainstem respiratory centers, the SDB likely precedes the vascular event in most cases.

Sleep Duration and Stroke Pathophysiology

A recent study found both short and long sleep durations to be associated with stroke, independent of age, sex, body mass index, physical activity, smoking, alcohol use, screen time (eg, time spent in front of TVs, computers, tablets, smart phones), country of birth, marital status, education, and employment status. Compared with a sleep duration of 7 hours (referent), the multivariate odds ratio (OR) of stroke for various sleep durations was as follows: less than 6 hours, OR = 1.54 (1.36–1.75); 6 hours, OR = 1.25 (1.14–1.38); 8 hours, OR = 1.08 (1.00–1.17); and 9 hours or more, OR = 1.50 (1.38–1.62).[36] The exact mechanism is unknown but likely related to effects on metabolic, endocrine, and autonomic nervous systems.

Conclusions. SDB is an independent risk factor for stroke. It meets the criteria of biological plausibility, predictiveness, dose-responsiveness, and pre-stroke measurability. SDB is associated with many known stroke risk factors, including incident hypertension, endothelial dysfunction, oxidative stress, vascular inflammation, prothrombotic and procoagulant factors, arrhythmias, diabetes, PFO, and carotid intima-media thickness. Treatment of SDB with CPAP improves many stroke risk factors, including reducing hypertension and carotid intima-media thickness, reversing right to left shunting in PFO, and reducing recurrence of atrial fibrillation following cardioversion. Unfortunately, despite the strength of the evidence, SDB is regularly unrecognized and undiagnosed in both primary care and neurology/stroke clinics across the country. Considering what is at stake, evaluation for SDB is essential to the workup of any TIA or stroke patient. The identification and treatment of SDB in these patients provides a tremendous opportunity for neurologists and stroke specialists to mitigate the adverse effects of cerebrovascular disease (**Case 8-1**).[37]

MOVEMENT DISORDERS AND SLEEP IMPAIRMENT

Sleep and movement disorders overlap in a number of important ways. This section focuses on the sleep-related ramifications of the dystonias, choreiform disorders, tremors, and tics. Other sections of this article address other movement disorder-related issues, including the relationship of sleep with Parkinson disease (PD) and dementia with Lewy bodies.

Sleep impairment and its secondary symptoms have substantial quality of life ramifications for patients with dystonia. Cervical dystonia is associated with reduced sleep quality and sleepiness, even when compared to other focal movement disorders.[38] A number of polysomnographic abnormalities have been reported, including problems with sleep initiation and maintenance, reduced sleep efficiency, abnormal or reduced REM sleep, and changes in spindle activity.[39] Similar to other nonmotor dystonia symptoms, the etiology of sleep abnormalities includes primary effects of dystonia and secondary effects of pain and medications (eg, benzodiazepines, anticholinergics). Some forms of dystonia, including blepharospasm and Meige syndrome, may persist during sleep, although frequency and severity are often decreased.

Sleep problems are present in nearly 90% of patients with Huntington disease

Case 8-1

An obese 59-year-old hypertensive man presented to his primary care physician because of a transient episode of difficulty speaking 2 days earlier. In the course of the examination, the physician found evidence for atrial fibrillation. Diagnostic testing included echocardiography significant for patent foramen ovale (PFO) with a positive bubble test indicating right to left shunting, and hypercholesterolemia. Carotid ultrasound was normal. The physician referred the patient to a cardiologist for cardioversion of his atrial fibrillation, and prescribed warfarin, metoprolol, and simvastatin. The patient's atrial fibrillation was successfully cardioverted 4 weeks after warfarin therapy, and warfarin was switched to aspirin 4 weeks after cardioversion. Three weeks later, the patient presented to the emergency department aphasic and hemiparetic from a large left middle cerebral artery distribution stroke and was found to have recurrent atrial fibrillation.

Comment. This obese older man with hypertension, atrial fibrillation, and PFO is at high risk for having sleep-disordered breathing (SDB). Because no evaluation and management of the SDB was done, the patient was at higher risk for recurrent atrial fibrillation following cardioversion and subsequent stroke. Although whether treatment of SDB with continuous positive airway pressure reduces incident stroke is unknown, it is clear that untreated sleep apnea increases the risk of recurrence of atrial fibrillation following cardioversion. PFO is also associated with SDB, but atrial fibrillation is a more likely explanation for the stroke mechanism in this patient. Evaluation for SDB should be performed in TIA and stroke patients as part of their stroke workup.

KEY POINT

■ Sleep disturbance is present in nearly 90% of patients with Huntington disease, with most rating it a significantly important factor in overall health impairment.

(HD), with nearly two-thirds rating sleep dysfunction as either very or moderately important factors contributing to overall health impairment.[40] As HD progresses, non-REM (NREM) sleep stages N1 and N2 are increased, and NREM sleep stage N3 and REM are decreased. In contrast to other neurodegenerative diseases, patients with HD show a higher density of sleep spindles compared to healthy control subjects. Actigraphy studies show patients with HD have significantly more movements and increased activity during sleep compared with controls. With increasing HD severity, sleep latency increases, sleep maintenance becomes more difficult, sleep efficiency reduces, wakefulness after sleep onset increases, circadian rhythmicity becomes compromised, and sleepiness ensues.[41] SDB, narcolepsy, and restless legs syndrome are not more common in patients with HD, as opposed to periodic limb movements of sleep (PLMS), which are increased in HD and may represent chorea rather than periodic limb movement disorder.[41] HD is associated with brainstem atrophy, even before caudate atrophy and in one small study, REM sleep behavior disorder (RBD) was observed in 12% of patients with HD.[42] In general, chorea and dyskinesias decrease and may even disappear during sleep, making these unlikely major sleep disrupters in HD, as opposed to dystonia, dementia, body pain, and nocturia, which more likely impair sleep in this disorder. Atrophy in the dorsolateral hypothalamus (site of hypocretin/orexin production) and anterior ventral hypothalamus (site of the suprachiasmatic nucleus) may explain sleepiness and circadian and other sleep disruption in this disorder.

