Sleep and Circadian Rhythm Regulation in Early Parkinson Disease

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IMPORTANCE Sleep disturbances are recognized as a common nonmotor complaint in Parkinson disease but their etiology is poorly understood.

OBJECTIVE To define the sleep and circadian phenotype of patients with early-stage Parkinson disease.

DESIGN, SETTING, AND PARTICIPANTS Initial assessment of sleep characteristics in a large population-representative incident Parkinson disease cohort (N=239) at the University of Cambridge, England, followed by further comprehensive case-control sleep assessments in a subgroup of these patients (n=30) and matched controls (n=15).

MAIN OUTCOMES AND MEASURES Sleep diagnoses and sleep architecture based on polysomnography studies, actigraphy assessment, and 24-hour analyses of serum cortisol, melatonin, and peripheral clock gene expression (*Bmal1*, *Per2*, and *Rev-Erbα*).

RESULTS Subjective sleep complaints were present in almost half of newly diagnosed patients and correlated significantly with poorer quality of life. Patients with Parkinson disease exhibited increased sleep latency ($P = .04$), reduced sleep efficiency ($P = .008$), and reduced rapid eye movement sleep ($P = .02$). In addition, there was a sustained elevation of serum cortisol levels, reduced circulating melatonin levels, and altered *Bmal1* expression in patients with Parkinson disease compared with controls.

CONCLUSIONS AND RELEVANCE Sleep dysfunction seen in early Parkinson disease may reflect a more fundamental pathology in the molecular clock underlying circadian rhythms.

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In the largest survey of nonmotor symptoms of Parkinson disease (PD), 64% of patients reported sleep problems, representing the second most common nonmotor complaint.[1] Such problems are typically attributed to motor impairment, nocturia, sleep-disordered breathing, neuropsychiatric symptoms, and medications[2] but may be an intrinsic feature of the disease itself.

Sleep is governed by the intricate interplay between sleep-wake homeostasis and circadian rhythms in the body. These rhythms are largely controlled by the suprachiasmatic nucleus (SCN) of the anterior hypothalamus and tuned to the 24-hour day by environmental cues such as light, motor activity, and food intake.[3] Clock genes form the molecular machinery of this circadian system, operating via autoregulatory feedback loops. The key loop involves the proteins BMAL1 and CLOCK, which form a heterodimer to regulate the expression of clock-controlled genes, thus driving SCN circadian output. The BMAL1/CLOCK complex also activates the expression of Pe-

riod (*Per*) and Cryptochrome (*Cry*) genes, whose products (PER and CRY) represent negative elements in the loop and inhibit the activity of BMAL1/CLOCK (and hence their own expression). In a separate stabilizing loop, the *Rev-Erbα* and retinoic orphan receptor genes fine-tune the oscillations generated by the main loop. Unlike other PER proteins, PER2 can directly interact with REV-ERBα to regulate *Bmal1* expression.[4]

The SCN transmits its circadian signal to peripheral tissues via neural and hormonal mechanisms, synchronizing circadian oscillations throughout the body.[3] Endocrine parameters, such as melatonin and cortisol profiles, can be used as surrogate markers of the central clockwork in vivo, since their rhythmic output is generated by the SCN.[5] It has also been shown that circadian clock gene expression can be readily measured in peripheral blood mononuclear cells[6] and displays significant circadian rhythmicity,[7] making it possible to study central (serum cortisol and melatonin levels) and peripheral (clock gene expression) circadian markers using human blood samples.

In this study we set out to define the sleep and circadian phenotype of patients with early-stage Parkinson disease.

Methods

We began by studying patients newly diagnosed with PD who were recruited to a community-based incidence study in Cambridgeshire, England (Parkinsonism-Incidence and Cognitive Heterogeneity in Cambridgeshire [PICNICS]). The study was approved by the Cambridgeshire Research Ethics Committee (REC 09/H0308/7) and performed according to the Declaration of Helsinki, with all participants providing written informed consent. Patients completed the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and Parkinson's Disease Questionnaire (PDQ-39) and underwent a range of other assessments (eAppendix in Supplement).

