Neurodegenerative Disorders and Sleep

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KEYWORDS

• Parkinson disease • Alzheimer disease • Dementia • Rapid eye movement sleep behavior disorder • Sleep apnea • Insomnia • Circadian rhythm disorder • Restless legs syndrome

KEY POINTS

- Sleep disorders are common in neurodegenerative conditions.
- Certain sleep disorders are more common in specific neurodegenerative conditions. REM sleep behavior disorder is more commonly seen in Parkinson disease than in Alzheimer disease.
- Common sleep disorders that may occur in most neurodegenerative conditions include insomnia, sleep apnea, restless legs syndrome, and circadian rhythm disorders.

INTRODUCTION

Cerebral neurodegenerative disorders, such as Parkinson disease (PD) and dementia, are increasing in prevalence as the population ages. These disorders are characterized by neuronal cell loss and abnormal accumulation of protein in cells of the brain. Symptoms, such as tremor, muscle rigidity, imbalance, and impaired cognition, progressively worsen with time. Not only are there challenges in managing the primary symptoms of these conditions, but many of these patients also suffer from sleep complaints, such as insomnia or hypersomnia. Others may suffer from abnormal movements during sleep, known as rapid eye movement (REM) sleep behavior disorder (RBD). This disorder may be dangerous and disruptive to sleep, and can sometimes precede the development of other symptoms of neurodegenerative disorders by years or even decades. High rates of sleep disorders, such as insomnia, hypersomnia, sleep apnea, restless legs syndrome (RLS), and circadian rhythm disorders, in older adults with neurodegenerative disorders are likely caused by the underlying symptoms of the disease along with damage to sleep-controlling regions of the brain. It is important to recognize and properly manage these sleep disorders because treatment may improve symptoms of the neurodegenerative condition and improve quality of life.

PARKINSON DISEASE AND OTHER SYNUCLEINOPATHIES

PD is a progressive neurodegenerative condition that causes motor symptoms of bradykinesia, shuffling gait, tremor, and rigidity. It is the second most common neurodegenerative condition affecting more than 1% of the population older than 60 years of age.[1] Patients commonly present with postural instability and falls. The pathologic hallmark of PD is Lewy bodies, which are intraneuronal α-synuclein inclusions. Lewy bodies first involve lower brainstem areas before spreading next to the substantia nigra and eventually areas throughout the brain. Motor symptoms of PD typically respond well to dopamine therapy early in the course of the disease. There are a variety of nonmotor symptoms of PD, including autonomic, olfactory, and mood dysfunction, and poor sleep. Sleep disorders are seen in most patients with PD.[2] The most common sleep disorders are

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insomnia, periodic limb movement disorder, sleep-disordered breathing, and RBD. In addition to PD, other synucleinopathies (which are central nervous system degenerative conditions caused by abnormal α-synuclein accumulation) include Lewy body dementia and multiple system atrophy, which are also associated with high rates of the same sleep disorders typically seen in patients with PD.

Sleep is disrupted in PD and other synucleinopathies for numerous reasons. The motor and nonmotor symptoms described previously can lead to poor sleep at night. Many medications used for PD can have side effects of sleepiness and poor sleep. In addition, the sleep-controlling centers of the brain are also affected by the underlying neurodegenerative process in the brain. 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 as areas of involvement in some animal models of PD.[3]

Insomnia

Insomnia is defined by a complaint of repeated difficulties with initiating sleep, maintaining sleep, or waking up earlier than desired that occurs despite adequate time and opportunity for sleep. The symptoms should result in some form of daytime impairment to meet criteria for this disorder.[4] Patients suffering from synucleinopathies, such as PD, commonly complain of insomnia. Patients with PD more commonly suffer from sleep maintenance insomnia as compared with sleep-onset insomnia. One study cites sleep problems in 60% of patients with PD, with 76% complaining of poor sleep.[2] Insomnia may occur from a variety of issues (**Box 1**). The motor symptoms of PD can cause issues with muscle cramps, stiffness, and difficulties with turning or rolling in bed. Nonmotor symptoms, such as autonomic dysfunction (which can lead to frequent nocturia) or mood disorders, also contribute to sleep disruption. Many medications used for PD can cause disrupted sleep at night or sleepiness during the daytime (causing less sleepiness overnight). Sleep-controlling areas of the brain may be damaged leading to insomnia. As the PD and nervous system degeneration progresses, insomnia also worsens in incidence and severity. Underlying mood disorders and worsening motor and nonmotor PD symptoms also contribute to worse insomnia later in the course of the disease. Polysomnography in patients with PD demonstrates prolonged sleep latency and fragmented sleep with reduced slow wave sleep and REM sleep. Insomnia may often result in subjective complaints 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.

Box 1
Common causes of insomnia in Parkinson disease

- Motor symptoms (cramps, stiffness, impaired turning in bed)
- Nocturia
- Depression and/or anxiety
- Medication side effect
- Inadequate sleep hygiene
- Restless legs syndrome
- Sleep apnea
- Circadian rhythm disorders

Diagnosis and evaluation of insomnia typically involves a good history of sleep habits, bedtimes, wake times, naps, and awakenings at night. Directed questions in regards to causes or exacerbating factors of insomnia, such as RLS, medications, motor symptoms of PD, sleep apnea, and circadian rhythm disorders, should be performed. Sleep logs, diaries, and sleep trackers, such as actigraphy or wearable devices, are helpful. Polysomnography may be necessary if insomnia is thought to be secondary to sleep apnea, periodic limb movement disorder, or parasomnias.

Management of insomnia includes identifying and addressing any underlying primary sleep disorders. In addition, good sleep habits and hygiene should be encouraged. Medications and their timing should be scrutinized and possibly altered. If motor symptoms of PD are keeping the patient up at night, dopamine therapy at night may be necessary to alleviate the symptoms to help induce and maintain sleep. Short-acting carbidopa/levodopa, long-acting carbidopa/levodopa, dopamine agonists, and transdermal dopamine (ie, rotigotine patch) have shown small benefits in motor symptoms during the night in small trials.[5] Sometimes the dopamine agent itself may be causing insomnia. A decrease in dose or change in timing of the doses may improve sleep.

Primary sleep disorders, such as RLS and circadian rhythm disturbances, need to be correctly identified as a cause of insomnia in patients with PD. RLS is seen in 15% to 20% of patients with PD.[6] RLS is difficult to distinguish from other causes of leg pain in this population, such as muscle spasms and arthritis. Serum ferritin and iron