When compared to age- and sex-matched controls, patients with essential tremor have poorer nocturnal sleep quality but not increased daytime sleepiness.[43]

KEY POINTS

- Sleep is impaired in 20% to 50% of children and young adults with Tourette syndrome.
- Obstructive sleep apnea is a common cause for headache upon awakening, particularly if it dissipates during the course of the day.
- Bruxism should be considered as a potential cause for headache upon wakening.
- Patients with cluster headache have an eightfold increased risk of obstructive sleep apnea when compared to age- and sex-matched controls.

However, pain and fatigue scores were elevated among patients with essential tremor, suggesting many misconstrue sleepiness as fatigue. RBD does not appear to be associated with essential tremor.

Caregiver observations indicate sleep problems in 20% to 50% of children and young adults with Tourette syndrome. Difficulties in falling and staying asleep, separation anxiety in the evening, and parasomnias were the most common problems.[44] Children with tic disorder and Tourette syndrome have objective sleep impairment indicated by reduced sleep efficiencies, prolonged sleep latencies, and increased arousal indices.[44,45] The disturbed sleep of children with Tourette syndrome is accompanied by increased short-lasting motor activity in NREM sleep, which likely represents tic activity during sleep.[44]

HEADACHE DISORDERS AND SLEEP

Sleep and headache have a complicated interrelationship. Although a history of headache upon awakening raises a concern for a space-occupying CNS lesion, this symptom is more likely to represent SDB, especially in obese men with tension-type headache pain that dissipates during the course of the day. In some instances, sleep improves headache, as exemplified by the typical patient with migraine lying in a dark, quiet room. In other instances, such as hypnic headache, sleep and specific sleep stages trigger the headache. Headache pain, or pain of any kind, adversely affects sleep architecture, duration, and quality; and patients with sleep disorders report over 4 times more headaches than healthy controls.[46]

Sleep disorders such as insomnia, SDB, sleep-related movement disorders, and circadian rhythm disorders are disproportionately observed in specific headache patterns (eg, chronic daily headache, awakening headache) and diagnostic groups (eg, migraine, cluster, tension-type). Variations in circadian timing of sleep and sleep duration outside typical norms (ie, 7 to 9 hours per night) are common headache triggers. Although sleep and headache associations are diverse, sleep dysfunction influences headache threshold through effects on sleep regulatory processes.[47] Relative to an age- and sex-matched chronic headache–free comparison group, headache patients slept significantly shorter durations (6.7 versus 7.0 hours), reported longer sleep latencies (31.4 versus 21.1 minutes), and took longer to resume sleep following nighttime awakening (28.5 versus 14.6 minutes).[48]

Chronic morning headache occurs in nearly 8% of the population, with sleep complaints more typical among those with tension-type than migraine headache.[49] Of migraine patients, 24% describe headache onset during sleep or upon awakening as opposed to 12% of tension-type headache patients.[46] Headache is more common among people with SDB than the general population, and habitual snoring is more typical of chronic daily headache than episodic headache. Morning headache is over 3 times more common in snorers and apneics compared to healthy controls. Bruxism is another potential cause for morning headache. In a study of over 1000 patients with migraine, sleep disturbance and oversleeping were recognized as headache precipitants by 50% and 37% of patients, respectively, while 85% reported sleeping as a means to relieve headache. Many reported occasional sleep-onset (53%) and maintenance (61%) difficulties. Almost two-thirds reported morning headaches.[50] Cluster headache patients have an eightfold increase in OSA compared to age- and sex-matched controls, and a 24-fold increase when overweight or obese.[51] Treatment of OSA has been shown to improve cluster headache control.[46]

Hypnic headache is a rare primary headache disorder in older adults characterized by moderate, throbbing, bilateral, or unilateral sleep-related headache attacks with typical onset in REM sleep. Headache duration can be anywhere from 15 minutes to 3 hours. In REM, dorsal raphe and locus coeruleus activity is absent and these areas, along with the periaqueductal gray, are essential components of the human antinociceptive system. Hypnic headache may therefore represent REM-related malfunction of these neuroanatomic regions, although this may not be specific since migraine and cluster headache onset also commonly occur in REM. Because many patients with hypnic headache experience headache onset at a consistent time of night, areas involved in circadian rhythm generation, such as the suprachiasmatic nucleus (SCN), also may be involved. The SCN has afferent and efferent connections with the periaqueductal gray, further strengthening this notion. Caffeine, either at bedtime or following headache onset, is an effective treatment but concerns for sleeplessness limit its use. Lithium, indomethacin, and melatonin are also helpful in some patients, along with other headache medications on a case-by-case basis.[52]

Because sleep and headache are so tightly linked, diagnosing and treating comorbid sleep disorders afford an opportunity to improve the headache problem. The most likely sleep disorders for headache causality are SDB, sleep deprivation, and circadian rhythm disturbances. A number of good screening instruments are available for clinical use to help identify headache patients that might benefit from consultation with a sleep medicine specialist (**Table 8-2**).

TABLE 8-2 Common Screening Instruments

- **Sleepiness**
  - Epworth Sleepiness Scale
  - Stanford Sleepiness Scale
  - Karolinska Sleepiness Scale
- **Sleep-Disordered Breathing**
  - Berlin Questionnaire
  - Multivariate Apnea Prediction Index
  - STOP-BANG questionnaire
- **Insomnia**
  - Insomnia Severity Index
- **Sleep Quality**
  - Pittsburgh Sleep Quality Index

EPILEPSY AND SLEEP

Sleep disorders and epilepsy are frequently comorbid. The relationship between the two can be reciprocal; sleep disorders can contribute to difficulty in managing seizures, and epilepsy can disrupt normal sleep, initiating or worsening sleep disorders. Patients with epilepsy commonly report poor sleep quality, increased nocturnal awakenings, early morning awakenings, difficulty initiating sleep, and excessive daytime sleepiness. Nineteen percent of generalized seizures occur during sleep, as compared to 51% of localization-related seizures. One in five patients with epilepsy has seizures exclusively during sleep. Examples of focal-onset epilepsy occurring predominantly during sleep include benign focal epilepsy with centrotemporal spikes, and nocturnal frontal lobe epilepsy. Many patients have ''awakening epilepsy,'' occurring within 2 hours of waking; juvenile myoclonic epilepsy is a classic example. **Table 8-3** provides a list of epilepsies with a predilection for occurrence out of sleep.

