Short Communication

Associations between Sleep Quality and Serum Levels of Neurofilament Light in Individuals with Premanifest Huntington Disease

Mitchell Turner[1,2] Danielle Bartlett[2] Govinda Poudel[3] Pauline Zaenker[1,2] Simon Laws[1,2] Johnny Lo[4] Mel Ziman[2] Travis Cruickshank[1,2,5]

[1] Centre for Precision Health, Edith Cowan University, Perth, WA, Australia
[2] School of Medical and Health Sciences, Edith Cowan University, Perth, WA, Australia
[3] Mary Mackillop Institute for Health Research, Australian Catholic University, Melbourne, VIC, Australia
[4] School of Science, Edith Cowan University, Perth, WA, Australia
[5] Perron Institute for Neurological and Translational Sciences, Perth, WA, Australia

Address for correspondence Mitchell Turner, Centre for Precision Health, Edith Cowan University, Perth, WA 6027, Australia (email: mitchel.turner@ecu.edu.au).

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Abstract

Objectives To evaluate the associations between sleep quality and serum levels of neurofilament light (NfL) protein in individuals with premanifest Huntington disease (HD).

Materials and Methods We recruited 28 individuals with premanifest HD from a pre-existing database (of the Huntington's Environmental Research Optimisation Scheme, HEROs). The participants filled out the Pittsburgh Sleep Quality Index (PSQI), a subjective measure of sleep quality, and blood was collected via routine venepuncture to measure peripheral NfL levels.

Results The PSQI scores (median: 5.0; interquartile range: 4.0–7.5) indicated poor sleep quality. General linear modelling revealed no significant ($p = 0.242$) association between PSQI scores and NfL levels. No significant differences were found between individuals with good and poor sleep quality for any demographic variable collected.

Discussion Contrary to studies on other neurological conditions, there was no association between sleep quality and NfL levels in individuals with premanifest HD. This was unexpected, given the influence of environmental factors (such as social network size) on neurodegeneration in individuals with premanifest HD.

Keywords
- sleep quality
- Huntington disease
- neurofilament proteins

Introduction

Poor sleep quality is a common and debilitating aspect of Huntington disease (HD). A survey of the HD community in the United Kingdom[1] revealed that up to 90% of individuals experience poor sleep. Evidence suggests that sleep difficulties arise prior to a formal diagnosis and persist over the course of the disease,[2–6] which may exacerbate cognitive, motor, and mood disturbances. The extent to which poor

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sleep impacts neurodegeneration in HD has been poorly explored to date.[7]

Poor sleep quality has been linked to worse neurological outcomes in individuals presenting with sleep disorders and other neurodegenerative conditions.[8–10] Neurofilament light (NfL) proteins are one of three neurofilament chains that contribute to the structure of neurons in the central nervous system.[10] Therefore, NfL is released into the cerebrospinal fluid and eventually the blood when neurons are damaged or die.[10] Elevated levels of serum NfL have been detected in individuals with chronic insomnia disorder.[10] In addition, higher NfL levels in the cerebrospinal fluid have been observed in individuals with mild to moderate Alzheimer disease with reduced sleep depth.[8] Poor sleep quality has also been associated with higher plasma NfL levels in individuals with mild traumatic brain injury.[9] Given these findings, there is a need to explore the associations between sleep quality outcomes and markers of neurodegeneration in individuals with HD.

To date, one study has explored associations between sleep and neuropathology in HD: Baker et al.[7] noted greater thalamic atrophy in individuals with poor sleep, indicating that poor sleep may hasten neurodegeneration in HD. While an important finding, this study[7] did not use a validated questionnaire to examine sleep, rather a sleep item from the Becks Depression Inventory, limiting the validity of the findings and emphasizing the need for additional studies.

The purpose of the present study was to evaluate the associations between sleep quality and serum NfL levels in individuals with HD. We hypothesized that poor sleep quality would be associated with elevated NfL levels in individuals with premanifest HD.

Materials and Methods

Study Approval, Registration, and Patient Consent

All research procedures were undertaken according to the Declaration of Helsinki. Approval was granted by the Human Research Ethics Committee at Edith Cowan University (13145). All participants provided written and informed consent prior to undertaking any assessment procedures.