To further investigate sleep dysfunction, we carried out more comprehensive analyses on a subgroup of 30 patients with PD (16 men, 14 women) recruited consecutively from the PICNICS study, as well as 15 healthy age- and sex-matched controls (recruited via local advertising).

Sleep Questionnaires

Sleep complaints were assessed using the Parkinson's Disease Sleep Scale (PDSS), Rapid Eye Movement (REM) Sleep Behavior Disorder Questionnaire (RBDQ-HK), and ESS.

Actigraphy Assessment

Along with keeping sleep diaries, all participants wore an activity monitor (Actiwatch; Cambridge Neurotechnology) on the nondominant wrist continuously during the 14-day period prior to their polysomnography assessment.

Polysomnography

Participants were admitted for 2 consecutive nights of polysomnographic recording based on their habitual bed times (first night was an acclimatization night and not analyzed). Sleep recordings were scored visually by trained raters using the American Academy of Sleep Medicine guidelines.[8] See eAppendix in Supplement for more information on the polysomnography protocol, parameters measured, and diagnostic criteria for primary sleep diagnoses.

Circadian Rhythm Analysis

A peripheral venous cannula was inserted prior to the start of sampling at 1 PM. Over the next 24 hours, patients adhered to their habitual bed times and blood was collected through a long catheter to prevent sleep disruption. Subjects remained sedentary apart from bathroom visits. Meal times were fixed and no daytime naps were allowed. Temperature was constant at approximately 21°C. Patients were not strictly shielded from external light but lighting levels were less than 5 lux once lights were turned off.

Serum melatonin and cortisol levels were measured every 90 minutes by enzyme-linked immunosorbent assays (eAppendix in Supplement). *Bmal1*, *Per2,* and *Rev-Erb*α gene expression was reported as a relative ratio to the constitutively

expressed nonrhythmic β-*actin* gene every 3 hours by 1-step real-time quantitative reverse-transcription polymerase chain reactions (eAppendix in Supplement). All samples were analyzed in triplicate and averaged.

Statistical Analysis

Full details of the statistical analyses performed are given in eAppendix in Supplement.

Results

Clinical Characteristics

Two hundred thirty-nine patients newly diagnosed with PD were recruited to the PICNICS study (**Table 1**). One hundred ninety-two patients (80%) returned the PSQI, 170 patients (71%) returned the ESS, and 206 patients (86%) returned the PDQ-39. Age, sex, Movement Disorders Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III score, and Addenbrooke's Cognitive Examination score for those patients who did not complete the questionnaires were not significantly different compared with those who did.

Patients with PD who completed the intensive sleep assessments (mean [SD], 22.9 [9.9] months since diagnosis) were younger compared with the PICNICS cohort as a whole (unpaired *t* test, *P* = .009), more likely to be taking dopaminergic medication (χ² test, *P* < .001), and had lower MDS-UPDRS Part III (Mann-Whitney test, *P* = .006) and Hoehn and Yahr scores (χ² test, *P* < .001) (eTable 1 in Supplement). Other important clinical characteristics, including PSQI and ESS scores, were similar. No participants undergoing intensive sleep assessments fulfilled criteria for moderate or severe depression (Beck Depression Inventory score of 19 or greater). Twenty-four patients (80%) were receiving dopaminergic therapy (40%, levodopa; 30%, dopamine agonist; 20%, rasagiline; and 13%,

Table 1. Clinical, Sleep, and Quality of Life Characteristics of 239 Participants in the PICNICS Cohort

Variable	Mean (SD)
Male, %	62
Age at diagnosis, y	68 (9)
Time since diagnosis, mo	2.2 (2.9)
Receiving dopaminergic therapy, %	42ᵃ
LEDD in treated patients, mg	316 (209)
MDS-UPDRS Part III score	32 (12)
Hoehn and Yahr score	1.8 (0.8)
ACE-R score	90 (7)
Global PSQI score	6.1 (3.9)
Total PDQ-39 score	26.1 (20.4)

Abbreviations: ACE-R, Addenbrooke's Cognitive Examination; LEDD, levodopa equivalent daily dose; MDS-UPDRS, Movement Disorders Society–Unified Parkinson's Disease Rating Scale; PICNICS, Parkinsonism—Incidence and Cognitive Heterogeneity in Cambridgeshire; PSQI, Pittsburgh Sleep Quality Index; PDQ-39, Parkinson's Disease Questionnaire.