Most sleep-related seizures occur out of NREM sleep, with NREM sleep stage N2 being the most common. This sleep stage likely facilitates focal spikes and epileptic activity through thalamocortical hypersynchrony, as represented by characteristic sleep spindles and K complexes. Hypersynchronous delta activity

KEY POINTS

- Hypnic headache is sleep specific, occurring relative to REM sleep at a consistent time of the night.
- Epilepsy and sleep-disordered breathing are mutually facilitatory, with higher rates of each disorder observed in patients with the other disorder when compared to the general population.
- One in five patients with epilepsy has seizures exclusively during sleep.
- Most sleep-related seizures occur out of non-REM sleep, most often non-REM sleep stage N2.

KEY POINT

- Nocturnal frontal lobe epilepsy can be difficult to distinguish from parasomnias, with stereotypia, minimal postevent confusion, and shorter duration providing clues that the event was epileptic in nature.

TABLE 8-3 Common Sleep-Related Epilepsies

- Nocturnal frontal lobe epilepsy
- Nocturnal temporal lobe epilepsy
- Benign focal epilepsy with centrotemporal spikes
- Juvenile myoclonic epilepsy
- Continuous spike-wave discharges during sleep
- Childhood epilepsy with occipital paroxysms
- Generalized tonic-clonic seizures upon awakening

in NREM sleep stage N3 also facilitates epileptiform activity. Nighttime interictal activity is more suggestive of the location of the seizure focus than daytime interictal activity.[53] Seizures are least likely to occur out of REM sleep, but when they do, they can provide the most accurate seizure localization of any sleep stage. Seizures and epileptiform abnormalities are typically observed during sleep stage transitions and unstable sleep characterized by cortical arousals. Temporal lobe epilepsy is the most common sleep-related epilepsy, not because of a particular sleep-related predilection, but because of the common nature of this seizure type. Frontal lobe seizures have the greatest penchant to occur out of sleep. Approximately 61% of frontal lobe seizures begin during sleep, as opposed to 11% of temporal lobe seizures. Temporal lobe seizures are more likely to generalize when they originate from sleep, and nocturnal temporal lobe epilepsy is thought to portend a more favorable outcome following epilepsy surgery.[54]

Autosomal dominant nocturnal frontal lobe epilepsy is a distinct clinical syndrome (**Table 8-4**). These patients have brief stereotyped hyperkinetic or tonic motor seizures that occur in clusters during sleep following sudden arousals. Kicking and movement of legs, arms, and trunk are seen. Patients typically maintain consciousness during the seizures, which usually last less than 60 seconds and are stereotyped in nature. Seizures usually begin in childhood and persist throughout life. The disorder demonstrates an autosomal dominant inheritance pattern with an approximate penetrance of 70%. Seizures involve deep mesial frontal generators and may lack ictal and interictal EEG correlates. For all these reasons, nocturnal frontal lobe epilepsy can be difficult to differentiate from NREM parasomnias (**Table 8-5**) (**Case 8-2**).[55]

Historically, sleep deprivation has been used to provoke epileptic-related EEG activity. Sleep itself may activate interictal activity in approximately one-third of patients with epilepsy and up to 90% of people with sleep-wake–related

TABLE 8-4 Characteristics of Autosomal Dominant Nocturnal Frontal Lobe Epilepsy

- Brief nocturnal seizures
- Prominent motor movements
- Little or no postictal confusion
- Frequent clusters
- Often misdiagnosed as sleep disorder
- Involves the neuronal nicotinic acetylcholine receptor α 4 (*CHRNA4*) subunit
- Two genetic loci identified (20q13.2-3 and 15q24)
- Mutations in neuronal nicotinic acetylcholine receptor genes *CHRNA4* and *CHRNB2*

TABLE 8-5 Pearls for Differentiating Non–REM Parasomnias From Nocturnal Frontal Lobe Epilepsy

Event Characteristic	Non–REM Parasomnia	Nocturnal Frontal Lobe Epilepsy
Timing in the sleep period	Early	Anytime
Sleep stage	Non-REM N3	Any, but Non-REM N2 is most common
Epileptiform discharges seen on polysomnography	No	Yes or no
Stereotypia present	No	Yes
Awakening	No	Yes
Duration of event	30 seconds to 30 minutes	30 seconds to 2 minutes
Postevent confusion	Yes	Typically minor

or state-dependent epilepsies. Sleep deprivation activates epileptiform discharges on sleep-wake EEGs and is therefore useful in evaluation of suspected epilepsy. Although the exact mechanism is unknown, sleep deprivation likely activates epileptiform discharges through direct effects of sleep loss. Neurologists should be aware that sleep deprivation–provoked seizures may

Case 8-2

A 28-year-old man was brought to clinic by his wife with the complaint that he was waking up screaming and thrashing at night. This had begun about 6 months earlier and occurred approximately every 2 weeks. The events would occur at any time of the night, but were slightly less likely during the final portion of the sleep period. The patient would awaken abruptly, thrashing and screaming incoherently. The events lasted about 30 seconds and ended abruptly; the patient may or may not have any memory of the event. The duration and characteristics of the event were consistent over time. Neither the patient nor his family had a history of sleepwalking, head injury, encephalitis, or epilepsy. His neurologic examination and routine EEG results were normal. He was admitted for 7 days of inpatient EEG monitoring during which two typical events were captured, but no ictal EEG correlate was found. The events resolved with a treatment trial of carbamazepine.

