INTRODUCTION

The autonomic nervous system is a diffuse network that regulates virtually all of the unconscious homeostatic mechanisms of the human body. In this sense, sleep can be thought of as a highly complex autonomic function. When sleep is disrupted, many of these homeostatic functions, such as sweating and temperature regulation, blood pressure and heart rate variability, and bowel and bladder function, can also be affected. In addition, many of the
primary disorders of autonomic dysfunction also greatly affect sleep. Healthy sleep is thus paramount to healthy autonomic functioning, and the treatment of any autonomic disorder should include treatment of comorbid sleep disorders. While virtually all of the primary sleep disorders can cause some degree of autonomic impairment, this chapter will focus primarily on the common sleep complaints seen in patients with autonomic disease.

ANATOMY OF THE AUTONOMIC AND SLEEP/WAKE SYSTEMS

The cell populations that regulate autonomic function and sleep utilize some of the same neurotransmitters—namely norepinephrine and acetylcholine. They are situated in close proximity to one another in the brainstem and hypothalamus (Fig. 12.1), and in some cases directly connect via complex neural pathways. The lateral zone of the hypothalamus, for instance, contains several important cell populations that regulate sleep and wake, hunger, and reward responses. Hypocretin (otherwise known as orexin) neurons located in this zone send projections to both sleep and autonomic nuclei. These pathways extend to all monoaminergic

FIGURE 12.1  Neuroanatomical locations of important autonomic and sleep nuclei. Red circles indicate autonomic nuclei; red arrows indicate efferent autonomic projections. ORX, orexin; Ach, acetylcholine; GABA, gamma-aminobutyric acid; NE, norepinephrine; LDT, laterodorsal tegmentum; PPT, pedunculopontine nucleus; NTS, nucleus tractus solitarius; IML, intermediolateral cell column.
nuclei and stimulate the release of their alerting neurotransmitters to help promote wakefulness. Hypocretin neurons also send projections to many autonomic regulatory centers including the periaqueductal gray, nucleus of the solitary tract, nucleus ambiguus, and dorsal motor nucleus of the vagus nerve. There are many animal studies to suggest that orexin exerts influence on several autonomic functions including heart rate and blood pressure regulation, energy metabolism, and gastrointestinal motility, and is implicated in the autonomic changes seen in narcolepsy patients. The lateral zone of the hypothalamus also contains autonomic neurons that send their efferent projections to the lateral medulla and the intermediolateral cell column of the spinal cord. These efferent pathways help regulate vascular tone and maintain our ability to undergo postural change without significant alterations in blood pressure and heart rate.

The lateral medulla is another location of interest, and contains many important afferent and efferent autonomic pathways. The baroreceptors, chemoreceptors, cardiac receptors, and respiratory receptors all send their projections to the nucleus solitarius in the lateral medulla, via the glossopharyngeal and vagus nerves. These pathways are integral to the regulation of breathing during sleep, and accomplish this task via central pattern generators in the dorsolateral pons, the dorsal respiratory group in the nucleus tractus solitarius, and the ventral respiratory group in the lateral medulla. They also rely on chemoreceptors in the carotid body that send afferent projections to the nucleus solitarius.

While not all of these autonomic circuits have direct connections to sleep circuits, it is important to note their neuroanatomical proximity. For this reason, any disease that preferentially affects these areas of the rostral brainstem or hypothalamus can potentially disrupt both sleep and autonomic function. One classic example is the neurodegenerative disorders of α-synuclein deposition, discussed later in this chapter.

**NORMAL AUTONOMIC FUNCTION DURING SLEEP**

As humans transition from the waking state to drowsiness and into sleep, parasympathetic vagal tone increases, and sympathetic tone decreases. The Boetzinger complex in the lateral medulla initiates a regular firing rate that stimulates a slowing of the respiratory rate and induces even, regular breathing, helping to promote gas exchange.

