Sleep and cerebral degenerative disorders

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Introduction

This article includes discussion of sleep and cerebral degenerative disorders, sleep disorders associated with Alzheimer disease, sleep disorders associated with Parkinson disease, sleep disorders associated with progressive supranuclear palsy, sleep disorders associated with corticobasal degeneration, sleep disorders associated with multiple system atrophy, and sleep disorders associated with diffuse Lewy body disease. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

Degenerative diseases of the central nervous system are a large and varied group of disorders that affect a range of neurologic function. Sleep disorders are commonly seen in patients with cerebral degenerative diseases. Much of this may be related to the underlying central nervous system damage to sleep regulatory centers of the brain. Research has shown that sleep disorders may serve as a biomarker to predict development of a future neurodegenerative disorder. Increasing new data has suggested that disrupted sleep may accelerate the degenerative process in conditions such as Alzheimer dementia and Parkinson disease. One potential mechanism is emerging evidence of the role of sleep in glymphatic clearance of metabolic waste products from the brain. Prompt attention to and treatment of sleep symptoms can result in significant improvement in quality of life or possibly delay in progression of disease.

Key points

- Sleep disorders, such as insomnia, sleep apnea, restless legs syndrome, certain parasomnias, and circadian rhythm disorders, are disproportionally more common in patients with cerebral degenerative disorders than in the general population.
- Sleep disturbances in the setting of neurodegenerative disorders are sometimes secondary to localized damage to areas of the brain that control and regulate sleep and alertness.
- REM-sleep behavior disorder is a parasomnia frequently seen in patients with Parkinson disease and other synucleinopathies and can sometimes predate the motor and cognitive symptoms of the condition by several years or even decades. It is the first time that a sleep disorder can be used as a biomarker to predict a neurodegenerative disorder.
- Treatment of the underlying sleep disorder can not only help in improving quality of life, but may improve motor or cognitive symptoms of the underlying cerebral degenerative condition.

Historical note and terminology

The relationship between sleep disorders and neurodegenerative diseases has become increasingly more lucid as research into both areas has made significant progress. Indeed, a link between the 2 has been noted since the earliest descriptions of some neurodegenerative disorders. In the early 19th century, James Parkinson and his coworkers described clinical sleep abnormalities associated with extrapyramidal disorders (Pauletto et al 2004). Subsequently, a variety of sleep disorders have been found in tandem with diseases such as Parkinson disease, multiple system atrophy, diffuse Lewy body disease (DLBD), corticobasal degeneration, and others. However, the underlying sleep abnormalities were not extensively explored until relatively recently. In the latter half of the twentieth century, the advent of more sophisticated diagnostic techniques, such as polysomnography and improved EEG recordings, as well as the discovery of new treatments, allowed for major advances in the field (Pauletto et al 2004). Research is exploring how disrupted sleep may serve as a risk factor for developing neurodegenerative disorders.

Clinical manifestations

Presentation and course

Sleep disorders are relatively common in neurodegenerative diseases, and the types and prevalence vary. The primary sleep disturbances in this class include insomnia, hypersomnia, parasomnias (including REM sleep behavior disorder), respiratory dysrhythmias, disturbed sleep-wake cycles, and excessive nocturnal motor activity (Bhatt et al 2005). For patients with neurodegenerative diseases, and dementia in particular, sleep disturbances may have a dramatic impact on function and quality of life. In this article, we describe some of the common presenting symptoms of these disorders and then discuss several of the neurodegenerative diseases in more detail. This review concentrates on Alzheimer disease, Parkinson disease, diffuse Lewy body dementia, progressive supranuclear palsy, corticobasal degeneration, Pick disease, multiple system atrophy, olivopontocerebellar atrophy, and striatonigral degeneration.

The descriptions of sleep disorders will refer to the International Classification of Sleep Disorders, 3rd edition, published in 2014 (American Academy of Sleep Medicine 2014).

A number of symptomatic complaints are common in cerebral degenerative disorders. Patients with insomnia describe inadequate nighttime sleep, and the term insomnia itself refers to difficulty with initiating or maintaining sleep. This may be represented by difficulty falling asleep, frequent awakenings, early morning wakening, or feeling unrefreshed after sleeping. This will often result in feelings of daytime fatigue, irritability, mood changes, poor attention, trouble with motor skills, and may result in decreased ability to function at baseline during waking hours. Hypersomnia, or excessive daytime sleepiness, is a complaint voiced by many patients with neurodegenerative disorders. Symptoms of hypersomnia include persistent sleepiness during waking hours, trouble with concentration, irritability, anxiety, and impaired function ability during the daytime. Patients may find themselves falling asleep at inopportune times and places, which is often not relieved by sleeping at night, and can lead to frequent daytime naps, difficulty with memory, and even automatic behaviors for which the patient is largely amnestic (Dyken and Yamada 2005). Fatigue, distinct from sleepiness, is also a common complaint.