Comment. This case of nocturnal frontal lobe epilepsy highlights the difficulty in differentiating nocturnal seizures from parasomnias. In this case, the events are stereotypic, have no predilection for the first third of the night (when non-REM sleep stage N3 is more prominent), are brief, and lack substantial postevent confusion, thereby arguing in favor of a diagnosis of nocturnal frontal lobe epilepsy. The lack of a family history suggests this is not the heritable type. Although events were captured on EEG monitoring, the lack of an ictal correlate does not obviate the diagnosis, as deep mesial frontal generators may insidiously trigger the events. The correct management in this case is a treatment trial, which if successful, helps confirm the diagnosis.

KEY POINT

■ Medication side effects should always be considered as a cause of sleepiness in a patient with epilepsy.

alter seizure semiology and therefore not confuse these as nonepileptic events.

Compared to the general population, patients with epilepsy experience substantially more sleep disturbance, characterized by increased sleep latency and number of awakenings during night as well as alterations in normal sleep architecture due to seizures, interictal epileptiform discharges, or medication side effects (**Table 8-6**).[56] Nearly two-thirds of patients with epilepsy have excessive daytime sleepiness as defined by the Epworth Sleepiness Scale, and night awakening is more common in patients with epilepsy than in normal controls, with increased seizure frequency portending increased sleep disturbance.

Epilepsy is more prevalent in patients with SDB than in the general population.[57] Possible reasons include OSA effects on sleep quality or duration and acute and chronic effects of intermittent hypoxia and sympathetic activation on epileptogenic regions of the brain. The reverse is also true: SDB is more prevalent in patients with epilepsy than in the general population.[58] Depending on epilepsy severity and SDB definition, between 20% and 80% of epilepsy patients have been reported to have comorbid SDB.[59] In a study of refractory epilepsy patients, 33% were found to have OSA, with seizures more likely to occur at night than during the day. Postulated reasons for this association include antiepileptic drug–associated weight gain (eg, valproate, gabapentin), hypothyroidism, polycystic ovarian disease, and the effect of chronic epilepsy on brainstem respiratory control centers and nuclei involved in airway patency.

TABLE 8-6 Effect of Antiepileptic Drugs on Sleep[a]

	Effects on Sleep						Effects on Sleep Disorders	
Drug	Efficiency	Latency	Stage N1	Stage N2	Stage N3	REM	Improves/Treats	Worsens
Phenobarbitol	–	↓	–	↑	0	↓	Sleep-onset insomnia	Obstructive sleep apnea (OSA)
Phenytoin	0	↓	↑	↑	↓	0 or ↓	None known	None known
Carbamazepine	0	0	0	0	0	0	Restless legs syndrome (RLS)	RLS
Valproate	–	0	↑	↓	0	0	None known	OSA
Ethosuximide	–	–	↑	–	↓	–	None known	None known
Gabapentin	0	0	0	0	↑	↑	RLS	OSA
Lamotrigine	0	0[b]	0	↑	↓	↑	None known	None known
Topiramate	0	↓	0	0	0	0	OSA[c]	None known
Tiagabine	–	–	–	–	↑	–	Insomnia	None known
Levetiracetam	–	–	–	–	↑	–	None known	None known
Pregabalin	↑	–	–	–	↑	–	None known	OSA

REM = rapid eye movement; ↑ = increase; ↓ = reduction; – = not reported; 0 = no change.

[a] Reprinted with permission from Eriksson SH, Curr Opin Neurol.[54] *journals.lww.com/co-neurology/pages/articleviewer.aspx?year=2011&issue=04000&article=00014&type=abstract.*

[b] Lamotrigine may be associated with insomnia.

[c] Due to change in weight.

Benzodiazepines and barbiturates may cause suppression in responsiveness of carbon dioxide and oxygen desaturation and increase upper airway musculature relaxation. Vagus nerve stimulation treatment for epilepsy has been reported to increase airway disturbance during sleep in some patients.[60] This therapy is thought to increase airway resistance from increasing lateral laryngeal muscular tone or by interfering with the respiratory sensory feedback.

Seizure control may improve with treatment of OSA. In one study, treatment of OSA produced a 50% or greater reduction of seizures, with some patients becoming seizure free. Excessive daytime sleepiness also improved, despite no changes or higher doses of antiepileptic drugs.[61] Another study showed that children with epilepsy treated surgically for their SDB had a 53% median seizure reduction, with about one-third becoming seizure free.[62] For all these reasons, symptoms of daytime sleepiness and poor sleep should not necessarily be considered the result of epilepsy until other causes have been evaluated. Epilepsy patients should be routinely asked about these symptoms and referred to a sleep specialist when appropriate with the goal of improving quality of life and seizure control.

NEURODEGENERATIVE DISEASES AND SLEEP

Neurodegenerative diseases, such as Alzheimer disease (AD) and PD, are commonly associated with sleep disorders such as SDB, RBD, restless legs syndrome, insomnia, and circadian rhythm sleep disorders (**Table 8-7**). Sleep disruption in people with neurodegenerative disease may lead to worsened cognitive status and functional ability, increased caregiver burden, and perhaps, most importantly, hastened institutionalization.

Persistent sleep disturbances are present in up to 44% of patients with AD.[63] Degeneration of cholinergic neurons in the SCN and ventrolateral preoptic nucleus, critical for homeostatic maintenance of the circadian rhythm and sleep initiation, leads to sleep-wake disturbances in AD. Sundowning, characterized by confusion, wandering, hyperactivity, restlessness, and agitation, is common and typically occurs during low-light hours in the late afternoon and early evening in these patients. People with mild to moderate dementia spend 15% of the day napping, while those with severe dementia spend 29% of the day napping, which leads to further sleep difficulty at night. Cholinergic medications, the primary treatment for AD, can cause insomnia and dream disturbances. Sedative-hypnotic medications, used for sleep induction or behavioral modification in AD, can have significant side effects such as sleep disruption and increased injury risk. Antipsychotic medications, if used for agitation or sleep induction, can cause daytime hypersomnia. Melatonin is sometimes used to regulate circadian rhythms but may not be effective as monotherapy for sleep disturbances in these patients. Nonpharmacologic treatments, including light therapy, exercise, and sleep-hygiene modification, are safe and effective alternatives.