ᵃ Twenty-four percent, levodopa; 16%, dopamine agonist; 5%, amantadine, and 4%, rasagiline. Twenty-nine patients (12%) were also taking antidepressants, 10 patients (4%) were taking opiates, 7 patients (3%) were taking benzodiazepines, and 3 patients (1%) were taking zopiclone.

Table 2. Primary Sleep Diagnoses in Patients With PD vs Controls

	%		P Value	
Primary Sleep Disorder	Patients With PD (n=30)	Controls (n=15)	Univariate[a]	Multivariate[b]
RBD	27	0	.04[c]	>.99
PLMS[d]	33	33	>.99	.56
RLS	3	0	>.99	>.99
OSA[e]	17	33	.47	.33
CSA	7	0	.54	>.99
EDS[f]	30	13	.28	.40

Abbreviations: CSA, central sleep apnea; EDS, excessive daytime sleepiness; OSA, obstructive sleep apnea; PD, Parkinson disease; PLMS, periodic limb movements of sleep; RBD, rapid eye movement sleep behavior disorder; RLS, restless legs syndrome.

[a] Fisher exact test used.

[b] Logistic regression used, adjusting for age and sex (and, in the case of OSA, the effect of body mass index).

[c] Significant difference at .05 level.

[d] Periodic limb movement index greater than 15 per hour.

[e] Moderate or severe OSA (apnea-hypopnea index greater than 15 events per hour).

[f] Defined as mean sleep latency less than 8 minutes.

amantadine). Four patients (13%) were taking antidepressants and 2 patients (7%) were taking benzodiazepines.

Sleep Complaints and Quality of Life

In the incident PICNICS cohort, global PSQI scores ranged from 0 to 20, with 94 patients (49%) classified as poor sleepers (global PSQI score greater than 5). Poor sleepers were significantly more likely to have problems with nonmotor activities of daily living, low mood, apathy, and impaired cognition (eTable 2 in Supplement). Moreover, the PSQI score was found to be an independent risk factor for increased PDQ-39 score ($\beta = 0.170$, $P = .007$).

In the intensive sleep subgroup, patients with PD had lower total PDSS scores compared with controls ($\beta = -0.373$, $P = .01$), reflecting their greater subjective sleep complaints. Specifically, they scored lower on subscores relating to sleep quality ($\beta = -0.372$, $P = .01$), sleep refreshment ($\beta = -0.422$, $P = .005$), and nocturnal motor impairment ($\beta = -0.408$, $P = .007$). Using the suggested RBDQ-HK cutoff score of 19, 9 patients (30%) and 1 control (7%) reported symptoms suggestive of REM parasomnia. The ESS scores were not significantly different between the groups.

Actigraphy Assessment

Patients with PD had reduced light to dark ratio ($\beta = -0.393$, $P = .01$), as well as higher intradaily variability ($\beta = 0.355$, $P = .02$) showing that they had more fragmented motor activity during the 24-hour period compared with controls. Apart from later sleep onset time ($\beta = 0.316$, $P = .04$), there were no actigraphy differences in nocturnal motor activity between patients with PD and controls (eTable 3 in Supplement).

Primary Sleep Diagnoses

Eight patients with PD had evidence of REM sleep behavior disorder (RBD) (Table 2). Ten patients with PD had periodic limb movements of sleep (defined as a periodic limb movement index greater than 15 per hour) compared with 5 controls. Two patients with PD had central sleep apnea (CSA), while 5 patients and 5 controls had evidence of moderate or severe ob-

structive sleep apnea (OSA) (moderate = 2 and severe = 3 in both groups). In all cases, individuals had not been diagnosed with these conditions prior to the sleep study. Patients with moderate or severe OSA were more likely to have increased body mass index (unpaired t test, $P < .001$).

