Sleep in Neurodegenerative Diseases

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KEYWORDS

• Parkinson disease • Insomnia • Excessive daytime sleepiness • Obstructive sleep apnea
• Nocturnal stridor • Restless legs syndrome • Periodic leg movements in sleep
• REM sleep behavior disorder

KEY POINTS

- Sleep disorders are common in patients with neurodegenerative diseases.
- Their origin is multifactorial.
- Insomnia, circadian changes, hypersomnia, REM sleep behavior disorder, sleep-disordered breathing, and restless legs syndrome are sleep disorders commonly found in neurodegenerative diseases.
- Some sleep disorders are red flags of some neurodegenerative diseases: stridor indicates the occurrence of multiple system atrophy; in the setting of dementia, REM sleep behavior disorder indicates dementia with Lewy bodies and not Alzheimer disease; the absence of REM sleep behavior in a patient with parkinsonism points toward Parkinson disease and not to multiple system atrophy.
- Therapy of sleep disorders should be individualized.

INTRODUCTION

Neurodegenerative diseases are characterized by neuronal loss in the nervous system and abnormal deposition of proteins (eg, phosphorylated α-synuclein, tau, β-amyloid, ataxins) in surviving cells. Common neurodegenerative diseases are Alzheimer disease, Parkinson disease (PD), dementia with Lewy bodies, multiple system atrophy, spinocerebellar ataxias, progressive supranuclear palsy, Huntington disease, and amyotrophic lateral sclerosis. Some diseases are idiopathic and sporadic (dementia with Lewy bodies, multiple system atrophy, progressive supranuclear palsy) and others are hereditary carrying genetic abnormalities (spinocerebellar ataxias, Huntington disease). In some diseases, the idiopathic presentation is the most common but genetic forms have also been reported (Alzheimer disease, PD, amyotrophic lateral sclerosis).

The origin of most of the neurodegenerative diseases is uncertain. They are manifested by an insidious onset and a progressive course of a variety of disabling neurologic symptoms and signs, such as dementia, parkinsonism (tremor, bradykinesia, rigidity, postural and gait imbalance), motor weakness, ataxia, cerebellar syndrome, dysautonomia, oculomotor abnormalities, bulbar symptoms, and chorea. In addition, sleep disorders are common, may be the first manifestation of the disease, and may impact on the quality of life. Sleep disorders occurring in neurodegenerative diseases are insomnia (difficulty in falling sleep, sleep fragmentation, early morning awakening), excessive daytime sleepiness (EDS), circadian rhythm changes, rapid eye movement (REM) sleep behavior disorder (RBD), periodic leg movements in sleep (PLMS), restless legs syndrome (RLS), central or obstructive sleep apnea (OSA), and nocturnal stridor. Some of these sleep

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disorders may occur during the prodromal stage of the disease, years before the emergence of the cardinal symptoms that define the diagnosis of the disease. This finding indicates that identification of such individuals will be of great interest when neuroprotective agents become available. Awareness of sleep disorders by neurologists and sleep specialists is important because correct counseling, management, and therapy may improve patients' quality of life. This article reviews the sleep disorders occurring in PD, as a prototypical disorder of the neurodegenerative diseases, because most of the sleep disturbances are present. Sleep disorders occurring in other neurodegenerative diseases are summarized in **Boxes 1–7**.

PARKINSON DISEASE

PD is clinically characterized by parkinsonism caused by neurodegeneration of the substantia nigra. Surviving neurons show cytoplasmatic inclusions, called Lewy bodies and Lewy neurites, where abnormal deposits of α-synuclein are the

Box 1
Sleep disorders in Alzheimer disease

- Alzheimer disease (AD) is the most common neurodegenerative disease and is characterized by neuronal loss and deposition of β-amyloid and neurofibrillary tangles in the hippocampus and cortex resulting in cognitive impairment.
- It is under debate if reduced sleep duration and OSA in the general population are risk factors for AD. The APOE-4 allele is a risk factor for AD and OSA.
- The link between AD and sleep disorders is bidirectional. Although degeneration of the suprachiasmatic and cholinergic nuclei by the disease produce severe sleep loss and disruption, these abnormalities may have a negative effect in cognition, perhaps by decreasing β-amyloid clearance in the brain.
- Sleep disorders are common, affecting up to 45% of patients having an important impact on patients and caregivers.
- Sleep disorders may be an early manifestation but their frequency and intensity usually progress with disease severity.
- The most common sleep problem is an exaggerated tendency to phase advancing characterized by frequent daytime napping, difficulties in falling asleep at night, nocturnal sleep fragmentation, and early morning awakening. This pattern is similar but more severe than that seen in the elderly and may be related, in part, to degeneration of the suprachiasmatic nucleus resulting in alterations in melatonin secretion rhythm.
- In extreme cases, patients present the sundowing syndrome, which is characterized by agitation, confusion, and aggressiveness in the dark hours of the evening and in the night.
- In the middle of the night patients may experience confusional awakenings with nocturnal wandering and agitation.
- Polysomnography shows reduced total sleep time and sleep efficiency, increased sleep-onset latency and wake time after sleep onset, reduced deep sleep and REM sleep amounts, and increased light sleep amount. In advanced cases sleep scoring is difficult because of the absence of alpha rhythm during wakefulness and loss of sleep spindles and K complexes.
- RBD is very rare.
- RLS seems to be not prominent, although its frequency may be underestimated because diagnosis requires patients describing their sensations in the legs. Specific RLS criteria for dementia have been developed.
- The frequency of OSA is high affecting between 40% and 70% and may aggravate cognitive dysfunction in AD.
- Management of sleep disorders is based in cognitive-behavioral strategies, sleep hygiene, and bright light therapy. In early stages acetylcholinesterase inhibitors may ameliorate the sleep pattern and cognition. Continuous airway pressure therapy is indicated in OSA. Although robust scientific evidence is lacking, several medications are commonly used to enhance sleep, such as melatonin, benzodiazepines, sedating antidepressants, and atypical neuroleptics (eg, quetiapine).

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