In PD, muscle rigidity, tremors, and dystonia can lead to difficulty with sleep initiation and maintenance. Carbidopa-levodopa, used to treat PD, may cause nightmares and insomnia. Depression and anxiety (and antidepressants such as selective serotonin reuptake inhibitors) may also perpetuate insomnia in these patients.

Cell loss in brainstem nuclei that modulate respiration, along with bulbar and diaphragmatic muscle dysfunction, increase the risk of SDB in neurodegenerative disease. Patients with PD are at risk of developing SDB due to hypokinesia and rigidity causing upper airway

KEY POINTS

- When approaching a sleep problem in a patient with neurodegenerative disease, medication side effects should always be considered as a causative factor, particularly with cholinergic, antipsychotic, and sedative hypnotic medications.
- Sundowning is common in patients with neurodegenerative diseases; treatment is best focused on nonpharmacologic measures, such as improved sleep hygiene and a consistent daytime schedule, that include light exposure and regular physical activity.

TABLE 8-7 Prevalence Estimates of Sleep Disorders in Neurodegenerative Disorders

Disorder	Sleep-Disordered Breathing	Hypersomnia	REM Sleep Behavior Disorder	Restless Legs Syndrome
Parkinson disease	Obstructive sleep apnea (OSA): 27–52% (apnea-hypopnea index [AHI] >5 events/h) 21–34% (AHI >15 events/h) 4–15% (AHI >30 events/h)	20–50% (sleep attacks 1–20%)	25–50%	Up to 52%
Multiple system atrophy	OSA: 15–37% Stridor: 30–42% Central sleep apnea (CSA): present Cheyne-Stokes respiration: present	28–50%	69–90%	28%
Dementia with Lewy bodies	Not characterized	Present	>50%	No known association
Alzheimer disease	OSA: 70–80% (AHI >5 events/h) Up to 53% (AHI >10 events/h) 38–48% (AHI >20 events/h)	Up to 69%	Case reports support this association	No known association
Spinocerebellar ataxia (SCA)	Stridor (SCA types 1 and 3): present OSA (SCA type 3): 20–25%	SCA type 3: 45%	SCA type 2: 80% SCA type 3: 46%	SCA type 3: 30–55% SCA types 1 and 6: 23% SCA type 2: 18%
ALS	Sleep-disordered breathing: 17–76% Hypoventilation (most common) CSA OSA	23%	No known association	19–25%

REM = rapid eye movement.

obstruction, restrictive lung disease (ie, chest wall rigidity and postural abnormalities), and autonomic dysfunction. However, patients with PD tend to have lower body weight, which reduces OSA occurrence. SDB may also be worsened by antianxiolytic and pain medications prescribed for these patients. In mild to moderate AD, treatment of OSA with CPAP improves nocturnal sleep quality and excessive daytime sleepiness. However, compliance with CPAP is a challenge in this population. Donepezil has been shown to improve OSA in AD, likely by stimulating the neurochemical regulation of breathing during sleep.[64]

Central sleep apnea and Cheyne-Stokes breathing pattern can be observed in neurodegenerative diseases and are related to degeneration of the ventral arcuate nucleus and the pre-Bötzinger complex of the medulla (neural areas responsible for respiratory chemosensitivity and rhythmogenesis).[65] Stridor in patients with multiple system atrophy or certain spinal cerebellar ataxias and nocturnal hypoventilation in ALS are associated with increased mortality.[66]

Excessive daytime sleepiness is frequent in patients with neurodegenerative disorders. The degree of excessive daytime sleepiness correlates with the severity of AD.[67] Sleep attacks can occur in patients with PD and dementia with Lewy bodies.[68] Dopamine agonists, used to treat symptoms such as tremor in PD, may also induce sudden sleep attacks.[69]

RBD (**Supplemental Digital Content 8-1**, *links.lww.com/CONT/A19*) is associated with disruption of the normal paralysis-inducing mechanisms of REM sleep and may herald the onset of PD or other synucleinopathies by 20 years or more (**Figure 8-2**).[70] Dream-enacting behaviors can lead to injury to the patient or bed partner and are typically treated with clonazepam or melatonin (**Case 8-3**). In PD, an increased frequency of restless legs syndrome and periodic limb movement disorder may be present, especially in patients not treated with levodopa.[71]

NEUROMUSCULAR DISEASE AND SLEEP

In general, sleep disorders from neuromuscular diseases occur because of sleep-related ventilatory difficulties (and respiratory failure), particularly in later stages of the disease. Respiratory compromise may be related to diaphragmatic weakness, restrictive lung disease from intercostal muscle weakness, kyphoscoliosis, or pulmonary microatelectasis from chronic hypoventilation. Contributing factors specific to SDB in myopathies include weakness of oropharyngeal muscles, tonsillar hypertrophy, obesity, and craniofacial dysmorphias. Breathing alterations become particularly evident during REM sleep when respiration becomes diaphragm dependent. Central apneas due to alterations in central respiratory drive may be present. Frequent nocturnal awakenings, daytime sleepiness and fatigue, morning headaches, and difficulty concentrating should cue the practitioner to perform an overnight polysomnogram and check for laboratory evidence of hypoxia and hypercapnia. Diurnal hypercapnia is indicated by a $PaCO_2$ greater than 45 mm Hg. Nocturnal hypoventilation is defined as a $PaCO_2$ greater than 55 mm Hg for 10 minutes or more or a 10 mm Hg or greater increase in $PaCO_2$ during sleep (in comparison to an awake supine value) to a value exceeding 50 mm Hg for 10 minutes or more. Nocturnal hypoxia can be indicated by a low mean saturation, high desaturation index, and

KEY POINTS

- REM sleep behavior disorder can herald preclinical synucleinopathies, and as such patients with REM sleep behavior disorder should be followed for signs and symptoms of these diseases over time.
- Indicators of sleep-disordered breathing in patients with neuromuscular disorders include disrupted nocturnal sleep, daytime sleepiness and fatigue, morning headache, and trouble concentrating.