Participants

In the present study, 28 individuals with premanifest HD were recruited from preexisting study databases. The inclusion criteria were cytosine-adenine-guanine (CAG) repeat length > 39 and a diagnostic confidence score ≤ 2. Individuals were excluded from the study if they had a clinically-diagnosed concomitant neurological, neuromuscular, respiratory, cardiovascular, and/or sleep disorder, and if they could not provide written and informed consent.

Sleep Quality

Sleep quality was assessed through the Pittsburgh Sleep Quality Index (PSQI), which is a widely used measure with proven validity in HD populations.[11,12] It comprises 19 items with 7 component scores: sleep quality, sleep efficiency, use of sleep medication, daytime dysfunction, sleep latency, sleep duration, and sleep disturbance. The component scores range from 0 to 3 and are summed to generate a global score which ranges from 0 to 21. Scores ≥ 5 indicate poor sleep quality.

NfL Measurement

Consistent with previous work,[13] blood was collected via routine venepuncture into 8-mL serum separator tubes (SSTs; Greiner Bio-one, Frickenhausen, Germany). The SSTs were centrifuged at $1{,}600 \times g$ for 10 minutes, with serum collected and stored as 500-µL aliquots within a -80°C freezer. The samples were shipped to Quanterix (Billerica, MA,United States) for an analysis of NfL concentrations (pg/mL) using the single molecule array (Simoa, Quanterix) HD-1 Accelerator program; they were analyzed in duplicate, and the intra-assay coefficient of variations was $< 10\%$.

Statistical Analysis

The influence of sleep quality on NfL was assessed using general linear modelling. All models included age and sex as covariates. False discovery rate corrections were applied to account for multiple comparisons and mitigate false-positive results. Chi-Squared tests, independent *t*-tests and Mann-Whitney U tests were conducted to identify differences in demographic variables between good (PSQI < 5) and poor (PSQI ≥ 5) sleep quality groups. The analysis was conducted using the R Studio software package, version 1.1 (R Foundation for Statistical Computing, Vienna, Austria, 2020).

Results

The demographic data of the 28 individuals with premanifest HD, separated into those with good and poor sleep quality, are presented in ►**Table 1**. Overall, the median and interquartile range of the PSQI scores were of 5.0 (4.0–7.5). Very few participants consumed alcohol or took medication in either group. No significant differences were observed between the two groups for any of the demographic variables; no significant ($p = 0.242$) relationship was found between PSQI scores and NfL levels (►**Fig. 1**). Additionally, sex ($p = 0.331$) and age ($p = 0.130$) did not significantly influence NfL levels of individuals with premanifest HD. There was no significant ($p = 0.981$) difference in the NfL levels of the patients in the two study groups (►**Fig. 2**).

Discussion

Emerging evidence indicates that sleep disturbances exacerbate neuropathological changes in individuals living with neurological conditions, including HD.[7] However, the extent to which reduced sleep quality is associated with biological markers of neurological damage, particularly serum NfL, has not been investigated to date.[7] In the present study, we have explored, for the first time, associations between sleep quality and serum NfL levels in people living with premanifest HD. In contrast to previous findings in other neurological conditions and our expectations, we found no associations between sleep quality and NfL levels.

Table 1 Demographics of the participants

Variable	Category	Good sleep quality	Poor sleep quality	*p*-value
Sex: n (%)	Female	7 (58.3)	11 (68.8)	0.836[a]
	Male	5 (41.7)	5 (31.2)	
Alcohol consumption: n (%)	No	9 (75)	11 (68.8)	0.160[a]
	Yes	1 (8.3)	1 (6.2)	
Use ofedication: n (%)	No	8 (66.7)	10 (62.5)	0.843[a]
	Yes	2 (16.7)	3 (18.8)	
Age: mean ± SD		47.3(±12.4)	43.2(±11.4)	0.373[b]
CAG: median (IQR)		42.5 (40–44)	43 (40.8–44)	0.524[c]
Age at onset: mean ± SD		57.9(±12.2)	55.0(±11.5)	0.526[b]
Years to onset: median (IQR)		10.3 (8.7–11.5)	9.5 (5.9–16.3)	0.963[c]
CAG repeats: median (IQR)		42.5 (40–44)	43 (40.8–44)	0.524[c]
DCL: median (IQR)		0 (0–1)	0 (0–0.2)	0.661[c]
UHDRS-TMS: median (IQR)		1 (0–7.5)	0 (0–3)	0.568[c]
CAPs: mean ± SD		0.9(±0.2)	0.9(±0.2)	0.870[b]
NfL: median (IQR)		12.4 (9.6– 22.9)	13.6 (7.9– 18.9)	0.981[c]

Abbreviations: CAG, cytosine, adenine, and guanine; CAPs, CAG age product score; DCL, disease confidence levels; IQR, interquartile range (Q1–Q3); NfL, neurofilament light protein; SD, standard deviation; UHDRS-TMS, Unified Huntington's Disease Rating Scale – Total Motor Score. Notes: [a]Chi-squared test; [b]independent *t*-test; [c]Mann-Whitney U test.

