Journal of Huntington's Disease 12 (2023) 163–165
DOI 10.3233/JHD-230573
IOS Press

Perspective

To Sleep to Dream . . . No More? The Quest for Restorative Sleep in Huntington's Disease, a Clinician's Perspective

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Accepted 6 June 2023
Pre-press 23 June 2023
Published 28 July 2023

Abstract. Sleep disorders are common in Huntington's disease (HD) but are complex; their bi-directional associations with psychiatric, cognitive, and motor dysfunction makes them especially important to both consider and to treat. The author provides a perspective in brief regarding sleep disturbances in HD, based on her experience caring for, and learning from, patients with HD for more than twenty years.

Keywords: Huntington's disease, sleep disorders, medical co-morbidities, psychiatric symptoms in HD

Restorative sleep plays a critical role in cognitive processing, emotional regulation, and general sense of well-being and it is not unexpected that altered sleep architecture can affect normal functioning. Alterations in sleep also appear to play important pathophysiological roles in not only exacerbating clinical symptoms in neurodegenerative disorders, but in contributing to pathophysiological mechanisms that promote degeneration. For example, gamma waves have been found to be critical to the clearance of amyloid plaques, and their absence has been implicated in Alzheimer's disease. Sleep disorders are common in Parkinson's disease, including rapid eye movement sleep behavior disturbance, and are often present prior to motor symptoms in Parkinsonian disorders, and are thought associated with the alpha synucleinopathy.

While sleep disorders, including alterations in circadian rhythms, have been recognized in Huntington's disease (HD), relatively little attention has been paid to this important issue. In our experience, as many as 80% of our patients report some type of sleep disorder or other at some point over the course of their illness. In some patients it becomes an issue of great distress and contributes to psychiatric and cognitive symptoms; in some cases, motor symptoms also appear worsened. On the other hand, cognitive, psychiatric, and motor disturbances can, either independently or in concert contribute to disruptions in sleep and so the cycle is complex and often difficult to tease apart.

Psychiatric symptoms in HD are complex and include anxiety, depression, irritability, perseveration, somatization, possibly even psychosis. Anxiety about sleep ironically often contributes to insomnia; anxiety more generally can be an issue. Depression is well known to interfere with sleep and can cause symptoms as varied as insomnia, difficulty maintaining sleep, with early arousals, or even excessive sleep. Poor sleep can in turn precede or exacerbate depression. Perseveration or obsessive thoughts are also common in HD and can interfere with sleep;

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some patients report experiencing an inability to quiet the mind, replaying vivid and frightening thoughts, images they might have seen or television or just worrying about seemingly minor things. Apathy and irritability in HD can also be made worse when sleep is disrupted, likely due to excessive daytime somnolence or fatigue and can exacerbate depression and create tensions in the home. Some of our patients have expressed suicidal ideation when efforts to improve sleep are not successful.

A careful history may often provide information about the sleep disorder. In some cases, conservative, simple behavioral modification strategies to improve sleep hygiene are all that are required. During the day, getting just 20 minutes of exercise or going outside to get 30 minutes of natural light early in the day can make a huge impact. At night, turning off all electrical devices, avoiding watching violent television shows (or in some cases just not listening to news), limiting caffeine or alcohol intake, or even making the room and bed as comfortable as possible can impact quality of sleep. Sometimes, making time to quiet our brains, such as listening to quiet music or meditating can be helpful. Some people will describe a heightened sense of hearing (hyperacusis); in these cases, using white or brown noise or noise canceling headphones may be all that is needed. Some people will report that they don't sleep at all even though caregivers may disagree; this might reflect poor quality sleep or may be related to perseverative concerns about not sleeping. Worrying about not sleeping only makes things worse.

When conservative strategies fail, medications may be tried, including low dose anxiolytics, antidepressants, or neuroleptics; however, some medications may actually exacerbate the sleep disorder including anti-depressants, mood stabilizing agents, or VMAT 2 inhibitors which are often used to treat chorea. In our experience, nonbenzodiazepine or sedative hypnotic drugs can be problematic (one patient developed a nocturnal sleep disorder and fell down the stairs one evening, fracturing a vertebral vertebra, an event for which she had little recollection) and provide limited benefit. Often, neuroleptics are used and can be effective, but they can actually impair cognitive performance and worsen apathy, so care should be taken when using these agents. Orexin antagonists have recently come to market and might provide benefit to patients.

In some cases, it may be difficult to tease out what is cause and what is effect and polysomnography may be helpful. Surprisingly, apnea has generally not been reported in the literature, although we have encountered patients who have been diagnosed with apnea, either obstructive or central. In the case of the former, bedside companions only occasionally report excessive snoring, periods of apnea or fitful sleep; excessive daytime somnolence is rarely reported and may be unappreciated or perceived as apathy, which is very common in HD. Central apnea, or central hypoventilation, might suggest alterations in the brainstem respiratory centers, including alterations in cerebral blood flow, which we have reported previously in cortical areas [1], but which may also be present in the brainstem. Patients often benefit from the use of continuous positive airway pressure, adaptive servo-ventilation, or bilevel positive airway pressure, which may make people feel not only more awake and energetic as but more cognitively present. Medications, such as acetazolamide, have been reported as potentially helpful for central sleep apnea, but have not been used by this clinician. Tranvenous phrenic nerve stimulation is a newer therapy that is being tested; however, some patients have developed worsening dysphagia or uncomfortable electrical sensations, so this procedure should be considered only as a last resort, at least for the moment. Although classical thought is that chorea is absent during sleep, periodic limb movements or restless legs syndrome (RLS) can be seen and, although perhaps counterintuitive, traditional treatments for RLS can often be beneficial.

Medical co-morbidities can also contribute to sleep disturbances and should be considered. Urinary symptoms including incontinence, frequency, urgency, or nocturia becomes more problematic in more advanced patients and can result in interruptions in sleep. In some cases, avoiding drinking too late in the evening can be of help; in other cases, medications to treat the underlying cause (frequency, urgency, or incontinence) should be considered. Gastroesophageal reflux is common in HD can also result in nocturnal arousals; this can be treated using anti-acids or proton pump inhibitors, for example, and using conservative maneuvers such as elevating the head of the bed and avoiding eating too close to bedtime. Thermoregulatory dysfunction, possibly due to nocturnal hypoglycemia or mitochondrial dysfunction, has received little attention in HD but can cause nocturnal hyperhidrosis, which is uncomfortable and can result in frequent nocturnal arousals. Peri- and post-menopausal symptoms can wreak havoc on sleep in women; in these situations, hormone therapy can provide some benefit. Melatonin

or melatonin receptor agonists, which can normalize circadian rhythm abnormalities, could be considered and are often helpful.

In short, sleep disturbances in HD are complex but undoubtedly contribute to cognitive, psychiatric, and motor symptoms and are more than likely to exacerbate the neurodegenerative process. Much remains to be elucidated regarding the precise mechanism(s) responsible but understanding them is crucial in order to develop effective treatments for patients. Future research is needed to evaluate the potential contribution of brainstem, hypothalamic and basal forebrain structures, which might affect not only sleep, but which may also contribute to neurocardiac and respiratory abnormalities. For, to sleep, to dream, to rest, is to repair...

FUNDING

This work was support by the National Institutes of Health (Grant numbers NS114562 and NS106384).

CONFLICT OF INTEREST

The author has no conflicts of interest to report.

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