As sleep progresses from stage 1 nonrapid eye movement (NREM) sleep to the deeper stages of 2 and 3 NREM sleep, parasympathetic vagal tone increases even more. The net result is a reduction in heart rate, blood pressure, and cardiac output. At the same time, sympathetic tone continues to decrease, leading to a reduction in peripheral vascular resistance and arterial blood pressure. The baroreceptors—stretch receptors in the aortic arch and carotid sinuses that help regulate arterial blood pressure—become more sensitive to changes in blood pressure, further promoting a state of regular respiration and gas exchange. Blood pressure in this stage is typically 10–20% lower than blood pressure during wake, a phenomenon referred to as “dipping.” Heart rate also reaches its nadir in stage 3 NREM sleep. For these reasons, NREM sleep can be thought of as a state of parasympathetic dominance, autonomic stability and metabolic recovery.

During REM sleep, cholinergic discharges in the pedunculopontine nucleus and laterodorsal tegmental nucleus of the pons result in muscle atonia that inhibits body movement and dream enactment. REM can be divided into tonic REM, without rapid eye movements, and phasic REM, with rapid eye movements. Parasympathetic tone dominates during tonic REM;
however, during phasic REM the sympathovagal balance reverses and sympathetic tone increases significantly. In this stage of sleep, blood pressure and heart rate may fluctuate dramatically, and blood pressure can reach levels much higher than those of the waking state. Sympathetic nerve activity has been demonstrated to be higher in phasic REM than during wake.\textsuperscript{10} In this sense, phasic REM can be thought of as a state of heightened sympathetic tone and relative autonomic instability.

The pressure to sleep is driven by the homeostatic sleep drive and the circadian cycle, and both likely affect autonomic balance in relation to sleep onset and sleep maintenance. The effect of circadian phase on autonomic tone has been questioned for some time, and it has long been observed that many disease states with some relation to sympathetic hyperactivity occur in the early morning hours or upon awakening, such as myocardial infarction, ischemic and hemorrhagic stroke, and congestive heart failure exacerbations. Some research indicates that parasympathetic tone is influenced by the circadian system, whereas sympathetic tone is influenced by the homeostatic sleep system;\textsuperscript{11} however, this has not been firmly established.

Arousals from any stage of sleep can trigger bursts of sympathetic activity and exacerbate any preexisting elevations in blood pressure and heart rate. If frequent enough, these sympathetic surges may carry over into the waking state, leading to increased diurnal sympathetic tone and hypertension. This is one theory for the relationship between sleep apnea and hypertension, as well as one explanation for the heightened sympathetic tone seen in some postural tachycardia syndrome (POTS) patients.

**MEASURING AUTONOMIC TONE DURING SLEEP**

**Peripheral Arterial Tone**

Due to the diffuse and relatively inaccessible nature of the autonomic nerves, measuring autonomic tone during sleep can be difficult. Beat-to-beat blood pressure monitors are typically used in the autonomic laboratory during autonomic tilt table testing, and can also be worn during sleep (Fig. 12.2). These devices measure peripheral arterial tone (PAT) by

![FIGURE 12.2  Extremity devices used to measure autonomic tone during sleep. (A) Pneumatic finger cuff used in the autonomic laboratory to measure peripheral arterial tone during tilt table testing (Nexfin, Edwards Instruments). (B) Pulse oximeter, from which photoplethysmogram and pulse transit time are derived.](image-url)
inflating a pneumatic finger cuff on the distal phalanx of the patient’s finger, thereby measuring small changes in blood volume with each heartbeat. The monitor connects to a small device worn on the wrist. When sympathetic tone increases, peripheral vasoconstriction results in attenuation of the PAT signal. The advantage of these devices is that they can provide accurate, real-time measurements of changes in arterial blood pressure during sleep. The disadvantage is that they can be uncomfortable and disruptive to sleep, thus limiting their use outside of the research setting.

