We need to consider the impact of sleep dysfunction on Huntington's disease patients, experts say

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A good night's sleep is essential for everyone. In individuals with Huntington's disease (HD), sleep disturbances constitute an additional

burden that may exacerbate disease outcomes and impact patients' quality of life. In a special issue of the *Journal of Huntington's Disease* , researchers review what is, and perhaps more importantly, what is not known about sleep and circadian rhythms in HD.

Disrupted sleep can alter metabolism and increases vulnerability to infection. Many of us have experienced the increased irritability, sluggish thinking, and physical exhaustion that comes with a poor night's sleep. We take for granted that we will recover from such disruptions, and that they will leave no lasting effect.

In fact, the reversibility of the deleterious effects of short-term disturbances of both sleep and circadian rhythms in healthy individuals is a testament to the robust pathways and homeostatic mechanisms that underpin the survival of our species. There is emerging awareness that both sleep and circadian rhythms abnormalities are associated with neurodegenerative diseases.

Guest Editor of this special issue Jenny Morton, Ph.D., ScD, professor of neurobiology, University of Cambridge, says, "Good quality sleep and healthy diurnal rhythms are fundamental to human health and wellness, although for the most part we greatly underappreciate the role they play in our lives. It is only when they become disordered that we pay attention.

"The critical question for the HD field is whether or not chronically disturbed sleep and/or circadian rhythms, that are so detrimental to the neurologically normal population, have a greater impact on people whose brains are rendered vulnerable by HD. We do not know the answer to this question, and it is time that we found out."

It remains unknown if sleep disorders precede pathogenesis (and thus represent a risk factor for the disease) or whether they only appear as a

debilitating symptom of the pathophysiological alterations. Either way, the contributing authors to this special issue make the case that sleep disturbances constitute an additional burden in patients with HD that will probably exacerbate disease outcomes.

Prof. Morton says, "It is clear from the articles in this special Issue that sleep and circadian dysfunction in HD patients is an understudied, indeed neglected, field. Yet a lack of study is not the only issue. The lack of recognition of the problem is as great a barrier to progress.

"Sleep dysfunction in normal people is taken seriously, and it is recognized that it exacerbates a range of cognitive symptoms, including deficits in executive function, memory consolidation, attention, and processing speed, as well as affective features such as impulsivity and emotional liability. Notably, most if not all these symptoms are present in HD at some stage in the course of the disease, yet the impact of sleep dysfunction on HD patient symptoms is rarely considered."

There is growing evidence from both clinical and animal model studies that sleep changes occur early in the clinical course of the disease. Difficulties with sleep initiation and maintenance that lead not only to decreased sleep efficiency, but also to progressive deterioration of normal sleep architecture are recognized as symptoms of HD.

In "Sleep Disorders and Circadian Disruption in Huntington's Disease," Sandra Saade-Lemus, MD, and Aleksandar Videnovic, MD, both of the Department of Neurology, Massachusetts General Hospital, Harvard Medical School, point out that despite evidence of sleep and circadian abnormalities, sleep alterations are underreported by patients and underrecognized by health professionals. This may explain why available investigations of sleep in HD patients are sparse, with small cohorts, and varying methodologies.

"Treatment of sleep and circadian disturbances in HD represents a big unmet need in HD. Well-designed intervention studies aimed at the treatment of poor sleep associated with HD are very much needed. Noninvasive and low cost circadian-based therapies such as light therapy may be promising for the management of sleep-wake disturbances in HD," concludes Dr. Videnovic.

HD is an autosomal-dominant hereditary neurodegenerative condition, characterized by a triad of motor, cognitive, and psychiatric features resulting from a polyglutamine expansion mutation in exon 1 of the huntingtin gene. Because there is currently no treatment that slows or halts the progression of the disease, contemporary treatment approaches address symptoms. Sleep dysfunction represents one such highly prevalent symptom. Despite this, current HD treatment approaches neither consider the impact of commonly used medications on sleep, nor directly tackle sleep dysfunction.

In the review "Sleep Dysfunction in Huntington's Disease: Impacts of Current Medications and Prospects for Treatment," Natalia Owen, MPhil student, Roger Barker, MBBS, MRCP, Ph.D., and Zanna Voysey, Ph.D., from the John van Geest Center for Brain Repair, and Wellcome Trust-MRC Cambridge Stem Cell Institute, Department of Clinical Neurology, University of Cambridge, discuss approaches to these two areas, evaluating not only literature from clinical studies in HD, but also parallel neurodegenerative conditions and preclinical models of HD.

Sleep disruption may not only exacerbate cognitive and affective symptoms, but also directly affect neurodegenerative processes by inducing neuroinflammation or impairing slow wave sleep-dependent glymphatic clearance of neurotoxic waste. If sleep deprivation is associated with an increase in neurotoxic proteins such as b-amyloid and tau, known contributors to neurodegeneration in Alzheimer's disease, it may also affect the HD brain. This is particularly relevant given the

recent links between tau and HD disease progression.

Senior author Prof. Roger A. Barker notes, "Given this feedforward relationship, addressing sleep pathology in HD potentially offers a treatment approach that not only could alleviate motor, cognitive, and psychiatric symptoms, but may also modify disease progression. Consistent with this, sleep interventions in preclinical models of HD have enhanced both behavioral and survival outcomes."

"The role of sleep and circadian disorders is an underappreciated but critically important aspect of HD. This special issue addresses gaps in our knowledge and expands our current understanding of how sleep dysfunction impacts individuals with HD," says JHD co-Editor-in-Chief Leslie M. Thompson, Ph.D., University of California, Irvine.

More information: Sandra Saade-Lemus et al, Sleep Disorders and Circadian Disruption in Huntington's Disease, *Journal of Huntington's Disease* (2023). DOI: 10.3233/JHD-230576

Natalia E. Owen et al, Sleep Dysfunction in Huntington's Disease: Impacts of Current Medications and Prospects for Treatment, *Journal of Huntington's Disease* (2023). DOI: 10.3233/JHD-230567

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