Changes in Sleep Architecture

On detailed polysomnography studies, patients with PD exhibited increased sleep latency ($\beta = 0.333$, $P = .04$), reduced sleep efficiency ($\beta = -0.411$, $P = .008$), increased stage 1 sleep ($\beta = 0.307$, $P = .03$), and reduced REM sleep ($\beta = -0.363$, $P = .02$) (Table 3). Two patients with PD exhibited no REM sleep whatsoever. These aspects of the sleep architecture were similarly affected in patients with and without OSA (eTable 4 in Supplement).

In patients with PD, there was no significant correlation between sleep efficiency and total PDSS score (Pearson correlation, $r = 0.156$, $P = .42$). The RBDQ-HK was poor at correctly identifying patients with polysomnography-confirmed RBD (positive predictive value, 33%), but significantly better at correctly excluding the condition (negative predictive value, 76%).

To investigate the effect of dopaminergic medications on sleep architecture, patients with PD were divided into subgroups according to whether they were taking levodopa, dopamine agonists, or neither. Accepting the small subgroup sizes, differences between groups were not statistically significant (eTable 5 in Supplement).

Excessive Daytime Sleepiness

Patients with PD had a tendency towards hypersomnolence compared with controls, considering both mean sleep latency (MSL) ($\beta = -0.259$, $P = .09$) and individual nap opportunities (repeated-measures 2-way analysis of variance, $F_{1,38} = 3.985$, $P = .053$). All 4 of the patients with severe excessive daytime sleepiness (MSL less than 5 minutes) were in the PD group. No sleep-onset REM episodes were observed. There was a strong correlation between ESS score and reduced MSL (Spearman correlation, $r = -0.548$, $P = .002$). Reduced MSL was associated with dopamine agonist use (unpaired t test, $P = 0.04$).

Table 3. Polysomnography Findings in Patients With PD vs Controls

Parameter	Mean (SD)		P Value		Effect Size
	Patients With PD (n=29)[a]	Controls (n=15)	Univariate	Multivariate[b]	
Sleep, h:min					
Start	21:30 (04:11)	20:55 (05:47)	.80	.58	0.10
End	06:55 (00:29)	06:44 (00:38)	.33	.32	0.29
Total sleep time, min	407 (69)	420 (48)	.52[c]	.49	0.27
Sleep latency, min	13 (13)	6 (4)	.13	.04[d]	1.75
REM latency, min	117 (100)	77 (42)	.26	.12	0.95
Sleep efficiency, %	78 (10)	85 (7)	.006[c,d]	.008[d]	1.00
AI, arousals/h	21 (7)	24 (17)	.94	.16	0.18
PLMI, events/h	17 (29)	16 (25)	.92	.51	0.04
AHI, events/h	11 (17)	18 (22)	.09	.20	0.32
DI, events/h	8 (15)	15 (21)	.004[c,d]	.12	0.33
Minimum oxygen saturation, %	86 (4)	80 (7)	.002[c,d]	<.001[d]	0.86
MSL, min[e]	11 (5)	14 (4)	.06	.09	0.75
Time in sleep stages, %					
Awake	21 (11)	15 (7)	.08	.05	0.86
Stage 1	10 (5)	7 (3)	.01[c,d]	.03[d]	1.00
Stage 2	49 (10)	51 (10)	.46	.35	0.20
Stages 3 and 4	8 (6)	11 (6)	.23	.33	0.50
REM	12 (6)	16 (6)	.02[c,d]	.02[d]	0.67

Abbreviations: AHI, apnea-hypopnea index; AI, arousals index; DI, desaturation index; MSL, mean sleep latency; PD, Parkinson disease; PLMI, periodic limb movement index; REM, rapid eye movement.

[a] Not possible to distinguish electroencephalography wakefulness from individual sleep stages in 1 patient with PD; therefore, these data are excluded from the analysis.