**Pulse Transit Time**

Pulse transit time (PTT) is a measurement of the time it takes for an arterial pulse wave to reach the periphery. PTT can be calculated from the finger photoplethysmograph (PPG) of the oxygen saturation monitor and the R-wave of the electrocardiogram (ECG) during a polysomnogram (PSG, Fig. 12.3). Blood pressure can be indirectly calculated by assuming that the speed of the PTT wave is inversely proportional to systolic blood pressure, for example an increase in blood pressure results in a shorter PTT and vice versa. The ECG R-wave is used to estimate the opening of the aortic valve and contraction of the left ventricle. The PPG is used to estimate the arrival of the pulse in the periphery, and from these two values the PTT is calculated. While not as accurate as the PAT, there is no inflation of the PPG finger probe, and thus the device can be worn with relative comfort during sleep. Since this method relies on the RR interval for its calculations, any arrhythmia, such as atrial fibrillation, can lead to significant artifact and invalidate PTT results.

**Spectral Analysis**

Spectral analysis of the RR interval is an indirect, noninvasive measurement tool. Spectral analysis of heart rate variability is often referenced in the literature as an estimate of sympathetic and parasympathetic tone during sleep, otherwise termed the sympathovagal balance. High-frequency RR signal (greater than 0.15 Hz) is associated with increased parasympathetic tone, and low-frequency RR signal (0.04–0.15 Hz) is associated with increased sympathetic tone. The high frequency signal is most influenced by the vagal-mediated respiratory sinus arrhythmia of deep breathing, while the low frequency signal is most likely influenced by a baroreflex-mediated heart rate response to blood pressure. In short, a greater LF/HF ratio suggests greater sympathetic drive, and a lower LF/HF ratio suggests greater parasympathetic drive. As in PPG analysis, arrhythmias can invalidate results.

**Microneurography**

Microneurography is a more invasive tool that has been utilized in the research setting as way to directly measure sympathetic output (Fig. 12.4). In this highly specialized technique, a small electrode is inserted into the sympathetic nerves, most commonly in the peroneal nerve as it courses through the anterior tibialis muscle. Researchers have used microneurography to measure sympathetic nerve activity during wake and the various sleep stages to measure sympathetic tone during sleep. It has been demonstrated that sympathetic burst activity is high during wake but even higher during REM sleep, and lowest during stage 3 NREM
FIGURE 12.3  Overnight polysomnogram demonstrating changes in pulse transit time, measured by photoplethysmography (PPG) from the pulse oximeter. This particular patient has runs of cyclical apneas, which are both obstructive and central in nature. The corresponding oxygen desaturations that follow both obstructive and central events result in sympathetic activation, vasoconstriction, and elevation in PPG tone, most pronounced toward the end of the apnea (arrows). This is a good example of the fact that both central and obstructive apneas can result in sympathetic activation, suggesting that it is likely the oxygen desaturation, and not the type of apnea, that triggers the autonomic response.
FIGURE 12.4  Microneurography technique and measurement of sympathetic nerve activity. (A) The microneurography needle is a fine tungsten microfilament that is inserted into unmyelinated sympathetic branches of a peripheral nerve, in this case the peroneal nerve. (B) Microneurography baseline recording demonstrating spontaneous bursts of muscle sympathetic nerve activity (MSNA). Source: Istvan Bonyhay, Harvard Medical School.
sleep. In addition, sympathetic bursts also occur during sleep stage transitions, and with the appearance of sleep spindles and K-complexes in stage 2 NREM sleep.