The parasomnias include a large group of disorders of arousal (NREM sleep parasomnias) or disorders associated with REM sleep. Patients with parasomnias may describe sleep walking, sleep terrors, confusional arousals, complex behaviors, nightmares, and sleep paralysis. REM sleep behavior disorder is the most common parasomnia associated with neurodegenerative diseases, and tends to present with dream enactment in the form of motor and verbal activity during sleep as a consequence of lack of the normal muscle atonia seen in REM sleep. The dream enactment activities can be mild or severe and may lead to injury to the patient and/or bed partner. REM sleep behavior disorder may predate other symptoms of Parkinson disease and other neurodegenerative diseases by up to several decades (Schenck et al 1996; Iranzo et al 2006; Claassen et al 2010). In 1 study, the estimated 5-year risk of neurodegenerative disease was 17.7%, the 10-year risk was 40.6%, and the 12-year risk was 52.4% (Postuma et al 2009). Others have shown even higher rates, such as over 90% at 14 years (Iranzo et al 2014). Furthermore, patients with Parkinson disease and REM sleep behavior disorder were found to be more likely to develop dementia as compared to patients who did not have this disorder at presentation (Postuma et al 2012) and may even predict future cognitive decline in memory and attention (Chahine et al 2016). The rates of phenoconversion from the onset of REM sleep behavior disorder diagnosis to expression of the alpha synucleinopathy is dose-dependent with time, that is the longer one waits from the onset of REM sleep behavior disorder diagnosis, the higher the risk of acquiring dementia.

Respiratory dysrhythmias or dysfunction may present as nocturnal stridor, apneic events (central, obstructive, or mixed), as well as cluster breathing, Cheyne-Stokes respiration, and other abnormalities in the rate, rhythm, and amplitude of respiration (Bhatt et al 2005). Disturbances in the normal circadian sleep-wake cycle are also common in many of these disorders. Symptoms include insomnia, excessive daytime sleepiness, inability to sleep at the desired time, and resultant impairment in daily function (Reid and Zee 2004). Although circadian rhythms may be affected by both external and intrinsic factors, in the case of the neurodegenerative disorders the primary problem is thought to be intrinsic. The “sundowning” phenomenon often seen in patients with dementia is related to this phenomenon.

In patients with Alzheimer disease, sleep abnormalities may appear early in the disease process and may be a prominent feature. One study demonstrated that the presence of parkinsonian features may be an independent risk factor for excessive daytime sleepiness in patients with mild Alzheimer disease (Park et al 2011). In dementia in general, reported abnormalities have included low sleep efficiency, high percentage of stage N1 sleep relative to other

stages, decrease in slow wave sleep, and increased frequency of arousals and awakenings (Bliwise 1993). Early in the disease course, circadian sleep-wake cycles are disturbed, and there is an increase in nighttime wakefulness, which worsens with disease progression. A number of distinct circadian rhythm abnormalities have been identified, and disturbances in the rest-rhythm activity have been identified (Witting et al 1990; Motohashi et al 2000). In addition, a number of studies have shown that melatonin levels may be abnormal in patients with Alzheimer disease, suggesting a possible link with circadian rhythm and diurnal variation (Uchida et al 1996; Mishima et al 1999). One study suggests a different pathogenesis, demonstrating an increase in cerebrospinal fluid orexin in patients with Alzheimer dementia resulting in sleep dysregulation along with deterioration and worsened cognition (Liguori et al 2014). Later in the disease, REM sleep time is decreased, and there is increased REM sleep latency, which, along with abnormalities of the circadian rhythm, results in excessive daytime sleepiness. Further decreases in REM sleep have been noted in patients with Alzheimer disease who have sleep-disordered breathing (Cooke et al 2006). Sundowning and other disturbances of the sleep-wake cycle are common in Alzheimer disease, and may be influenced and exacerbated by a number of factors, including foreign environment, medications, and infection (Hoyt 2005). Irregular sleep-wake disorder becomes more common as the degenerative disorder progresses. Irregular sleep-wake rhythm disorder is a circadian rhythm disorder where no major sleep period (typically < 4 hours) is noted throughout a 24-hour period (per actigraphy or sleep logs), resulting in variable and disorganized sleep and wake episodes throughout the 24-hour cycle (American Academy of Sleep Medicine 2014). One case series suggested higher rates of REM sleep without atonia in patients with Alzheimer disease, though not as high as in those with Parkinson disease (Gagnon et al 2006a).

Obstructive sleep apnea has also been linked to Alzheimer disease, though the data for this are derived from smaller studies that are not typically specific to Alzheimer disease, and involve other types of dementia and cerebrovascular disease (Ancoli-Israel et al 1989; Ancoli-Israel et al 1991a). Some smaller studies have even suggested that there may not be a clear statistical difference between Alzheimer disease and controls in sleep disordered breathing (Bliwise et al 1989). It should be noted that this is a disorder seen in a greater percentage of patients over 65 years than in the general population, though it is also influenced by risk factors similar to those seen in younger patients (Ancoli-Israel et al 1991b; Ancoli-Israel et al 2001). One study demonstrated that among a cohort of older women, those with sleep-disordered breathing had an increased risk of developing cognitive impairment when compared with those without this risk (Yaffe 2011).