[b] Linear regression used, adjusting for age and sex (and, in the case of AHI, the effect of body mass index).

[c] Unpaired t test; otherwise Mann-Whitney test used.

[d] Significant difference at .05 level.

[e] In 2 patients with PD, MSL is based on 4 rather than 5 Multiple Sleep Latency Test nap opportunities.

Reduced Melatonin Production

The time-dependent variation in melatonin concentration was statistically significant in controls ($F_{16,176} = 1.873$, $P = .03$) but not in patients with PD ($F_{16,320} = 0.738$, $P = .47$) (Figure 1A). Patients with PD had a reduced area under the curve (β = −0.341, $P = .048$) and a reduced melatonin nadir (β = −0.461, $P = .004$) (eTable 6 in Supplement). There was a significant main group effect on melatonin concentration ($F_{1,33} = 4.532$, $P = .04$). There was no change in the timing of melatonin onset or offset. Cosinor analysis confirmed a robust circadian melatonin profile in the majority of participants—only 5 patients (18%) and 1 control (7%) were arrhythmic—and there was no evidence of a melatonin phase shift in patients with PD compared with controls (Mann-Whitney test, $P = .45$).

The mean gap between sleep and circadian assessments was 5.8 months (SD, 3.6), but habitual sleep times were not significantly different between these visits (Mann-Whitney test, $P = .68$). We found that reduced slow-wave sleep was associated with reduced melatonin area under the curve in patients with PD (Spearman correlation, $r = 0.483$, $P = .02$), while reduced REM sleep was associated with reduced melatonin acrophase (Spearman correlation, $r = 0.446$, $P = .02$) and reduced melatonin area under the curve (Spearman correlation, $r = 0.479$, $P = 0.02$). Lower melatonin onset concentration was associated with increased sleep latency in patients with PD (Pearson correlation, $r = −0.323$, $P = 0.04$). Melatonin parameters were not associated with disease characteristics such as motor phenotype or treatment status (de novo vs treated patients).

Elevated Serum Cortisol Levels

The time-dependent variation in cortisol concentration was not statistically significant in either group owing to large interin-

dividual variation (Figure 1B). Patients with PD had an increased acrophase (β = 0.502, $P = .001$), increased amplitude (β = 0.485, $P = .002$), and increased area under the curve (β = 0.615, $P < .001$) (eTable 7 in Supplement). There was a significant main group effect on cortisol concentration ($F_{1,30} = 15.720$, $P < .001$). There was no change in the timing of cortisol onset or offset. Cosinor analysis revealed that 11 patients (41%) and 1 control (7%) had arrhythmic cortisol profiles, and there was no evidence of a cortisol phase shift in patients with PD compared with controls (Mann-Whitney test, $P = .36$). There was no correlation between cortisol and objective sleep measures.