AUTONOMIC DISORDERS WITH PROMINENT SLEEP DISRUPTION

Postural Tachycardia Syndrome

POTS is an autonomic syndrome of inappropriate tachycardia triggered by postural change. It is defined as a sustained heart rate increase of ≥30 beats per minute within the first 10 min of standing or head-up tilt, with a normal blood pressure response, along with symptoms of orthostatic intolerance. These symptoms typically include lightheadedness, dizziness, nausea, visual blurring, and presyncope; however, patients may also report palpitations, chest pain, exercise intolerance, mental clouding or “brain fog,” fatigue and lack of refreshing sleep. Of all these symptoms, fatigue, and lack of refreshing sleep can be the most debilitating. Although it can be difficult for patients to distinguish the sensation of sleepiness from that of fatigue, it is important for the clinician to attempt to tease this out in the history. Does the patient describe symptoms of sleepiness, such as the overwhelming desire to sleep or nap? Do they find themselves dosing off in meetings or while driving? Or do they describe more of a sensation of fatigue, of body or muscle “tiredness?” This can be helpful in attempting to understand what is driving the symptoms, and where to focus the workup and treatment. The Epworth sleepiness scale (ESS) was designed to measure the former, and various fatigue scales, such as the fatigue severity scale and fatigue visual analog scale the later. If framed in this context, patients will often be able to label their symptoms as either sleepiness or fatigue, though it is not uncommon for them to describe both.

Patients with POTS tend to describe more fatigue than sleepiness, similar to patients with CFS or fibromyalgia. In one study, up to 50% of patients reported symptoms of insomnia, and up to 90% reported fatigue. POTS patients often have difficulty falling and staying asleep, and their ESS scores tend to be low. Other patients may feel that even if they do sleep they never wake feeling refreshed, no matter how many hours they think they might have slept.

The literature on sleep in POTS is growing, and at the time of this publication there have been five studies evaluating the nature of the sleep complaints in this patient population. Thus far it has been demonstrated that patients report more sleep complaints than controls, have greater subjective symptoms than objective findings and some element of sleep-state misperception, and demonstrate no consistent abnormalities on PSG to objectively explain the severity of their symptoms. Two studies demonstrated prolonged REM latency on PSG. Patients in one study had mild OSA, with a mean AHI of 6.6, however a third of these patients were also diagnosed with Ehlers–Danlos hypermobility subtype (EDS-HT), which may predispose patients to upper airway collapse.

Researchers in another study used spectral analysis to evaluate heart rate variability in various sleep stages. While they did report a reduction in LF/HF variability during sleep stage transitions in patients, there was no significant difference in stage-specific LF, HF, or LF/HF ratio when compared to controls. Nevertheless, it has been suggested that POTS patients might have altered heart rate variability during sleep, indicative of a hyperadrenergic state. Twenty-four-hour blood pressure monitoring has demonstrated a nondipping pattern...
in 55% of POTS patients, which is suggestive of either increased sympathetic tone or diminished parasympathetic tone during sleep.\textsuperscript{28}

Patients with POTS tend to have a predisposition to an evening chronotype,\textsuperscript{22} often finding it difficult to fall asleep until late into the evening. The reason for this is unclear; however, many patients note symptoms of hyperarousal, such as palpitations, racing thoughts, increased sweat output, and other symptoms of a hyperadrenergic state. The subtleties of circadian rhythm disorders in these patients have not been systematically evaluated, though there may be a connection between melatonin secretion and the autonomic system. Melatonin acts on two receptors, MT1 and MT2. MT1 receptors, when stimulated, lead to vasoconstriction of peripheral arterioles,\textsuperscript{29} and MT2 receptor stimulation leads to vasodilation.\textsuperscript{30} In addition, the stimulation of MT1 receptors in the suprachiasmatic nucleus may reduce central sympathetic output by stimulating GABA-ergic signaling to the paraventricular nucleus, which in turn inhibits adrenergic nuclei in the lateral medulla.\textsuperscript{31} Many POTS patients are treated with nonselective beta-blockers, which can theoretically impair melatonin secretion via blockade of pineal beta-1-receptors,\textsuperscript{32} though these medications may also provide relief from nocturnal palpitations and are sometimes dosed at bedtime for this purpose. Interestingly, in one small study, 3 mg of melatonin dosed in the morning produced a moderate decrease in standing tachycardia in patients with POTS, although it did not improve symptoms of orthostatic intolerance.\textsuperscript{31}