As previously stated, in the present study, no significant difference in NfL levels was observed between individuals with good and poor sleep quality, as indicated by established PSQI cutoff values.[7] We expected associations between sleep quality and NfL levels, since previous findings have shown that lifestyle factors, such as cognitive reserve, and social network size and diversity, are associated with NfL levels in individuals with premanifest HD. These results differ from findings in other neurological disorders, such as Alzheimer disease and traumatic brain injury, which have shown that NfL levels are negatively influenced by poor sleep.[8,9] The discrepancy in findings may be attributed to the varied methods of collecting NfL (such as in the cerebrospinal fluid, plasma, or serum). However, this is unlikely, particularly given that Werner et al.[9] used the same method to collect NfL as the present study.

Similar to previous investigations,[11,12] in the present study, the median PSQI values obtained from the premanifest HD group indicated poor sleep quality. However, it is noteworthy that only 16 out of the 28 (57%) individuals assessed had poor sleep quality according to the PSQI (score ≥ 5). This is markedly lower than what has been previously reported by Goodman et al.,[1] who found that up to 90% of people living with HD experience sleep issues. The discrepancy in findings may be attributed to the fact that Goodman et al.[1] sampled individuals at all stages of the disease, with sleep disturbances more prominent in manifest HD. It is also noteworthy that Goodman et al.[1] used an unvalidated sleep survey,

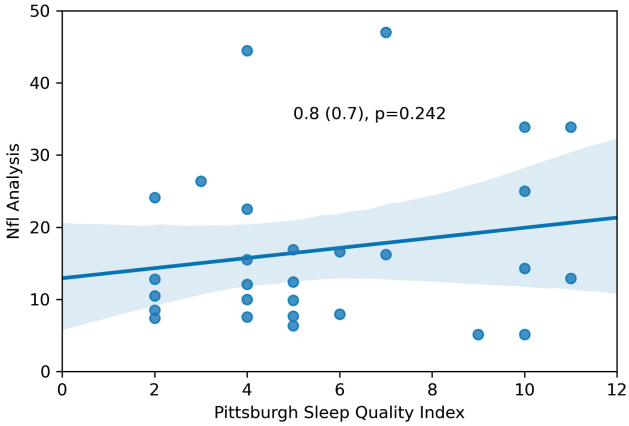

Fig. 1 Outcome of general linear modelling between PSQI scores and NfL levels (pg/mL); the slope estimate, standard error, and *p*-value are reported.

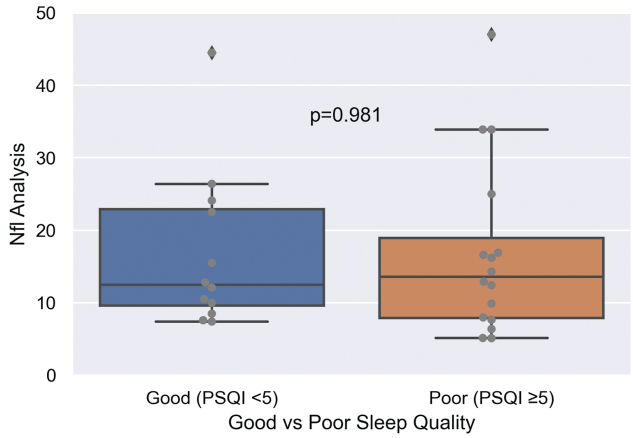

Fig. 2 Boxplots showing the distribution of NfL levels between individuals with good and poor sleep quality.

which may have overestimated sleep issues in the cohort, compared with the PSQI, which was used in the present study.