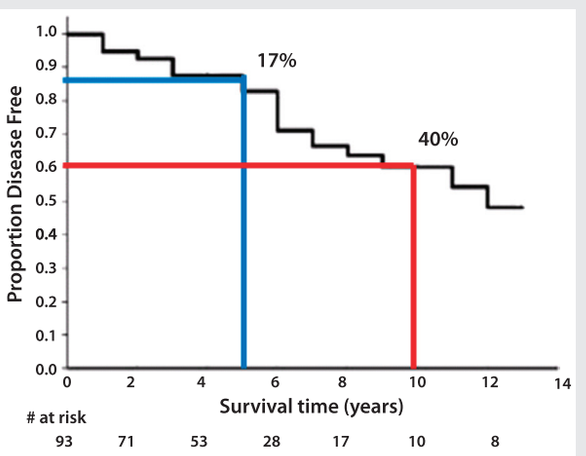

FIGURE 8-2 Survival curve of patients with idiopathic REM sleep behavior disorder. At 5 years' survival time, 17% of patients went on to develop a neurodegenerative disorder, and at 10 years' survival time, 40% of patients developed a neurodegenerative disorder.

Modified from Postuma RB, et al, Neurology.[68] © 2009, with permission from American Academy of Neurology. *www.neurology.org/content/72/15/1296.abstract*.

Case 8-3

A 68-year-old, right-handed man presented with symptoms of loud snoring and nocturnal awakenings related to nocturia and dreams in which he is fighting off an animal such as a lion or an ape. He would awaken from these dreams swinging his arms and yelling and in the past had struck his wife in bed. He found these behaviors embarrassing since they had occurred on long plane flights and tour bus rides. His medical history included lumbar stenosis, prostate carcinoma status-post resection, and diverticulosis. He took a baby aspirin, multivitamin, and calcium daily. He had no family history of neurodegenerative disease, but two brothers also had undiagnosed dream-enacting behaviors.

His vital signs were within normal range, he was not orthostatic, body mass index was 24 kg/m^2, and general examination was nonrevealing. His Mini–Mental State Examination score was 29/30. No signs of dysarthria, hypophonia, or ataxic speech were present, and the remainder of the neurologic

