Hypersomnia in Neurodegenerative Diseases

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KEYWORDS

• Hypersomnia • Hypersomnolence • Excessive daytime sleepiness • Neurodegenerative diseases • Alzheimer disease • Parkinson disease • Multiple system atrophy • Progressive supranuclear palsy

KEY POINTS

- Hypersomnia is a common complaint in many patients with neurodegenerative diseases and is usually multifactorial in cause.
- Circadian rhythm disorder, or non-24-hour syndrome, is a common cause of hypersomnia in patients with Alzheimer disease.
- Dopaminergic therapy is an important factor associated with hypersomnia in Parkinson disease.
- Although sleep-disordered breathing has not been demonstrated to be more prevalent in patients with neurodegenerative disorders, it contributes to hypersomnia when present.
- Other primary sleep disorders (eg, restless legs syndrome, periodic limb movements in sleep, rapid eye movement [REM]–sleep behavior disorder), disrupted sleep architecture, and depletion of orexin neurons are common in many neurodegenerative diseases, but the extent of their contribution to hypersomnia remains unclear.

INTRODUCTION

The term, "neurodegenerative diseases" refers to a broad, highly heterogeneous group of disorders affecting both the central nervous system (CNS) and the peripheral nervous system, characterized by insidious, irreversible, relentlessly progressive loss of previously intact neurologic function, worsening with age. In most cases, they are sporadic and the exact cause remains unknown (although a genetic basis had been identified in a few disorders and in small subsets of others). The degenerative process usually begins before clinical symptoms develop and involves abnormal intracellular processing and deposition of proteinaceous material; in many cases, a characteristic histopathological pattern is found. **Box 1** lists some common neurodegenerative conditions seen in clinical practice. A detailed discussion of the pathophysiology, clinical findings, diagnosis, and treatment of neurodegenerative diseases is beyond the scope of this article but readers are referred to several excellent resources on the subject.[1,2]

Sleep disorders are very common in patients with neurodegenerative diseases.[3] Patients complain of both daytime hypersomnia and disturbed nocturnal sleep, the latter of which may be related to associated sleep-disordered breathing (both obstructive sleep apnea [OSA] and central sleep apnea [CSA]), sleep fragmentation caused by parasomnias, restless legs syndrome (RLS), periodic limb movements of sleep (PLMS), circadian rhythm disorders, side-effects of agents used in the treatment of the underlying condition, and factors intrinsic to the disease itself causing degeneration of putative

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Box 1
Molecular neurobiologic classification of neurodegenerative diseases

Tauopathies
- Alzheimer disease (AD)
- Progressive supranuclear palsy (PSP)[a]
- Corticobasal degeneration (CBD)
- Frontotemporal dementia (FTD)

Synucleinopathies
- PD with or without dementia
- Diffuse Lewy body disease (DLBD) with dementia[a]
- Multiple system atrophy (MSA)[a]

Polyglutamine triplet repeat disorders
- Huntington disease (HD)
- Spinocerebellar ataxia (SCA)

Hypoprogranulinopathies
- FTD with parkinsonism linked to progranulin gene on chromosome 17 (FTDP-17P)

Miscellaneous subheading
- Torsion dystonia
- Chorea-acanthocytosis
- Amyotrophic lateral sclerosis (ALS)

[a]Clinically classified as atypical parkinsonian syndromes.

From Chokroverty S. Sleep and neurodegenerative diseases. Semin Neurol 2009;29(4):447; with permission.

sleep-wake centers. Associated complaints may also include daytime fatigue, lack of concentration, impaired motor skills, morning headaches, and absence of symptom relief from additional sleep. Management of such complaints can be challenging, and unfortunately these complaints frequently get overlooked in general practice and neurology clinics. Nevertheless, they often have profound impact on quality of life of both patients and caregivers, and successful management can be very rewarding for all concerned. This article discusses the mechanisms underlying hypersomnia in patients with the more common neurodegenerative diseases, as well as currently available treatment options and recommendations.

DETERMINANTS OF WAKEFULNESS AND SLEEP

The mechanisms underlying cycling between wakefulness, nonrapid eye movement (NREM) sleep and rapid eye movement (REM) sleep are quite complex with multiple theories proposed. Although the following brief discussion is intended to serve the purpose of describing sleep dysfunction in neurodegenerative diseases, interested readers are referred to several other resources that discuss the role of various centers and neurotransmitters in sleep neurobiology in much greater detail.[4,5]

There are multiple CNS centers that control wakefulness and sleep, with several neurotransmitters involved in these pathways.[6] Variation in firing rates in the neurons in these centers results in the cycling between wakefulness, NREM sleep, and REM sleep. These centers are all discrete but highly interrelated through widespread projections that are both facilitatory and inhibitory, thereby modulating wake or sleep activity in the CNS as a whole.

Multiple independent centers are responsible for promoting the wakeful state. The ascending reticular activating system (ARAS), consisting of several groups of neurons with a diffuse, widespread presence in large sections of the brainstem (but particularly the mesencephalon) and extending into the posterior hypothalamus, mediates wakefulness through a variety of neurotransmitters, such as acetylcholine, glutamate, and monoamines like histamine, dopamine, norepinephrine, and serotonin, through projections to the thalamus and, from there, to the cortex. Wake-promoting aminergic neurons are also present in the noradrenergic locus coeruleus (LC) and serotonergic dorsal raphe nucleus (DR) of the pons (which also serve as REM-off cells; see later discussion). The tuberomammillary nucleus (TMN) of the posterior hypothalamus is the main source of brain histamine, and increases its firing rate during wakefulness, with lower firing rates during NREM sleep and the lowest during REM sleep. Orexin-A and B (also known as hypocretin-1 and 2), are secreted by the lateral and posterior hypothalamus, which have widespread, heavy projection to multiple other centers, causing excitation of TMN, LC, and DR (thereby promoting wakefulness and suppressing REM sleep), and inhibition of the ventrolateral preoptic (VLPO) and median preoptic (MnPO) nuclei of the anterior hypothalamus (thereby suppressing NREM sleep). The cholinergic basal forebrain increases its firing rate during wakefulness and REM sleep, and decreases its firing rate in NREM sleep.

NREM sleep, in turn, is promoted by centers such as the VLPO and MnPO nuclei, which secrete the inhibitory neurotransmitters, γ-aminobutyric acid (GABA), and galanin. These in turn have reciprocal projections to multiple other centers, including inhibitory pathways to the wake-promoting