POTS patients frequently describe a sensation of generalized hyperarousal that prevents them from falling asleep even in the setting of extreme exhaustion, a presentation often referred to by sleep psychologists as “tired but wired.” This sensation is experienced by many insomnia patients and is supported physiologically by several studies that have examined functional imaging and EEG analysis. PET imaging in chronic insomnia patients during sleep has demonstrated increased activation and hypermetabolism in the arousal networks of the hypothalamus and brainstem, as well as their efferent projections in the medial prefrontal cortex and amygdala.\textsuperscript{33} EEG frequency analysis has demonstrated that these patients have increased beta (14–35 Hz) and gamma (35–45 Hz) activity, frequencies that are typically associated with waking cortical activity.\textsuperscript{34} Many patients with sleep-state misperception, or “paradoxical insomnia” may in fact have increased beta and gamma frequencies during sleep. While these studies have not been performed in POTS patients, it would not be surprising if they too had evidence of hyperactive arousal networks, as Bagai et al. had suggested in their POTS actigraphy study. The hyperarousal model, with its focus on heightened hypothalamic–pituitary–adrenal tone, increased catecholamine secretion, and excessive cortical activity during wake and sleep, may provide a window into the understanding of the autonomic complaints of patients with POTS.

Why do some patients with POTS exhibit symptoms of hyperarousal? One often overlooked fact is that arousals from any source, if frequent enough, can result in increased sympathetic tone. This has been demonstrated in the literature on insomnia, obstructive sleep apnea, periodic leg movements and restless leg syndrome (RLS).\textsuperscript{1} Prior to an electrocortical arousal, there is a typical cardiac response that occurs: initial tachycardia, which often precedes the arousal by several seconds, followed by bradycardia. With every arousal there is a small elevation in sympathetic tone. If the arousals become frequent enough, this elevation can persist after the patient has returned to sleep,\textsuperscript{35} and even into the next day.

Based on these results, it is difficult to say with any confidence that the sleep-related complaints of POTS patients are the result of a primary sleep disorder unique to POTS. A more plausible explanation is that these patients experience disrupted sleep from a combination of
systemic factors, such as body fatigue, chronic pain, hyperactivity of arousal networks and, in some cases, sleep-state misperception. There are unfortunately many questions that remain to be answered about this condition. Like systemic exertion intolerance disease (previously chronic fatigue syndrome), fibromyalgia, and Ehlers–Danlos syndrome (EDS), POTS is a multifactorial syndrome with many possible etiologies, and thus there is unlikely to be one single associated sleep disorder or treatment algorithm that applies to all patients. In the interim we can only hope that with more detailed research over the coming decades, the mechanisms of POTS and other conditions of chronic fatigue will be understood in greater detail, allowing us to develop targeted treatments that address the underlying disease and not just symptom management.

Ehlers–Danlos Syndrome

EDS is a connective tissue disorder of abnormal collagen production characterized by joint hypermobility, vascular fragility, and skin hyperextensibility. Of the six subtypes of EDS—classical, hypermobility, vascular, kyphoscoliosis, arthrochalasia, and dermatosparaxis—EDS-HT is the most common, with an estimated prevalence of 1 in 5000. This disorder has been identified in increasing amounts of patients with autonomic impairment, especially those with POTS.

Patients with EDS-HT may report a wide array of neurological, autonomic, and sleep-related symptoms including orthostatic intolerance, migraine, gastrointestinal pain and nausea, insomnia, fatigue, and nonrestorative sleep. Many of the same sleep-related complaints seen in patients with POTS are also seen in this patient population. An association with obstructive sleep apnea has been suggested, and while the prevalence of OSA in EDS is unknown, it is likely more common than OSA in the general population. The underlying pathophysiology of collagen deficiency in EDS-HT may lead not only to hyperelastic joints and hyperextensible skin but also a hyperelastic upper airway, increasing the likelihood of collapsibility during sleep. This same mechanism may be involved in the pathogenesis of autonomic impairment, with decreased arteriolar contractility leading to vasomotor instability and orthostatic intolerance, though this has not been proven. In short, even though this condition is being recognized with increasing regularity in the autonomic clinic, the genetic abnormalities and pathophysiology of EDS-HT have yet to be elucidated, and there are many clinical questions that warrant further exploration.