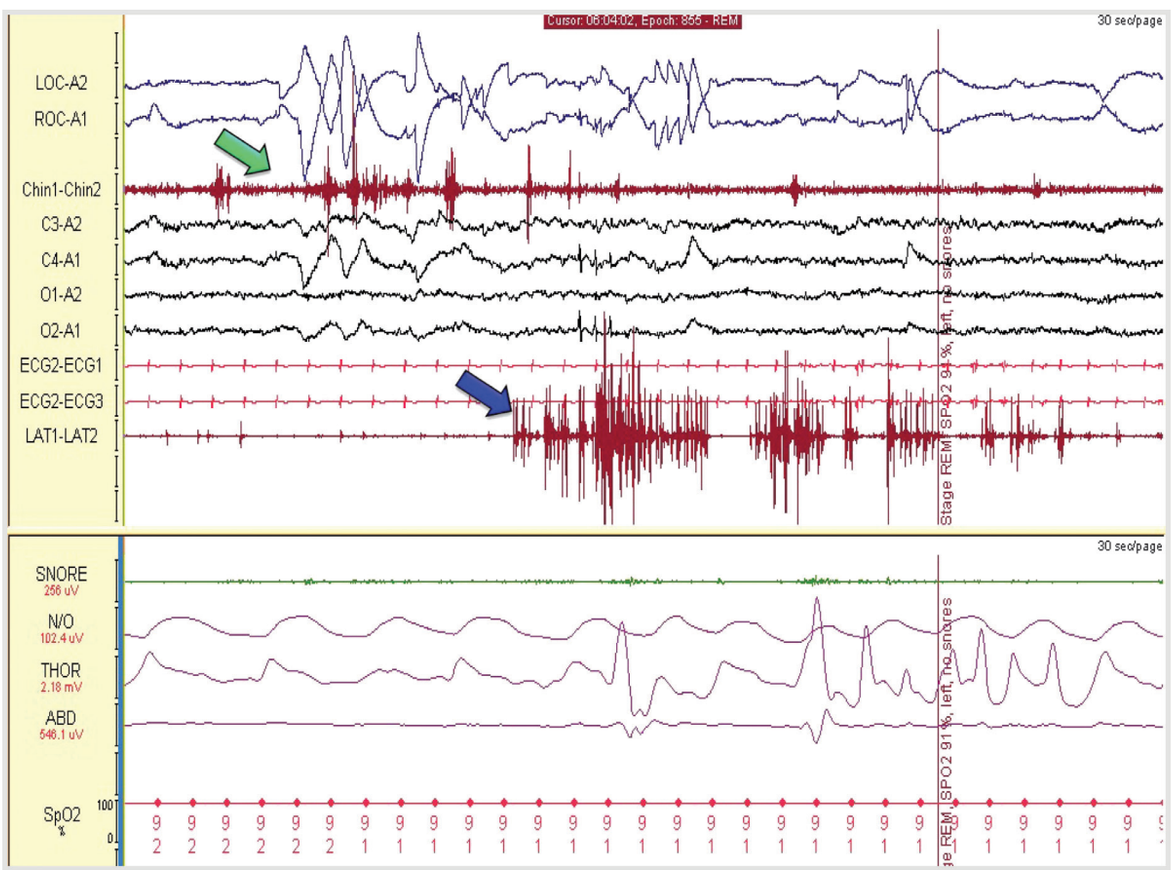

FIGURE 8-3 Thirty-second polysomnogram fragment showing increased chin tone in REM sleep and limb movements. Channels are as follows: electrooculogram (left: LOC-A2, right: ROC-A1); chin EMG (Chin1-Chin2); EEG (left central [C3-A2], right central [C4-A1], left occipital [O1-A2], right occipital [O2-A1]), two ECG channels; limb EMG (LAT1-LAT2); snore channel; nasal-oral airflow (N/O); respiratory effort (thoracic [THOR], abdominal [ABD]); and oxygen saturation (SpO2). Tonic EMG activity is consistent with REM sleep behavior disorder when present in more than 50% of the total 30-second epoch duration with an amplitude of at least twice the background EMG muscle tone or more than 10 μV. Phasic EMG activity includes any burst of activity lasting between 0.1 and 5.0 seconds with an amplitude exceeding twice the background EMG activity irrespective of its morphology. The *green arrow* points to increased muscle tone in the chin EMG lead while the *blue arrow* points to increased muscle tone in the limb EMG lead.

Figure courtesy of Alon Y. Avidan, MD, MPH, FAASM.

Continued on page 163

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examination results were normal. Overnight polysomnography showed minimal sleep-disordered breathing, oxygen desaturation nadir of 91%, and increased muscle tone during REM sleep (**Figure 8-3**). No epileptiform discharges were seen.

Clonazepam 0.5 mg nightly was prescribed, and the patient was ensured a safe sleeping environment. He tolerated the medication, and the dream-enacting behaviors ceased. During the next 2 years, no signs of tremor, gait impairment, or dementia were apparent.

Comment. This case of REM sleep behavior disorder (RBD) highlights protean aspects of the disease. This disorder typically involves older men, can precede the onset of synucleinopathies such as dementia with Lewy bodies in some but not all patients, and may result in substantial injury to patients or their bed partners. Increased chin EMG tone in REM sleep is the polysomnographic hallmark of the disease. Exposure to selective serotonin reuptake inhibitors or tricyclic antidepressants can provoke the disorder. Treatment focuses on creating a safe sleeping environment (eg, remove sharp furniture edges and mirrors, lock bedroom doors, close windows) and benzodiazepines, most commonly clonazepam. Melatonin and dopamine agonists have also been used with some success. All patients with RBD should undergo a thorough neurologic examination and be followed over time for evidence of parkinsonism. In the event of focal findings, neuroimaging is recommended since RBD can also be precipitated by brainstem lesions of almost any cause.

high hypoxemic burden such as an oxygen saturation of 88% or less for 5 consecutive minutes. Other indicators of SDB in neuromuscular disease include a maximal inspiratory pressure of less than 60-cm water and a forced vital capacity of less than 50% predicted.[72] Daytime predictors of sleep hypoventilation in Duchenne muscular dystrophy are a forced expiratory volume of less than 40% and a base excess greater than 4 mmol per liter.[73]

Noninvasive positive-pressure ventilation (NPPV) is the most common initial treatment for SDB in neuromuscular disorders and improves survival and quality of life in patients with ALS.[74] This may involve bilevel positive airway pressure with expiratory pressure set to prevent airway obstruction and inspiratory pressure set for ventilation purposes. Ventilation is often a greater concern than airway obstruction and may necessitate pressure-support windows as large as 10-cm water or more. In many cases, the presence of central apneas necessitates a back-up rate to deliver a breath if the patient fails to trigger an inspiratory effort. Another NPPV option is average volume-assured pressure support, which automatically adjusts pressure support to maintain a target tidal volume. Regardless of NPPV type or settings, supplemental oxygen may also be required and tracheostomy becomes a consideration in advanced disease.

Myotonic dystrophy type 1 (DM1) is the most common adult-onset form of muscular dystrophy, and hypersomnia is a key clinical feature of the disease. Subjective and objective sleepiness (assessed by the Epworth Sleepiness Scale and multiple sleep latency test, respectively) is present in 70% of patients with DM1.[75] Excessive daytime sleepiness in DM1 is frequently persistent and unaffected by napping, unlike that of patients with narcolepsy, who tend to feel refreshed after naps. Patients with DM1 frequently meet diagnostic criteria for narcolepsy, and methylphenidate and modafinil are effective treatments for sleepiness in these patients. Regarding myasthenia gravis, 40% to 60% of clinically stable patients have SDB.[76]

Insomnia is associated with neuromuscular diseases and often induced by steroids for treatment of disorders such

KEY POINT

- Objective tests indicating nocturnal hypoventilation in neuromuscular disease include daytime $PaCO_2$ greater than 45 mm Hg, nocturnal oximetry showing oxygen saturation of 88% or less for 5 consecutive minutes, nocturnal $PaCO_2$ of greater than 55 mm Hg for 10 minutes or more or a 10 mm Hg or greater increase in $PaCO_2$ during sleep (compared to wake) to a value exceeding 50 mm Hg for 10 minutes or more, maximal inspiratory pressure of less than 60-cm water, and forced vital capacity of less than 50% predicted.

KEY POINTS

- When treating patients with neuromuscular disorders with bilevel positive airway pressure, improving ventilation is often more important than relieving airway obstruction, and wide pressure-support windows may be necessary.
- Multiple sclerosis lesions in brain areas subserving sleep onset, alertness, and REM sleep paralysis can precipitate insomnia, sleepiness, and REM sleep behavior disorder.
- Insomnia is common in multiple sclerosis and likely due to many disease-related factors, such as pain, spasticity, bladder dysfunction, depression, anxiety, and medication side effects.
- Sellar or suprasellar malignancies can indirectly cause sleep-disordered breathing by endocrinologic dysfunction causing obesity.

as inflammatory myopathies. PLMS are increased in DM1 compared to controls and associated with sleep disturbance.[77] Lastly, restless legs syndrome is increased in ALS and associated with increased sleep complaints.[78]

DEMYELINATING DISEASE AND SLEEP

As with stroke or tumor, lesion location in multiple sclerosis (MS) is critical to the presence or absence of sleepiness, insomnia, or specific sleep disorders. Hypothalamic lesions involving the tuberomammillary nucleus or hypocretin/orexin production can cause sleepiness. Pontine lesions involving areas such as the sublaterodorsal tegmental nucleus can precipitate RBD. Lesions involving the ventrolateral preoptic nucleus can predispose to insomnia. For these reasons, attention to lesion location on neuroimaging can prove insightful when addressing sleep concerns in MS.