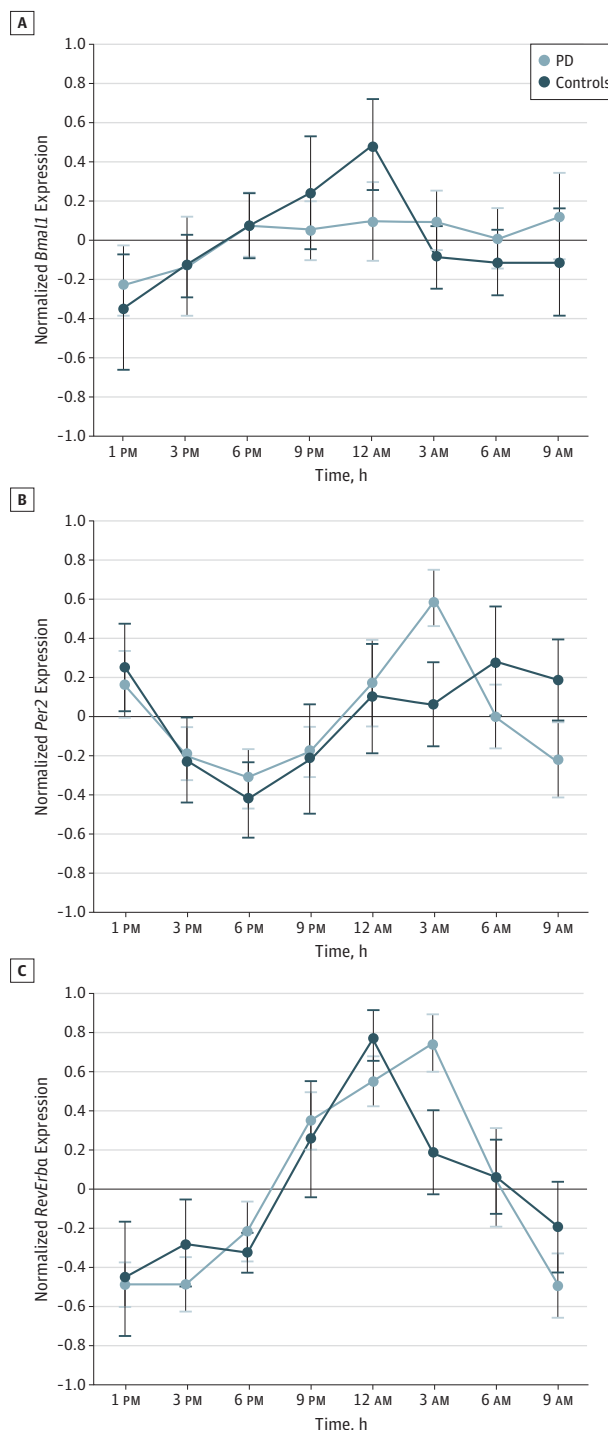## Peripheral Clock Gene Expression Differences

The main finding was a lack of time-dependent variation in *Bmal1* expression in patients ($F_{7,175} = 0.794$, $P = .59$) compared with controls ($F_{7,84} = 2.229$, $P = .04$) (Figure 2A). Neither *Per2* or *Rev-Erb*α showed statistically significant time-dependent variation in patients or controls, despite visually similar 24-hour expression profiles in both groups (Figure 2B and C). No interaction was found between group and time for any of the 3 genes studied; however, patients with PD did have increased expression of *Per2* and *Rev-Erb*α at 4 AM (unpaired t test, $P = .04$ and $P = .03$, respectively). There was no evidence of a phase shift in *Bmal1*, *Per2*, or *Rev-Erb*α on cosinor analysis (Mann-Whitney test, $P = .86$, $P = .44$, and $P = .84$, respectively). Overall, few patients showed peripheral clock gene expression profiles that were rhythmic: 2 patients (7%) and no controls (0%) for *Bmal1*, 3 patients (10%) and 3 controls (20%) for *Per2*, and 5 patients (22%) and 3 controls (20%) for *Rev-Erb*α. There were no significant differences in sleep architecture in patients with rhythmic vs nonrhythmic clock gene profiles.