There is currently no accepted treatment for the sleep complaints of those with either EDS-HT or POTS, although anecdotal evidence exists for the use of various traditional and nontraditional hypnotics, such as the benzodiazepine receptor agonists and α-2-δ ligands for sleep initiation insomnia, and long-acting stimulants, such as modafinil for fatigue and excessive daytime sleepiness. It is preferable to select a medication with a dual purpose, for example gabapentin if there is a strong pain component or nortriptyline if the patient has a history of migraine headaches. Some patients with nocturnal palpitations may benefit from bedtime dosing of a low dose, short acting beta-blocker, such as propranolol. Stimulants should only be considered when all other primary sleep disorders—such as OSA and RLS—have been ruled out or appropriately treated, and if used should be done so with caution, noting that these medications may worsen tachycardia and thus lead to some anxiety for patients.
Fatal Familial Insomnia

Fatal familial insomnia (FFI) is a rare but illustrative disorder of sleep and autonomic dysfunction. FFI is an autosomal dominant prion disease resulting from a missense mutation in the prion protein gene. Patients with FFI develop spongiform degeneration of the mediodorsal and anterior thalamic nuclei, areas that regulate both sleep and autonomic control. Insomnia occurs early in the disease, followed by apathy and confusion.

Autonomic instability is prominent and manifests as hypertension, tachycardia, elevated body-core temperature and hyperhidrosis, all features of a hyperadrenergic state. Patients become “nondippers” and sympathetic tone is elevated during both wake and sleep. PSG demonstrates a progressive reduction and disappearance of spindles, K complexes, and slow wave sleep, indicating a disruption in thalamocortical circuits. Plasma melatonin concentrations diminish as the disease progresses, leading to complete disruption of circadian rhythms. The mean age at onset is 51 years of age, and death typically occurs within 8–72 months.

Migraine

Autonomic hyperactivation occurs frequently in migraine and other autonomic cephalgias, and many of the pathways involved in pain generation also project to nuclei of the autonomic and sleep/wake systems. It is therefore not surprising that patients with chronic or refractory migraine report both sleep disruption and autonomic complaints, which can be difficult to differentiate from those of a primary autonomic disorder. Patients with migraine, for instance, may find it difficult to fall asleep because of headache, wake in the middle of the night or in the early morning hours with headache, and develop a strong component of insomnia that only serves to exacerbate their headaches. There are also circadian components to many headache syndromes that are often overlooked. Treatment should focus primarily on migraine control; once the headaches are treated, the autonomic symptoms and sleep disruption typically improves as well, though psychophysiological insomnia may persist. For a complete review of this topic, the reader is directed to the chapter in this text on sleep and headache.

Disorders of α-Synuclein Deposition

The α-synucleinopathies are neurodegenerative disorders resulting from the deposition of the protein α-synuclein in the central and/or peripheral nervous system. When these protein deposits occur exclusively in the peripheral autonomic nerves, the disease is termed pure autonomic failure (PAF). Parkinson’s disease (PD), multiple system atrophy (MSA), and dementia with Lewy bodies (DLB) are diseases of both central and peripheral α-synuclein deposition (Table 12.1). With the exception of PAF, REM behavior disorder (RBD) is extremely common in these disorders and, along with symptoms of autonomic impairment, may precede the development of motor symptoms by several decades. It is estimated that up to 80% of patients with idiopathic RBD (iRBD) may eventually develop some form of α-synucleinopathy, with an estimated median latency between RBD and motor symptoms of 12–14 years. Within the α-synucleinopathies, RBD is estimated to occur in 30–50% of patients with PD, 50–80% of patients with DLB, and 80–95% of patients with MSA. In this sense, RBD can be thought of as the strongest nonmotor predictor of future clinical disease.
Autonomic impairment is another early nonmotor manifestation, also occurring during the prodromal period, often in tandem with dream-enacting behavior. This association is likely due to the proximity of the cholinergic REM nuclei and the autonomic nuclei in the brainstem. In the Braak model of neurodegeneration, these nuclei become impaired before the motor nuclei are affected, as the deposition of α-synuclein progresses in a rostral–caudal fashion from the lower brainstem to the cortex. Many patients with RBD have some degree of autonomic impairment, and many patients with α-synucleinopathies and autonomic impairment also have RBD. This is a good example of disease states cosegregating due to the neuroanatomical proximity of their control nuclei. The topic of RBD, including workup and treatment, is also covered in the movement disorders section of this text.