Patients with progressive supranuclear palsy have a high prevalence of comorbid sleep disorders. Initially, the most common problems are insomnia and delayed sleep onset. Decreased REM sleep and spindle formation have also been reported. Some studies have found that as the disease progresses, sleep latency shortens and insomnia becomes more severe due to associated increased sleep fragmentation (Aldrich and Foster et al 1989). Polysomnographic findings also include increased sleep fragmentation, reduced sleep time, variable latency to REM sleep, reduction or absence of REM sleep, and general reduction in sleep spindles and K complexes (Petit et al 2004). Other problems associated with progressive supranuclear palsy, such as immobility and dysphagia, contribute to interrupted sleep patterns. Notably, it has been suggested that REM sleep behavior disorder and respiratory disturbances are not as pronounced in progressive supranuclear palsy when compared with Parkinson disease and other synucleinopathies. However, some research suggests that REM sleep without atonia and REM-sleep behavior disorder may in fact be as common in progressive supranuclear palsy as in Parkinson disease (Arnulf et al 2005; Sixel-Doring et al 2009).

Corticobasal degeneration is a less commonly diagnosed entity, and to date extensive studies on sleep disturbances are limited. Case reports have described patients with REM sleep behavior disorder (Kimura et al 1997), periodic limb movement disorder, REM sleep without atonia (Wetter et al 2002), and insomnia (Roche et al 2007).

Parkinson disease has been among the most studied of the neurodegenerative disorders with respect to sleep disorders. Sleep abnormalities in Parkinson disease have been reported since the initial descriptions of the disease itself. A variety of well-described sleep symptoms and disturbances affect Parkinson patients. Complaints of insomnia, parasomnias, daytime sleepiness, and sleep onset and maintenance difficulties are common (Bhatt et al 2005). Fatigue is also a prominent complaint, though is subjective and in some studies does not appear to clearly correlate with depression, disease severity, or duration of disease in Parkinson disease patients (Abe et al 2000). Fatigue and sleep disorders do seem to correlate with quality of life of Parkinson patients (Stocchi et al 2014). Sleep studies in Parkinson patients have revealed several distinct abnormalities. These include deficiencies in slow wave sleep, total sleep time, sleep latency, efficiency, and overall architecture (Thorpy and Adler 2005), as well as a decrease in REM sleep (Simuni 2004; Yong et al 2011). Sleep fragmentation, altered dream phenomena, and hallucinations appear to be common in Parkinson disease patients according to some studies (Pappert et al 1999). A community-based study in

1998 suggested a significantly increased prevalence of sleep disorders in the Parkinson disease population compared with controls, with the most common complaints being sleep fragmentation and early awakening (Tandberg et al 1998). Airway obstruction (sleep apnea) or restrictive pulmonary function is also common in Parkinson patients (Maria et al 2003), however, thus far it has not been clearly demonstrated whether the prevalence of obstructive sleep apnea in Parkinson disease is significantly increased over that of controls (Happe et al 2001; Arnulf et al 2002; Maria et al 2003; Diederich et al 2005; Dhawan et al 2006; Trotti and Bliwise 2010). Parkinson disease patients may suffer from more obstructive sleep apnea due to limited mobility at night (not being able to turn over in bed), resulting in more sleep in the supine position, which is when obstructive sleep apnea is most prevalent (Cochen De Cock et al 2015). Similarly, restless legs syndrome and periodic leg movements are also common in Parkinson disease. Some studies have suggested increased prevalence compared to the general population, but other studies have not shown clear evidence of significant differences, and no clear prospective trials have to date been completed (Tan et al 2001; Ondo et al 2002; Nomura et al 2006). Evidence suggests that the prevalence of REM sleep behavior disorder is increased in Parkinson disease, as is REM sleep without atonia (Wetter et al 2001; Onofrj et al 2002). In 1 large cohort, the overall frequency of REM sleep behavior disorder was 46% in Parkinson disease patients, with rates increasing with age and disease duration (Sixel-Doring 2011). It is important to distinguish between REM sleep behavior disorder and nightmares as the treatment can differ significantly (Simuni 2004). In addition, symptoms themselves may be correlated to medication effect. A case series described rare occurrences of adult-onset sleepwalking in patients with Parkinson disease (Poryazova et al 2007), though another study asserts that Parkinson patients have a higher prevalence of other parasomnias such as nightmares, night terrors, sleepwalking, and enuresis (Ylikoski et al 2014). Circadian rhythms and sleep cycles will also be affected for a variety of reasons in Parkinson disease. Finally, a variety of other factors common in Parkinson disease may have significant impact on sleep, including depression, pain, motor difficulties, autonomic abnormalities, nocturia, nightmares, and medication. The motor symptoms themselves likely play a significant role in causing sleep symptoms because when these motor symptoms are targeted with therapy at night, such as long-acting dopamine or rotigotine patch, sleep is improved (Vallderiola et al 2015). Excessive daytime sleepiness is a commonly described problem in Parkinson disease, and can result in significant adverse effects on daily life, social interactions, and work performance. A number of studies have shown that medication side effects (particularly of dopamine agonists and L-dopa) can result in increased daytime sleepiness, though large population studies have also demonstrated increased daytime sleepiness in Parkinson disease patients irrespective of medications (Thorpy and Adler 2005) or prior to treatment for Parkinson disease (Tholfsen et al 2015). Central hypersomnia has also been described in patients with Parkinson disease, including a narcolepsy phenotype due to neurologic disease, with low hypocretin levels measured in the cerebrospinal fluid (Wienecke et al 2012). Regardless of the exact etiology, these symptoms must be taken seriously if adverse effects such as motor vehicle accidents are to be avoided. Circadian rhythm disturbances have also been described in patients with Parkinson disease (Videnovic and Golombek 2013), including disruption of circadian markers such as cortisol and melatonin levels (Breen et al 2014; Videnovic et al 2014).