Figure 1. Twenty-Four-Hour Melatonin and Cortisol Rhythms in Patients With Parkinson Disease (PD) vs Controls
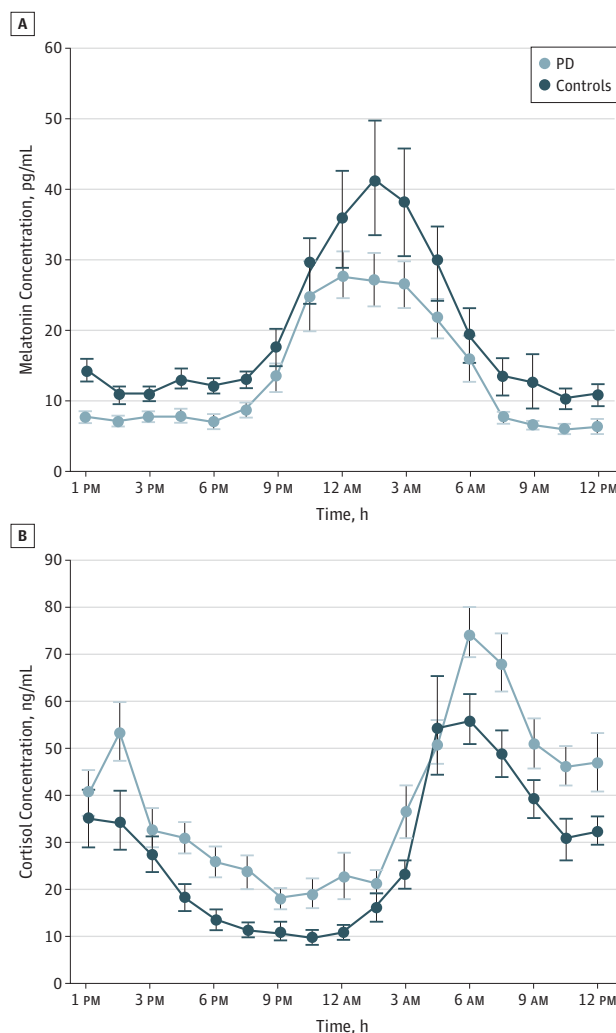
These graphs show the mean (SEM) serum melatonin and cortisol concentrations at each time point. In healthy individuals, melatonin levels typically rise in the late evening while cortisol levels peak in the early morning. A, Significant group effect on melatonin concentration on repeated-measures 2-way analysis of variance and lack of a statistically significant time-dependent variation in melatonin concentration over the 24-hour sampling period. Patients with PD also had a reduced area under the curve and a reduced melatonin nadir. There were individual missing melatonin data points in 6 patients with PD (1.1% of total data set) and 1 control (0.4% of total dataset). B, Significant group effect on cortisol concentration on repeated-measures 2-way analysis of variance. Patients with PD also had an increased acrophase, increased amplitude, and increased area under the curve. There were individual missing cortisol data points in 7 patients with PD (1.3% of total data set) and 4 controls (1.6% of total data set).

Discussion

In this study, we have confirmed that sleep complaints are common in patients newly diagnosed with PD and correlate significantly with poorer quality of life. We have found that patients with PD have an abnormal sleep macro-architecture including increased sleep latency, reduced sleep efficiency, and reduced

Figure 2. Twenty-Four-Hour Clock Gene Expression in Patients With Parkinson Disease (PD) vs Controls

These graphs show the mean (SEM) normalized gene expression levels for the 3 clock genes studied at each time point in peripheral blood mononuclear cells. We sought to investigate whether patients with PD exhibited the same peripheral clock gene expressions oscillations as one would expect in healthy individuals. Loss of the time-dependent variation in *Bmal1* was seen in patients with PD over the 24-hour period (A), together with higher expression of Per2 and RevErbα at 4 AM (B and C, respectively). There were individual missing data points in 2 patients with PD (0.8%) and no controls.

REM sleep and that this relates to alterations in relevant circulating hormone profiles. These abnormalities are also linked to differences in peripheral clock gene expression.

Almost half of our newly diagnosed PD cohort were poor sleepers according to the PSQI, a validated sleep questionnaire that has been recommended for PD research.[9] In the population-based Norwegian ParkWest study, only 17.8% of patients with early untreated PD were found to have sleep problems based on the Neuropsychiatric Inventory sleep subscore.[10] Our findings more closely resemble the frequency of sleep problems reported in prevalent cohorts.[1,11] There was discordance between subjective and objective sleep measures in our study, suggesting that other factors may influence patients' perceived sleep quality. For instance, we found that poor sleepers were more likely to exhibit low mood, apathy, and impaired cognition.