**Pure Autonomic Failure**

Patients with PAF typically present in their fifth or sixth decade and may note symptoms of orthostatic hypotension, diminished sweat output, and gastrointestinal or genitourinary dysfunction, but without cognitive impairment or behavioral changes. If followed for long enough, some of these patients may eventually convert to PD, MSA, or DLB, as predicted in the Braak model. If patients are eventually diagnosed with one of the central α-synucleinopathies, it is most likely to be MSA. In one small study, 4 out of 10 patients originally diagnosed with PAF were eventually diagnosed with MSA at follow-up exams 5–7 years later. Therefore, it is typically recommended to follow patients for a minimum of 5 years before a definite diagnosis of PAF can be reached.

Sleep data on patients with PAF is limited. In one study, both PAF and MSA patients demonstrated reduced sleep efficiency on PSG; however, RBD was seen in all patients in the MSA group, and in no patients in the PAF group. This observation supports the concept of PAF as a purely peripheral disorder without brainstem involvement. However, the results of other studies have disputed this notion. One small case-series described RBD in three patients with PAF. Another small survey study described frequent nocturnal vocalizations in 9 of 13 PAF patients (69%), suggestive of possible RBD. PSGs were not performed in these patients and RBD could not be confirmed. This is a very interesting topic and a potential area for future research, though a challenging one owing to the relative rarity of PAF and the clinical overlap with disorders of central autonomic impairment, such as MSA.

**Multiple System Atrophy**

Of all the α-synucleinopathies, RBD is most commonly seen in MSA, affecting 80–95% of patients by some estimates. Sleep-disordered breathing is also common in these patients,
and affects patients with both parkinsonian and cerebellar subtypes. Both obstructive and central sleep apnea (CSA) have been reported with relative frequency. OSA is more common, and has been reported in up to 37% of patients. CPAP may be considered as a potential treatment, however it should be noted that MSA patients can have a floppy epiglottis, making CPAP a relative contraindication. It is not clear how to screen for these patients effectively and there is currently no consensus statement in this regard; therefore, PAP therapy is still generally recommended as first line therapy. CSA and Cheyne–Stokes respirations may occur due to degeneration of brainstem chemoreceptors. This may be the presenting sleep related breathing pattern; however, at other times CSA emerges once the patient is started on CPAP, termed treatment-emergent CSA. Adaptive servo-ventilation devices may be considered in these cases.

Stridor during sleep occurs with some regularity, and is thought to be secondary to selective deterioration of the vocal cord abductors. It manifests as a harsh, high-pitched, inspiratory tone, and is often more disturbing to the bed partner than snoring. The pathophysiology of the vocal muscle weakness is unknown, and examination of motor neurons in the nucleus ambiguous has failed to confirm selective deterioration of neurons serving the vocal cord musculature. Patients with stridor have a greater incidence of OSA, as well as a greater risk of sleep-related death. CPAP has been demonstrated to reduce the severity of stridor. In severe cases, symptoms may persist during the waking hours. In these cases, tracheostomy may be the only effective treatment.

RLS is not as common as it is in PD patients; however, some studies estimate prevalence rates as high as 23%. Patients with MSA also report a high degree of excessive daytime sleepiness, sleep fragmentation, unrefreshing sleep and insomnia due to rigidity, pain, and frequent nocturnal urination secondary to autonomic detrusor hyperactivity. Patients with PD report many of the same sleep complaints, though MSA patients tend to have more severe urinary dysfunction.