The conflicting findings between our study and previous articles in the literature may result from the fact that subjective sleep quality is not as influential in premanifest HD as CAG repeats.[7] Future studies should investigate objective sleep measures, such as polysomnography (PSG), in relation to central NfL measures. Moreover, future studies should include larger samples of individuals with premanifest HD, as neurodegeneration in this population can be influenced by several variables other than sleep, such as medication use and alcohol consumption.[14] Larger sample sizes would also enable moderation analyses on the role of the CAG expansion on associations between NfL and sleep quality.

It is important to acknowledge the limitations of the present study when analyzing the results. One significant limitation is the absence of a control group, which makes it difficult to determine whether the relationship between sleep quality and NfL levels is unique to premanifest HD. It is important to note that the present study was designed as cross-sectional and did not collect longitudinal data. Therefore, the findings only reflect the correlation between sleep quality and NfL levels at the time of testing, and it is essential to acknowledge that this relationship may vary over time.

Conclusion

While sleep quality has been explored in premanifest HD, the present is the first study to explore the association between sleep quality and neurodegeneration. Contrary to the literature on other neurological disorders, in the present study, we found no association between sleep quality and NfL levels. However, despite using different measures of sleep and neurodegeneration, the findings agree with those made by Baker et al.,[7] who reported no association between sleep problems and overall brain volume in individuals with premanifest HD. Future studies with objective sleep measures are required to determine the influence of sleep on neurodegeneration in premanifest HD.

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Conflicts of Interests
The authors have no conflict of interests to declare.

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References

1 Goodman AO, Morton AJ, Barker RA. Identifying sleep disturbances in Huntington's disease using a simple disease-focused questionnaire. PLoS Curr 2010;2:RRN1189
2 Lazar AS, Panin F, Goodman AO, et al. Sleep deficits but no metabolic deficits in premanifest Huntington's disease. Ann Neurol 2015;78(04):630–648
3 Neutel D, Tchikviladzé M, Charles P, et al. Nocturnal agitation in Huntington disease is caused by arousal-related abnormal movements rather than by rapid eye movement sleep behavior disorder. Sleep Med 2015;16(06):754–759
4 Goodman AO, Rogers L, Pilsworth S, et al. Asymptomatic sleep abnormalities are a common early feature in patients with Huntington's disease. Curr Neurol Neurosci Rep 2011;11(02):211–217
5 Piano C, Della Marca G, Losurdo A, et al. Subjective assessment of sleep in Huntington disease: reliability of sleep questionnaires compared to polysomnography. Neurodegener Dis 2017;17(06): 330–337
6 Maffi S, Scaricamazza E, Migliore S, Casella M, Ceccarelli C, Squitieri F. Sleep Quality and Related Clinical Manifestations in Huntington Disease. J Pers Med 2022;12(06):864
7 Baker CR, Domínguez D JF, Stout JC, et al. Subjective sleep problems in Huntington's disease: A pilot investigation of the relationship to brain structure, neurocognitive, and neuropsychiatric function. J Neurol Sci 2016;364:148–153
8 Targa A, Dakterzada F, Benítez I, et al. Decrease in sleep depth is associated with higher cerebrospinal fluid neurofilament light levels in patients with Alzheimer's disease. Sleep 2021;44(02): zsaa147
9 Werner JK Jr, Shahim P, Pucci JU, et al. Poor sleep correlates with biomarkers of neurodegeneration in mild traumatic brain injury patients: a CENC study. Sleep 2021;44(06):zsaa272
10 Zhang P, Tan C-W, Chen G-H, et al. Patients with chronic insomnia disorder have increased serum levels of neurofilaments, neuron-specific enolase and S100B: does organic brain damage exist? Sleep Med 2018;48:163–171
11 Tanigaki WK, Rossetti MA, Rocha NP, Stimming EF. Sleep dysfunction in Huntington's disease: perspectives from patients. J Huntingtons Dis 2020;9(04):345–352
12 Diago EB, Martínez-Horta S, Lasaosa SS, et al. Circadian rhythm, cognition, and mood disorders in Huntington's disease. J Huntingtons Dis 2018;7(02):193–198
13 Cruickshank T, Bartlett D, Govus A, et al. The relationship between lifestyle and serum neurofilament light protein in Huntington's disease. Brain Behav 2020;10(05):e01578
14 Symonds AL, Macerollo A, Foy K, Alusi SH, Davies R. Genetic and Environmental Contributors to Neurodegeneration: An Exploration of the Effects of Alcohol on Clinical Features of Huntington's Disease Using the Enroll-HD Global Platform. Int J Environ Res Public Health 2021;18(10):5113