Fatigue and sleepiness are common complaints in MS and are frequently intertwined. In a cross-sectional survey of 1063 people with MS, those with MS had more sleep disturbances (and daytime somnolence) compared to a group of chronically ill patients and a group of healthy individuals.[79] Conversely, multiple studies dispute sleepiness as an MS symptom.[80,81] Fatigue may be related to sleepiness, as sleep disruption can cause or worsen fatigue through CNS activation and increased inflammation. When focusing on fatigued subsets of MS patients, those with fatigue are significantly sleepier than nonfatigued patients with MS,[82,83] although this is disputed by other studies showing normal Epworth Sleepiness Scale scores and sleep latencies on the multiple sleep latency test between the two groups.[84,85] SDB is more frequent in fatigued (27.0%) versus nonfatigued MS patients (2.5%), and the presence of a sleep disorder is associated with an increased risk of fatigue in MS. Sleepiness and fatigue in MS are commonly treated with modafinil, although its effectiveness is uncertain.

Narcolepsy and RBD occur more frequently in patients with MS. Case reports suggest an association between acute disseminated encephalomyelitis and neuromyelitis optica with hypersomnia and secondary narcolepsy. Insomnia is common in MS, present in up to 40% of patients. Common MS symptoms, such as pain, spasticity, bladder dysfunction, depression, anxiety, and medications (ie, immunomodulators, such as interferon and corticosteroids) all likely contribute to difficulty falling and staying asleep. Restless legs syndrome may be seen in MS patients and is associated with greater disability,[86] although these symptoms may be confused with other frequent MS complaints such as paresthesias, dysesthesias, pain, and spasticity. PLMS are also highly prevalent in MS.[84] Intrathecal baclofen, for treatment of spasticity, reduces PLMS but increases obstructive and central respiratory events, especially in patients receiving bolus compared to continuous intrathecal administration.[87] Generally speaking, poor sleep in MS is an independent predictor of quality of life.[88]

CNS MALIGNANCIES AND SLEEP

Malignancies disrupt sleep through both direct and indirect effects. Cerebral tumors, especially those located in the sellar or suprasellar regions (ie, craniopharyngioma, pilocytic astrocytoma, and pituitary adenoma) can induce sleepiness through direct neoplastic involvement or pressure exertion on the hypothalamus, with a corresponding reduction in hypocretin (orexin) as the likely causative factor. Sellar or suprasellar tumors may also cause endocrine dysfunction, indirectly producing sleepiness and sleep disturbances by

promoting obesity and subsequent OSA. Insomnia in these patients may result from alterations in melatonin production by the pineal gland. Brainstem gliomas and hemispheric tumors (ie, those with bilateral hemisphere invasion or edema causing increased intracranial pressure and/or cerebral herniation) have also demonstrated somnogenic capabilities, with disruption of the reticular activating system as the likely cause. In addition, paraneoplastic disorders such as anti-Ma2 encephalitis are associated with sleepiness.[89] Numerous case reports document secondary narcolepsy and sleepiness related to treatment of cerebral tumors with radiation and surgical instrumentation and/or resection. Radiation therapy has been implicated in "somnolence syndrome," a poorly described hypersomnia in children receiving cranial irradiation for acute lymphocytic leukemia. Chemotherapeutics and immunomodulators used to treat cerebral tumors may induce insomnia or somnolence. Methylphenidate, amphetamines, and modafinil are effective in the treatment of sleepiness in children with brain tumors.

SDB may be caused by tumors involving the brainstem leading to dysfunction of the respiratory centers and nuclei involved in diaphragmatic and bulbar muscle control. RBD may present when a brainstem lesion disrupts the normal paralysis-inducing mechanisms of REM sleep. Restless legs syndrome has been described as the initial complaint in a patient with a foramen magnum tumor,[90] and PLMS have been observed in patients with thoracic spinal cord tumors.[91]

CONCLUSIONS

Sleep dysfunction and neurologic disorders are deeply intertwined, and the neurologist is well served to consider the interaction of sleep with almost every patient entering the clinic. SDB is a risk factor for stroke and, as with all stroke risk factors, its investigation should be considered in every TIA and stroke patient for secondary prevention. Whether diagnosing and treating SDB is a good stroke primary prevention strategy is yet to be definitively determined, but in the meantime it is probably reasonable and safe to assume that treating SDB will positively affect future risk of cerebrovascular disease. Sleep affects all headache disorders, and two disorders (hypnic and sleep apnea headache) are sleep specific and may occur upon awakening. Neurodegenerative diseases, MS, and CNS malignancies can influence sleep quality, continuity, and sleepiness and precipitate SDB or RBD by involving nuclei and pathways involved in automatic control of respiration, dream-related paralysis, alertness, and circadian rhythmicity.

VIDEO LEGEND

Supplemental Digital Content 8-1

REM sleep behavior disorder. Video montage of REM sleep behavior disorder demonstrating vigorous, aggressive, and violent behaviors during REM sleep in an older adult male patient. Note violent and aggressive dream enactment correlating with dream sequence, placing both the patient and the bed partner at risk for injury.
links.lww.com/CONT/A19

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KEY POINT

- Secondary narcolepsy can occur from treatment of CNS malignancies with surgical resection or radiation therapy in the perihypothalamic region.

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