Hypothalamic volume loss is associated with reduced melatonin output in Parkinson's disease

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ABSTRACT

Background: Recent studies have suggested that melatonin – a hormone produced by the pineal gland under circadian control – contributes to PD-related sleep dysfunction. We hypothesised that degenerative changes to the neural structures controlling pineal function (especially the suprachiasmatic nuclei of the anterior hypothalamus) may be responsible for reduced melatonin output in these patients. Our aim was to compare hypothalamic volumes in PD patients with matched controls, and determine whether volume loss correlated with reduced melatonin output in the PD group.

Methods: 12 PD patients and 12 matched controls underwent magnetic resonance imaging to determine hypothalamic volume. In addition, PD patients underwent 24-hour blood sampling in a controlled environment to determine serum melatonin concentrations using enzyme-linked immunosorbent assays.

Results: PD patients had significantly reduced hypothalamic grey matter volume compared to matched controls. Melatonin levels were significantly associated with hypothalamic grey matter volume and disease severity in PD patients.

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INTRODUCTION

Sleep disturbances are one of the most common non-motor complaints in Parkinson's disease (PD) and have been attributed to a variety of factors. Understanding the relative contribution of each is crucial in order to identify the most effective treatment strategies for individual patients. Some of these relate to the clinically identified features of the disease such as motor impairment, nocturia, pain or neuropsychiatric symptoms. Dopaminergic and other medications may also exacerbate patients' sleep problems. However, the sleep dysfunction in PD may be due to neuronal loss in key structures and circuits involved in regulation of the sleep-wake cycle.

Two recent studies have reported that reduced melatonin output in PD patients is associated with altered sleep architecture including reduced slow wave and REM sleep[1] and excessive daytime sleepiness.[2] Altered melatonin patterns have also been observed in Huntington's disease[3] and Alzheimer's disease[4], both of which have prominent sleep and circadian abnormalities. Since melatonin is a hormone produced by the pineal gland under circadian control, we propose that degenerative changes to the neural structures controlling pineal function (especially the suprachiasmatic nuclei (SCN) of the hypothalamus) may reduce melatonin output and contribute to certain aspects of sleep dysfunction in PD.

The aim of this study was to compare hypothalamic volumes in PD patients with matched controls, and determine whether volume loss correlated with reduced melatonin output in the PD group.

METHODS

Patients

12 PD patients were selected from a previously studied sleep cohort.[1] All patients who had also undergone magnetic resonance (MR) imaging as part of the parallel ICICLE-PD study (Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation – Parkinson's Disease) were included in the analysis, alongside 12 unrelated matched controls from the MRC-CBU healthy volunteer panel. The ICICLE-PD protocol has been published elsewhere.[5] All participants provided written consent, the study was performed according to the Declaration of Helsinki, and the protocol was approved by the local research ethics committee.

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Statistical analysis

All data were approximately normally distributed based on Shapiro-Wilk testing, therefore unpaired t-tests were used to compare clinical parameters and volumetric values between patients and controls. Pearson rank correlation testing was used to study the relationship between melatonin output and relative hypothalamic grey matter volume, as well as the relationship between melatonin output and disease severity (adjusted for LED).

RESULTS

Age, gender, duration of education and ACE-R were not significantly different between PD patients and controls (**Table 1**). PD patients had mean disease duration of 3.3 years, mean LED of 366mg, and mean UPDRS part III score of 23.9. None of the participants were taking hypnotics. The mean duration between melatonin testing and MR imaging in the PD group was 1.92 months (SD 3.42).

Compared to controls, PD patients had significantly reduced relative hypothalamic grey matter volume (2.56×10^{-7} [SD 2.78×10^{-7}] versus 2.69×10^{-7} [SD 2.07×10^{-7}]; p=0.005) (**Figure 1C**).

Having verified that there were significant differences between patients and controls in terms of hypothalamic volume, we found that melatonin levels were significantly associated with relative hypothalamic grey matter volume in the PD group (r=0.591, p=0.028) (**Figure 1D**).

Partial correlation between melatonin levels and disease severity, correcting for LED, showed a significant inverse relationship (r=-0.681, p=0.021) (**Figure 1**). There was no significant relationship between melatonin output and LED (r=0.180, p=0.76).

DISCUSSION

There is increasing evidence from clinical and animal studies that there is circadian dysregulation in a variety of neurodegenerative diseases.[7] We previously reported significant reductions in melatonin concentration in 30 early-stage PD patients.[1] Videnovic and colleagues also found a significantly diminished amplitude of melatonin secretion in serum samples of 20 PD patients on dopaminergic therapy under modified constant routine conditions.[2]

There is evidence from neuropathological[8] and imaging[9] studies that the hypothalamus is directly affected by PD. The central clock within the hypothalamus, the SCN, is likely to contribute to this volume loss since it has been shown that mice overexpressing alpha-synuclein exhibit a reduced SCN firing rate[10]. This could weaken their ability to communicate neural and hormonal signals from the central clock to the pineal gland, which secretes melatonin into the blood.

This study thus adds to the existing literature by suggesting that hypothalamic volume loss – which we have now shown in this new PD cohort – may be responsible for reduced melatonin output which has been linked to sleep disturbances in PD.

The major limitation of this study is the relatively small number of patients, which precluded the use of linear regression and adjustment of confounders. Furthermore, patients were not strictly shielded from external light during the melatonin sampling period which may have influenced the results. Although we lacked serum melatonin measurements in the control group, the critical test for our hypothesis was the correlation between hypothalamic volume and melatonin levels in PD patients. It is not yet possible to perform dedicated imaging of the SCN within the hypothalamus using 3Tesla MRI, therefore ultra-high field imaging or clinico-pathological studies will be required to allow more thorough dissection of the relative role of the different hypothalamic nuclei to this deficit.