When reviewing sleep complaints in this population of patients, it is also important to consider the changes in sleep architecture associated with normal aging. These include (but are not limited to) sleep fragmentation, reduced sleep efficiency, decreased sleep quality, and reduction on the amount and amplitude of slow wave sleep, along with other predictable changes (Avidan 2005). These changes often complement the more pronounced difficulties seen in patients with neurodegenerative disorders.

Prognosis and complications

In general, the cerebral degenerative diseases described above are progressive disorders that tend to worsen with time. Sleep disorders in these patients are linked to the underlying disease process. Thus, as the disease itself worsens, the sleep disorders also tend to progress.

Clinical vignette

A 78-year-old man with diagnosed Parkinson disease presented to his physician's office with his wife. He described that his motor symptoms were under good control, but for the last year he had been having increasing sleepiness during the day, forcing him to take naps regularly. He had initially thought that this might be a side effect of his medications, but after several trials of different medications and doses, he did not notice any relief. When his wife was asked about her husband's sleep, she remarked that she noticed that he had been talking significantly more in his sleep, and more recently had begun to act out his dreams on a regular basis. On a few occasions he had even struck

her while apparently trying to fight during his dream. She noticed that he had displayed some of these symptoms a few years before he was diagnosed with Parkinson disease. A baseline polysomnogram was performed and revealed abnormal augmentation of his limb and chin EMG tone during REM sleep, suggesting that the patient's symptoms were most likely due to REM sleep behavior disorder, a problem commonly associated with Parkinson disease.{embed="pagecomponents/media_embed" entry_id="9010"} A trial of clonazepam therapy at 0.25 mg prior to bedtime was initiated and helped to control his symptoms, though he continued to describe daytime sleepiness. Notably, his polysomnogram had not shown evidence of obstructive sleep apnea, which can be worsened by benzodiazepine therapy. His neurologist suggested that if this continued to be a problem, melatonin could be tried as a possible alternative.

Biological basis

Etiology and pathogenesis

The etiology of sleep disorders in cerebral degenerative disorders is thought to be secondary to the underlying disease processes. Abnormalities, particularly in the brainstem and hypothalamus, caused by cell death and protein deposition as well as other processes play a major role in disruption of normal sleep cycles. In idiopathic REM sleep behavior disorder, loss of dorsal lateral nigral hyperintensities typically only seen in patients with Parkinson disease are noted on MRI even though no motor symptoms have developed yet in these patients (De Marzi et al 2016). It should also be noted that other factors can have a significant effect on sleep in these patients, including medication side effect, normal changes in sleep architecture with age, comorbid psychiatric abnormalities, social stressors, and even sleep disorders unrelated to the primary cerebral degenerative disorder.

Neurodegenerative diseases are often divided into 2 categories: the synucleinopathies and the tauopathies. These names derive from the abnormalities in underlying molecular mechanisms. In the tauopathies (including Alzheimer disease, progressive supranuclear palsy, Pick disease, and corticobasal degeneration) abnormal structure or phosphorylation of microtubule-associated proteins leads to both intra- and extracellular protein deposition. The synucleinopathies (Parkinson disease, diffuse Lewy body dementia, multiple system atrophy, striatonigral degeneration, and olivopontocerebellar atrophy) result from abnormalities of the protein alpha-synuclein, which accumulates abnormally in neurons and glia, as well as extracellularly. Abnormalities in related proteins ubiquitin and parkin are also important in the synucleinopathies.

In the cerebral degenerative disorders there can be direct effects on regions of the brain involved in sleep regulation, which contribute to the clinical symptoms and findings in workup. Effects of disease on the normal sleep-wake regulating centers of the brain are common. In particular, involvement of the brainstem and the hypothalamus has major effects. For example, animal studies have suggested a relationship between insomnia and the ventrolateral (hypothalamic) preoptic nucleus (Lu et al 2000; Gaus et al 2002). Damage to the lower brainstem hypnogenic neurons near the nucleus tractus solitarius can also result in difficulties in sleep initiation. Hypersomnolence can result from almost any lesion that affects the reticular activating system (including the pons, midbrain, thalamus, hypothalamus, and forebrain), with the dorsolateral hypothalamic nucleus playing a key role.

Additionally, other factors not directly related to underlying neurodegenerative disease may significantly influence sleep in this group of patients. These include such items as other medical conditions (pain, psychiatric disorders, etc.), medication side effects, physical discomfort related to the disease, the social environment, and sleep abnormalities related to aging. These must also be taken into account as contributing factors.