We found that 8 patients in our intensive sleep subgroup had RBD, which is not surprising since RBD can predate the typical motor features of PD by many years.[12] In line with other studies,[13] OSA was no more common in nonobese patients with PD than in the general population. Similarly, CSA was uncommon in idiopathic PD and its presence should raise the possibility of an atypical parkinsonian syndrome such as multiple system atrophy.[14] Finally, we replicated our previous findings, showing that significant excessive daytime sleepiness can be present from the earliest stages of disease and is associated with dopamine agonist use.[15]

Pooled analysis has not been undertaken on previous case-control studies investigating sleep architecture in PD owing to differences in methods and parameters measured.[16] Bušková and colleagues[17] compared 15 patients with early untreated PD vs 15 matched controls and found that patients with PD had a tendency for reduced sleep efficiency, increased wakefulness, and reduced REM sleep. Yong and colleagues[18] reported similar findings in their prevalent cohort and Diederich and colleagues[19] concluded that there was a progressive destructuring of the sleep architecture in patients with more advanced PD.

We hypothesized that the sleep-wake disturbances in early PD might reflect a disruption to the neural circuitry controlling circadian rhythms. Decline in SCN activity is already believed to be responsible for reduced melatonin output and sleep-wake disruption in older healthy adults.[20,21] There is evidence from neuropathological[22] and imaging[23] studies that the hypothalamus is affected in PD. Moreover, it has been shown that mice overexpressing α-synuclein exhibit a reduced SCN firing rate, potentially weakening their ability to communicate neural and hormonal signals from the central clock.[24]

We sought to investigate this further using hormone and clock gene assays. We found a sustained elevation of serum cortisol levels in patients with PD, in line with previous research reporting basal hypercortisolemia in PD.[25] We also found that patients with PD had reduced circulating melatonin levels compared with elderly controls, similar to a previous study.[26] Although Fertl and colleagues[27] found no differences in melatonin output in 9 patients with de novo PD compared with controls, they did report that patients with PD with a nontremor-dominant phenotype (who may have more ex-

tensive pathology) had lower melatonin levels. Differences in melatonin output significantly correlated with reduced slow-wave and REM sleep in our study, which fits well with trials showing that exogenous melatonin administration increases both sleep propensity and REM sleep continuity in patients with PD.[28,29]

To our knowledge, only 1 previous study has analyzed peripheral clock gene expression in patients with PD. Cai and colleagues[30] quantified *Per1* and *Bmal1* expression in leucocytes of 17 patients with PD and 16 controls at 4 overnight time points. Similar to our findings, they discovered reduced *Bmal1* expression compared with controls (but only in drug-naive patients). One possible explanation for altered *Bmal1* expression in PD is that dopamine is capable of regulating BMAL1/CLOCK heterodimer activity,[31] meaning that dopamine deficiency might directly affect this central component of the molecular clock. Alternatively, damage to the SCN itself could be responsible for clock gene dysregulation. However, the precise nature and extent of circadian rhythm disruption in PD needs to be investigated further because sleep may be crucial in the clearance of degradation products of neural activity that accumulate during wakefulness,[32] and circadian disruption may accelerate PD-related pathology.[33]

One of the main strengths of this study is the recruitment of a community-based incident cohort of newly diagnosed PD cases. This is the first study, to our knowledge, to analyze patients and controls alongside 24-hour hormone and clock gene rhythms to try and understand the circadian correlates of sleep dysfunction in PD. We assessed sleep phenotype in a variety of different ways to probe different aspects of the PD sleep phenotype.

The major limitation of our study is the fact that the number of participants undergoing comprehensive sleep assessment was relatively small. Ideally, we would have liked to study all patients over time but this was not practical since many patients were unwilling to undertake intensive studies of this nature. It also was not possible to include only unmedicated patients in an epidemiological study of this type where many patients start therapy at the time of diagnosis. There were no significant differences in sleep complaints between those in the intensive sleep subgroup compared with the PICNICS cohort as a whole, nor were there significant differences in sleep architecture between patients taking different combinations of dopaminergic drugs. Furthermore, our hormone and clock gene measurements were based around patients' habitual bedtimes rather than a free-running environment and were not carried out at exactly the same time as polysomnography assessments.

Conclusions

In summary, our study has defined the sleep phenotype of an early-stage PD cohort and related this to the patient's clinical characteristics, quality of life, and underlying circadian rhythms. In doing so, we have provided preliminary evidence that PD-related sleep dysfunction may reflect a more fundamental pathology in the circadian system.

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