**Parkinson’s Disease**

Sleep disorders are extremely common in PD, reported in up to two thirds of patients. The sleep complaints are myriad and span the entire spectrum of sleep medicine, largely owing to the neuroanatomical deposition of Lewy bodies throughout the brainstem and cortex. The severity of these sleep complaints tends to correlate with the severity of the disease itself. For a detailed review of the sleep complaints in these patients, the reader is directed to the movement disorders chapter of this text. Parkinson’s patients with RBD are more likely to develop axial rigidity, have less response to levodopa therapy, and have an increased risk of falls, suggesting a more diffuse disease process. Patients with RBD are also more likely to develop autonomic impairment, and symptoms of autonomic impairment predict the conversion to clinically apparent neurodegenerative disease.

**Dementia with Lewy Bodies**

Patients with DLB have many of the same sleep issues as those with PD, though the extent of nocturnal rigidity depends on the degree of Parkinsonism in each individual patient. In addition, DLB patients have varying levels cognitive impairment, which is in turn associated with its own set of sleep problems, such as sundowning and circadian rhythm abnormalities.
Autonomic complaints are common, and many patients are diagnosed with orthostatic hypotension. Thus it is not surprising that there is a high prevalence of RBD, again indicating involvement of brainstem structures integral to both sleep and autonomic control.

**Idiopathic RBD**

Symptoms of autonomic impairment are common in patients with iRBD. In a large multicenter case–control study, 318 patients with iRBD were administered the scale for outcomes in PD-autonomic (SCOPA-AUT), a standardized 25-item autonomic questionnaire that addresses several domains including gastrointestinal, urinary, cardiovascular, thermoregulatory, pupillomotor, and sexual function. Patients with iRBD reported greater impairment than did controls, especially in relation to gastrointestinal, urinary, and cardiovascular function. There is also evidence that these patients have a higher conversion rate to clinically apparent neurodegenerative disease. In addition, within the α-synucleinopathies, the presence of RBD seems to be correlated with a greater degree of autonomic dysfunction.

Patients with iRBD have reduced heart rate variability during REM sleep. They also have more significant systolic blood pressure falls on active standing. Postuma and coworkers demonstrated an average systolic blood pressure reduction of 15.2 mmHg in these patients on active stand tests, compared to 3.7 mmHg in age-matched controls. Most patients reported symptoms of orthostatic intolerance, though did not meet criteria for orthostatic hypotension.

This data was corroborated by Frauscher and coworkers, who performed autonomic testing on iRBD patients and compared them to both controls and patients with PD. While patients with iRBD did not demonstrate orthostatic hypotension on tilt testing, they had slightly greater blood pressure falls on active stand than controls did. In addition, the Valsalva ratio, a measurement of cardiovagal function, was reduced in iRBD patients.

Patients with iRBD have evidence of postganglionic cardiac sympathetic denervation, as measured by cardiac scintigraphy, further supporting the theory of prodromal autonomic impairment. Thus autonomic impairment, like RBD itself, can be thought of as a feature that may help to identify at-risk patients, providing a potential window for disease modifying therapies should such therapies become available to clinicians in the future.

**CONCLUSIONS**

Sleep is a complex and highly orchestrated autonomic function, and when disrupted can lead to diurnal symptoms of both sleepiness and autonomic impairment. Healthy sleep is critical to homeostasis, and should be one of the primary goals in the treatment plan for all patients with autonomic disorders. Each disorder has its unique set of sleep complaints, thus a detailed history should always include questions about the patient’s sleep. While some associations have been firmly established, such as the association between RBD and the neurodegenerative disorders of α-synuclein deposition, others remain elusive, such the symptoms of fatigue and sleepiness in patients with POTS or EDS-HT. With greater awareness of these conditions and associations, the practicing neurologist can query his patients for these symptoms, and if present and successfully treated, lead to significant improvement in their quality of life.
48. Schenck CH, Boeve BF, Mahowald MW. Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. Sleep Med. 2013;14:744–748.