In Alzheimer disease, the main pathologic findings are diffuse neurofibrillary tangles and beta-peptide protein deposits. Disruption of the circadian sleep-wake cycle is a prominent feature, and some studies have suggested that the overall amplitude of melatonin and the rhythm itself may be decreased in Alzheimer disease, though exact mechanisms have not yet been elucidated. Also implicated has been the suprachiasmatic nucleus of the hypothalamus, which has been shown in postmortem studies to suffer cell loss compared to normal controls (Bliwise 2004). In addition, decreased REM sleep in Alzheimer disease may be due to loss of cholinergic neurons, particularly in areas such as the nucleus basalis of Meynert or the pedunculopontine tegmental and laterodorsal tegmental nuclei. There are several studies showing an association between sleep disruption or deprivation and beta-amyloid levels in normal controls, suggesting sleep as an accelerating factor in the progression to Alzheimer disease (Spira et al 2013). This same type of hypothesis has been suggested for sleep disruption from sleep apnea and subsequent progression to Parkinson disease (Chen et al 2015). Two metaanalyses and reviews demonstrated sleep disruption (subjective reports) as a risk factor for

development of Alzheimer dementia (Bubu et al 2017; Shi et al 2017). One potential mechanism explaining the role of disrupted sleep in development of dementia includes evidence of abnormal sleep-dependent glymphatic clearance of metabolic waste products from the brain. Another mechanism suggests that sleep and circadian disruption contribute to cognitive decline by activating neuroendocrine and neuroinflammatory signaling pathways that suppress hippocampal neurogenesis (Kent and Mistlberger 2017).

In progressive supranuclear palsy brainstem lesions are the major contributing factor. There have been suggestions that locus ceruleus or pontomesencephalic nuclei may be involved. In addition, degeneration of nigrostriatal neurons may result in deafferentation of frontal lobes from the striatum (Hoyt 2005).

Corticobasal degeneration is characterized clinically by corticospinal tract and extrapyramidal features, tremors, apraxia, myoclonus, dystonia, cognitive dysfunction, and prominent cortical and basal ganglia atrophy. It is 1 of the lesser studied of the neurodegenerative disorders with respect to sleep, however, REM sleep behavior disorder has been described in several reports (Wetter et al 2002). Midbrain and pontine structures have been shown to be affected in this disease, and it is postulated that such involvement may account for the sleep disorders (Kimura et al 1997). Gliosis seen in corticobasal degeneration, particularly in frontal and parietal areas and subcortical regions, may have effects similar to those noted in progressive supranuclear palsy (Bhatt et al 2005).

In Parkinson disease, involvement of the pedunculopontine nucleus, locus ceruleus, pontine ceruleus alpha nucleus, and raphe nuclei are implicated in disorders of REM sleep and slow wave sleep, and have been directly localized in some animal studies (Takakusaki et al 2004). The pedunculotegmental nucleus involved pathways mediating both locomotion and REM sleep, and loss of cholinergic neurons, may be the underlying etiology of disorder in this area (Thorpy and Adler 2005). Fatigue, a common symptom in Parkinson disease patients, may be due to reduced serotonergic function in the basal ganglia and limbic structures as observed in PET studies of patients with Parkinson disease (Pavese et al 2010). Decreases in melatonin production and hypothalamic neuron loss have been noted in patients with Parkinson disease, likely contributing to circadian rhythm dysfunction (Breen et al 2016). Similarly, diffuse Lewy Body disease, characterized by dementia, extrapyramidal symptoms, and psychosis (visual hallucinations are classic) shows the effects of Lewy body deposition and neuronal degeneration in the substantia nigra, locus ceruleus, and raphe nuclei (Bhatt et al 2005).

Epidemiology"

The prevalence of sleep disorders among patients with cerebral degenerative disorders varies based on disease but is likely underreported in general. Overall estimates have put prevalence at 40% to 80%. The numbers vary from disease to disease. For instance, sleep disorders are seen in 74% to 98% of idiopathic Parkinson disease patients, and sleep apnea is estimated in 33% to 53% of patients with probable Alzheimer disease (Bhatt et al 2005).

Prevention

As curative treatments for most of the underlying cerebral degenerative disorders have yet to be discovered, primary prevention of the associated sleep disorders is difficult due to the intrinsic pathology. However, treatment of sleep disorders themselves is extremely important with respect to prevention of other comorbidities. For example, treatment of sleep apnea is essential as it has been associated with increased risk of cardiovascular disease, hypoxia during sleep, cerebral vascular disease, and impaired glucose tolerance.

Differential diagnosis

The differential diagnosis is broad for patients with sleep disorders. Apart from primary disease as a direct causative mechanism, other primary sleep disorders must be considered. In the elderly, a number of sleep disorders are possible, including sleep apnea, restless legs syndrome, periodic limb movement disorder of sleep, insomnia (due to a variety of mechanisms), circadian rhythm abnormalities, and parasomnias, amongst others (Avidan 2005). In addition, other factors may contribute to sleep disturbances, including comorbid medical conditions, medication effects, psychiatric disorders, and other primary neurologic disorders.

Diagnostic workup

Perhaps most important in the initial evaluation of sleep disorders in patients with neurocognitive deficits is a detailed history and physical exam. Often it is necessary to interview several family members or others who have close contact

with the patient as he or she may not be able to provide adequate history. One study demonstrated a discrepancy between subjective and objective sleep reports in patients with early to moderate stage Alzheimer disease, suggesting usefulness of actigraphy in addition to sleep logs in this patient population (Most et al 2012). Close attention should be paid to sleep history as well as to neurologic and medical problems that could affect sleep (including pain), and a careful psychiatric evaluation is essential as this is often comorbid in neurocognitive disorders. A thorough inspection of medications and timing of doses is important.