In summary, we have shown that melatonin levels are associated with hypothalamic grey matter volume loss and disease severity in PD patients. This provides anatomical

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TABLE 1: Clinical characteristics of PD patients and controls

Variable	PD	Controls	p-value[d]
Number of participants	12	12	na
Gender ratio (male:female)	6:6	6:6	1.0
Age (years)	66.7 (5.5)	66.3 (5.2)	0.92
Duration of education (years)	18.3 (2.9)	17.2 (2.8)	0.33
ACE-R	95.2 (3.1)	96.1 (3.0)	0.48
Disease duration (years)[a]	3.3 (1.1)	na	na
LEDD (mg)[b]	366 (161)	na	na
MDS-UPDRS part III[c]	23.9 (9.0)	na	na
BDI	7.3 (17.8)	3.3 (3.6)	0.011*

Results expressed as mean (SD) unless stated otherwise

LED=Levodopa Equivalent Daily Dose, ACE-R=Addenbrooke's Cognitive Examination-Revised, MDS-UPDRS=Unified Parkinson's Disease Rating Scale, BDI=Beck Depression Inventory

[a]Disease duration from date of diagnosis; [b]All but two PD patients were taking dopaminergic medication; [c]Based on MDS-UPDRS assessments performed within the last six months; [d]Unpaired t-tests performed

FIGURE LEGEND

Panels A and B show the region of interest used to calculate hypothalamic volume for each participant. **Panel C** is a graphical representation of the significant reduction in relative hypothalamic grey matter volume in PD patients compared to matched controls (with Standard Error of the Mean error bars). **Panel D** demonstrates the significant correlation between relative hypothalamic grey matter volume and total 24-hour melatonin output (with both axes showing partial residuals). In both graphs, relative hypothalamic grey matter volume was calculated by dividing grey matter volume by whole brain volume (both measured in voxels).

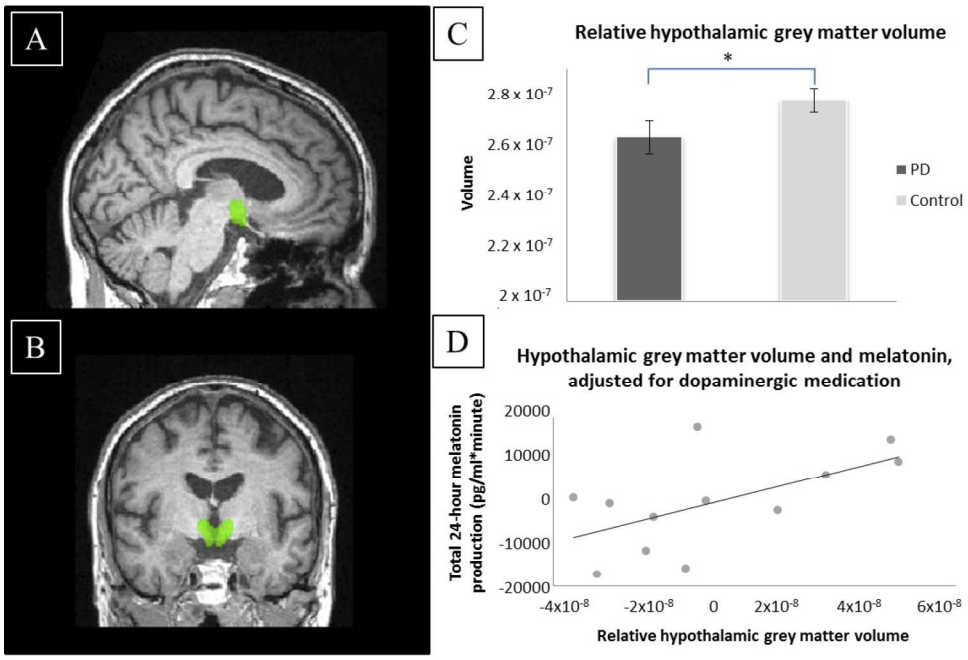

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TABLE 1: Clinical characteristics of PD patients and controls

Variable	PD	Controls	p-value[d]
Number of participants	12	12	na
Gender ratio (male:female)	6:6	6:6	1.0
Age (years)	66.7 (5.5)	66.3 (5.2)	0.92
Duration of education (years)	18.3 (2.9)	17.2 (2.8)	0.33
ACE-R	95.2 (3.1)	96.1 (3.0)	0.48
Disease duration (years)[a]	3.3 (1.1)	na	na
LEDD (mg)[b]	366 (161)	na	na
MDS-UPDRS part III[c]	23.9 (9.0)	na	na
BDI	7.3 (17.8)	3.3 (3.6)	0.011*

Results expressed as mean (SD) unless stated otherwise

LED=Levodopa Equivalent Daily Dose, ACE-R=Addenbrooke's Cognitive Examination-Revised, MDS-UPDRS=Unified Parkinson's Disease Rating Scale, BDI=Beck Depression Inventory

[a]Disease duration from date of diagnosis; [b]All but two PD patients were taking dopaminergic medication; [c]Based on MDS-UPDRS assessments performed within the last six months; [d]Unpaired t-tests performed

FIGURE LEGEND

Panels A and B show the region of interest used to calculate hypothalamic volume for each participant. **Panel C** is a graphical representation of the significant reduction in relative hypothalamic grey matter volume in PD patients compared to matched controls (with Standard Error of the Mean error bars). **Panel D** demonstrates the significant correlation between relative hypothalamic grey matter volume and total 24-hour melatonin output (with both axes showing partial residuals). In both graphs, relative hypothalamic grey matter volume was calculated by dividing grey matter volume by whole brain volume (both measured in voxels).