Polysomnography is generally the most informative test to consider when pursuing a diagnosis of a sleep disorder. This can help to delineate abnormalities of sleep architecture and severity of pathology, including parasomnias, respiratory disturbances (including obstructive sleep apnea), and abnormal motor activity. Concurrent video monitoring may be helpful. Increased EMG tone in the chin and limbs during REM sleep can be helpful in the diagnosis of REM sleep behavior disorder in patients who have a history of dream enactment behavior. Increased tonic chin EMG activity during REM sleep was found to predict future development of Parkinson disease in patients with idiopathic REM sleep behavior disorder as compared to patients who had solely increased phasic chin EMG activity during REM sleep (Postuma et al 2010). Multiple sleep latency testing can provide useful information about daytime sleepiness, hypersomnolence, and narcolepsy. Actigraphy is another useful means of gathering information by measuring limb movements while both asleep and awake, though it provides less detail into sleep architecture than does polysomnography or multiple sleep latency testing, and is not as well studied (Stavitsky et al 2010). One study suggests that using a combination of questionnaires along with actigraphy can be helpful in diagnosing REM sleep behavior disorder with good specificity, but not sensitivity (Louter et al 2014). One other study validated the use of the Mayo Sleep Questionnaire as having adequate sensitivity and specificity in the diagnosis of REM sleep behavior disorder among the elderly (Boeve et al 2013). Home sleep apnea testing in 1 small study of Parkinson disease patients led to high failure rate and other difficulties such as underestimation of the degree of sleep-disordered breathing (Gros et al 2015).

Further testing options should be based on the clinical scenario. Pulmonary function testing, along with arterial blood gas, may be useful for assessing baseline respiratory disease and abnormalities in acid-base balance, which can contribute to sleep disorders or be a manifestation of them. Polysomnography includes partial EEG monitoring, but if nocturnal seizures are suspected, then formal EEG monitoring can be helpful. EMG testing can identify neuromuscular disorders often associated with cerebral degenerative disorders.

Management

Many of the cerebral degenerative disorders do not yet have definitive cures or treatments, but when possible, treatment of the underlying disease and symptoms can have a beneficial effect on sleep symptoms. Treatments commonly used to reduce motor symptoms of Parkinson disease seem to also assist in consolidating sleep and improving alertness. This has been noted with Parkinson disease medications such as rotigotine (Pierantozzi et al 2016), rasagiline (Panisset et al 2016), as well as with deep brain stimulation (Baumann-Vogel et al 2017). In addition, attention to and management of other factors that can contribute to sleep disturbances is necessary. For example, maintaining regular sleep-wake schedules and avoiding prescription and over-the-counter medications that may affect sleep is important (Ancoli-Israel 2005). Specific treatment of sleep disorders should be tailored to the sleep disorder diagnosis. Keep in mind also that many sleep disorders are multifactorial in nature, and many are associated with older age in general. For all patients with dementia, adherence to proper sleep hygiene, such as maintaining a regular sleep wake schedule, are recommended.{embed="pagecomponents/media_embed" entry_id="9011"}

Disorders involving excessive motor activity during sleep, including restless legs syndrome and periodic limb movements of sleep, can be treated with commonly available medications. Dopaminergic medications, including levodopa, pramipexole, pergolide, and ropinirole are first line treatment for restless legs syndrome. They have been shown in a number of studies to be effective in treating symptoms of restless legs syndrome (Allen and Earley 1996; Earley and Allen 1996; Montplaisir et al 2006; Paulus and Trenkwalder 2006).

Insomnia is a manifestation best approached by addressing the possible underlying triggers. Various measures to improve sleep hygiene may be attempted, including avoidance of stimulants such as caffeine and nicotine, exposure to light during the day and synchronization of circadian rhythms, avoiding heavy meals and fluids prior to bed time, exercising regularly, avoiding temperature extremes, and using the bedroom only for sleeping purposes (Avidan 2003; Neubauer 2005). Pharmacologic therapy, particularly sedative hypnotics, may be used judiciously as they may have significant adverse side effects in the elderly and particularly in patients with significant cerebral degenerative

disorders. These include such medications as zolpidem, zaleplon, eszopiclone, ramelteon, and triazolam, amongst others. One randomized, placebo-controlled trial studied eszopiclone in 30 patients with Parkinson disease and insomnia. Eszopiclone did not significantly increase sleep time but did subjectively improve quality of sleep and was reasonably tolerated as compared to placebo (Menza et al 2010). Doxepin has also been shown to be effective in improving insomnia symptoms in 1 small randomized trial in Parkinson disease patients (Rios Romenets et al 2013). A Cochrane database review suggested lack of evidence to help guide treatment for sleep problems in dementia, particularly with benzodiazepines and nonbenzodiazepine hypnotics. There was some evidence to support the use of trazodone (low dose of 50 mg) and no evidence that melatonin (up to 10 mg) helped sleep (McCleery et al 2016). Nonpharmacologic interventions, including stimulus control therapy, sleep restriction therapy, psychotherapy, and cognitive behavioral therapy, should be considered and have been shown to be effective in improving sleep efficiency and decreasing awakenings at night (Humbert et al 2017). Given barriers such as access and expense, pilot studies have shown improvement in insomnia in Parkinson disease patients using computerized cognitive behavioral therapy (Patel et al 2017). Prolonged release melatonin helped improve sleep maintenance and cognitive functioning in mild to moderate Alzheimer disease patients in 1 randomized, placebo-controlled, multicenter study (Wade et al 2014). Evidence-based review guidelines by the American Academy of Sleep Medicine suggest clinicians not use melatonin as treatment for insomnia, based upon doses of 2 mg of melatonin (Sateia et al 2017).

Low dose (50 mg) of trazadone improved sleep in 1 randomized, placebo-controlled study of 30 dementia patients (Camargos et al 2014). Table 1 provides additional suggestions for the treatment of insomnia in patients with dementia.

Table 1. Suggested Treatment of Insomnia in Dementia

- Cognitive-behavioral therapy
- Circadian cues (Campbell et al 1993; Lack et al 2005)
  - Light: bright-light therapy used in the delay portion (ie, the evening, 7:00 PM to 9:00 PM) may help normalize circadian rhythms in patients with advanced sleep phase syndrome*
  - Physical activity: 3 to 6 hours before bedtime
- Hypnotics (Larsen and Tandberg 2001)
  - Short-acting nonbenzodiazepine agents: eszopiclone, zaleplon, zolpidem
  - Trazadone 50 mg
- Melatonin agonists
  - Ramelteon

* Exact length of treatment and dosing needed have yet to be clearly established.

(Olanow et al 2001)

Treatment of excessive daytime sleepiness likewise centers on treatment of the factors causing disruption of nocturnal sleep or poor overall quality of sleep. A variety of factors may be implicated, including sleep disordered breathing, pain, and medication effect, among others. As mentioned previously, dopamine agonists in Parkinson disease can be problematic in this respect. Comorbidities such as other medical and psychiatric issues should also be explored and treated. Sleep disordered breathing, including obstructive sleep apnea, is 1 of the most commonly encountered problems. Treatment for obstructive sleep apnea includes nasal continuous positive airway pressure (primary), bi-level positive airway pressure, weight loss, and avoidance of exacerbating factors such as medications and alcohol. Continuous positive airway pressure has been shown in some small studies to reduce subjective daytime sleepiness in Alzheimer disease (Chong et al 2006). One randomized placebo controlled trial demonstrated decreased arousals and more stage 3 sleep with use of CPAP as compared to placebo CPAP (Cooke et al 2009a). Another randomized, placebo-controlled crossover study of Parkinson patients showed improvements in sleep architecture and objective measures in sleepiness when treated with CPAP (Neikrug et al 2014). Trials with CPAP have shown benefits of slowing cognitive decline (Cooke et al 2009b; Troussiere et al 2014) and improving cognition (Ancoli-Israel et al 2008) in patients with Alzheimer disease who suffer from sleep apnea. It should be noted that in patients with severe neurodegenerative disorders, particularly dementia, compliance with continuous positive airway pressure may be more difficult. In patients with multiple system atrophy, 1 retrospective study demonstrated that over 66% discontinued CPAP after a year (Shimohata et al 2014), with over 75% of Parkinson disease patients dropping out in another study due to issues with CPAP tolerance (Terzaghi et al 2017). In patients with more severe respiratory compromise, particularly in those patients with neuromuscular weakness, nocturnal ventilatory support and tracheostomy may be required. One study

demonstrated improvements in both sleep apnea and hypoventilation with adaptive servoventilation in patients with multiple system atrophy (Hamada et al 2015). In those patients with persistent sleepiness, a trial of stimulant medications may be in order with modafinil, armodafinil, or methylphenidate. One study demonstrated improvement in excessive daytime sleepiness in Parkinson disease patients when given sodium oxybate (Ondo et al 2008). Another study explored the use of a selective adenosine A2A receptor antagonist, istradefylline, which not only helped motor symptoms, but also improved alertness (Suzuki et al 2017).

In those patients exhibiting parasomnias, an important initial part of management is ensuring safety for the patient and any bed partners. The most commonly encountered parasomnia in patients with cerebral degenerative disorders is REM sleep behavior disorder, which is treated primarily with clonazepam. Although no large randomized trials have been performed yet to evaluate medical therapy, clonazepam has been shown to have beneficial effect in several smaller studies (Schenck et al 1993; Olson et al 2000) and is generally accepted as first line treatment (Aurora et al 2010). The initial starting dose is generally 0.5 mg per night and may be increased up to 2 mg. It should be noted that clonazepam can have other adverse side effects, including possibly contributing to a worsening of obstructive sleep apnea or worsening balance in patients already with ataxia. No other benzodiazepines have thus far been shown to be effective in treatment of REM sleep behavior disorder. Melatonin has also been implicated as a possible therapeutic option in studies using doses of 3 to 12 mg and has more support in the literature than other substances with the exception of clonazepam (Kunz and Bes 1997; Kunz and Bes 1999; Boeve et al 2003). Ramelteon has also been studied in an open-label trial for REM sleep behavior disorder with positive results (Kashihara et al 2016). Pramipexole and acetylcholinesterase inhibitors can be considered according to the guidelines, including a study on rivastigmine in refractory REM sleep behavior disorder (Di Giacopo et al 2012). Only very limited data (case series) have shown effectiveness of desipramine, clozapine, and carbamazepine (Aurora et al 2010). A customized bed alarm has been shown to have utility as an effective method to prevent sleep-related injury in REM sleep behavior disorder. This intervention is most suitable in cases of pharmacologically refractory REM sleep behavior disorder and for those patients who are unable to tolerate drug therapy (Howell 2011).

Principal therapy for REM sleep behavior disorder is shown in Table 2, and the following diagram depicts second-line therapy.{embed="pagecomponents/media_embed" entry_id="9012"}

Table 2. Treatment for REM Sleep Behavior Disorder

- Formal neurologic exam (Abad and Guilleminault 2004; Ferini-Strambi et al 2005; Gagnon et al 2006b)
- Level A: Safety intervention: removal of sharp objects from the bedroom, sleeping in a sleeping bag until the condition is managed, covering the windows, etc. (Boeve et al 2003)
- Avoid aggravating drugs: caffeine, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressant
- Level B: Clonazepam nightly (approximately 90% effective) (Boeve et al 2003)
- Level B: Melatonin (doses between 3 and 12 mg nightly) (Kunz et al 1999; Boeve et al 2003)
- Levodopa, dopamine agonists
- Anticonvulsants
- Pressurized bed alarm (Howell et al 2011)

Data suggest that melatonin may have an advantage over clonazepam given that the latter is a respiratory depressant and has a long half-life, placing patients at increased risk of falls (McGrane et al 2015). Melatonin was less likely to lead to sedation and had less frequent adverse effects than clonazepam. According to a review, most patients responded positively to melatonin 6 mg with restoration of abnormal behavior, but treatment with a combination of melatonin and clonazepam may be needed for refractory patients (McCarter et al 2013).

Disorders involving excessive motor activity during sleep, including restless legs syndrome and periodic limb movements of sleep, can be treated with commonly available medications. Dopaminergic medications, including levodopa, pramipexole, pergolide, and ropinirole, are first-line treatment for restless legs syndrome. They have been shown in a number of studies to be effective in treating symptoms of restless legs syndrome (Allen and Earley 1996; Earley and Allen 1996; Montplaisir et al 2006; Paulus and Trenkwalder 2006).

Patients with disturbances of circadian rhythm may benefit from the use of light treatment or exogenous melatonin in

an attempt to reset the intrinsic circadian clock. The combination of 5 mg of melatonin at bedtime and 1 hour of morning light exposure, but not each on its own, was found to improve daytime wakefulness and improve sleep disruption in a randomized controlled trial in patients with Alzheimer disease (Dowling et al 2008). A systematic review found improvement in agitation, sundowning, sleep quality, or daytime functioning in dementia patients with use of melatonin at night (de Jonghe et al 2010). Timed light therapy for 1 hour intervals twice daily for 2 weeks in Parkinson disease patients improved sleepiness as well as sleep quality in 1 randomized trial (Videnovic et al 2017).

Outcomes

A variety of new treatments are becoming available that can significantly improve symptoms. This is important because in this patient population (just as in others), sleep disorders can have a severe and detrimental effect on daily function, including alertness, memory, and mentation. Treatment of sleep problems themselves is often possible and can result in a significant improvement in quality of life.

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

Former authors

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ICD and OMIM codes

ICD codes

ICD-9:
Alzheimer's disease: 331.0
Parkinson's disease: 332.0
Progressive supranuclear palsy: 333.0
Multiple system atrophy: 333.0
Diffuse Lewy body disease: 333.0

ICD-10:
Alzheimer's disease: G30
Parkinson's disease: G20
Progressive supranuclear palsy: G23.1
Other degenerative disease of the nervous system, not elsewhere classified: G31.0

Profile

Age range of presentation

19-44 years
45-64 years
65+ years

Sex preponderance

male=female

Family history

family history typical
family history may be obtained

Heredity

heredity may be a factor

Population groups selectively affected

None selectively affected

Occupation groups selectively affected

None selectively affected

Differential diagnosis list

central sleep apnea
restless legs syndrome
periodic limb movement disorder of sleep
insomnia
circadian rhythm abnormalities
parasomnias
comorbid medical conditions
medication effects
psychiatric disorders
other primary neurologic disorders

Associated disorders

Shy-Drager syndrome
Olivopontocerebellar atrophy
Huntington disease
Parkinsonism

Other topics to consider

Alzheimer disease
Basal ganglia: functional anatomy and neuropharmacology
Central sleep apnea
Corticobasal degeneration
Dopa-responsive dystonia
Huntington disease
Hypersomnolence
Insomnia
Multiple system atrophy
Parkinson disease
Parasomnias
Primary dystonia
Progressive supranuclear palsy
Rapid eye movement sleep behavior disorder
Sleep and medical disorders
Sleep and multiple sclerosis
Sleep disorders
Sleep disorders associated with dementia
Sleep disorders associated with parkinsonism