Cell Communication and Signaling

RESEARCH

Open Access

Clinical features, plasma neurotransmitter levels and plasma neurohormone levels among patients with early-stage Parkinson's disease with sleep disorders

Cui-Hong Ma[1,2†], Ning Ren[1†], Jing Xu[3] and Lei Chen[1*]

Abstract

Background Sleep disorders occur frequently among patients with Parkinson's disease (PD). Neurotransmitters and neurosteroids are known to be involved in various neurophysiological processes, including sleep development. We aimed to assess the associations of peripheral neurotransmitter and neurosteroid levels with various sleep disorders in early-stage PD.

Methods Fifty-nine patients with early-stage PD and 30 healthy controls were enrolled. Demographic and clinical data were collected, and sleep conditions were comprehensively assessed with clinical questionnaires and polysomnography. Blood samples were obtained from all participants at 1:00 AM and 9:00 AM. The concentrations of plasma neurotransmitters and neurohormones were detected via high-performance liquid chromatography tandem mass spectrometry.

Results Sleep disorders were common nonmotor symptoms (81.4%) and coexisted in approximately half of the patients. Dysautonomia was significantly associated with the presence of multiple sleep disorders. RBD was associated with dysautonomia and was negatively correlated with the plasma melatonin concentration at 1:00 AM ($r=-0.40$, $p=0.002$) in early-stage PD patients. The RLS group had higher PSQI scores, and RLS was negatively associated with the 5-hydroxytryptamine levels ($r=-0.40$, $p=0.002$) at 1:00 AM and glutamine levels ($r=-0.39$, $p=0.002$) at 9:00 AM. SDB was associated with cognitive impairment, a greater body mass index, and lower plasma acetylcholine concentrations at 1:00 AM.

Conclusion Combined sleep disturbances are common in early-stage PD. Dysautonomia is closely related to various sleep disorders, including RBD, EDS, and insomnia. Changes in peripheral neurotransmitter and neurohormone levels may be involved in the development of sleep disorders.

Keywords Parkinson's disease, Sleep disorders, Plasma neurotransmitter and neurohormone levels

†Cui-Hong Ma and Ning Ren contributed equally to this work and should be considered as co-first authors.

*Correspondence:
Lei Chen
chrislinn@163.com
Full list of author information is available at the end of the article

Plain English Summary

Many people with Parkinson's disease (PD) experience sleep problems. Chemicals in the body called neurotransmitters and neurosteroids play a role in sleep regulation. This study looked at how levels of these chemicals in the blood might be linked to sleep disorders in people with early-stage PD. We found that sleep problems were very common in PD patients (81.4%), and about half had multiple sleep issues. Dysautonomia was linked to multiple sleep disorders. REM sleep behavior disorder (RBD) was linked to dysautonomia and lower levels of melatonin at 1:00 AM, restless legs syndrome (RLS) was associated with poorer sleep quality and lower levels of serotonin and glutamine at different times. Sleep-disordered breathing (SDB) was linked to memory problems, higher body weight, and lower levels of acetylcholine at 1:00 AM. Understanding these links could help improve sleep treatments for PD patients.

Background

Sleep disorders are among the most common non-motor symptoms of Parkinson's disease (PD) [1]. PD-related sleep disorders include rapid eye movement sleep behaviour disorder (RBD), restless legs syndrome (RLS), excessive daytime sleepiness (EDS), insomnia, and sleep-disordered breathing (SDB) [2]. Sleep disturbances are commonly present in the prodromal and early stages of PD [3, 4] and may occur alone or in various combinations. Sleep dysfunction in PD is multifaceted and involves medication-related side effects, nocturnal PD motor symptoms, an impaired sleep–wake cycle, and coexisting sleep and neuropsychiatric disorders. It is associated with a broad range of neurological structures and diverse neurotransmitters [5]. Previous studies have confirmed that the principal neuroendocrine system and the crucial neurotransmitter systems that mediate sleep, including melatonin, acetylcholine, norepinephrine, serotonin, dopamine, and gamma-aminobutyric acid, are disrupted in PD [6–9]. One previous study reported that the levels of dopamine and serotonin in the cerebrospinal fluid were significantly decreased in PD patients with RLS [10]. Additionally, several studies have supported the involvement of peripheral neurotransmitters in PD-related sleep dysfunction, with changes in blood neurotransmitters and neurohormones in patients [11–13]. The circulating levels of the aforementioned mediating substances may alternate with the circadian rhythm and play a role in the peripheral mechanisms of sleep disorders. However, few studies have systematically explored the associations between the diurnal and nocturnal levels of blood neurotransmitters and neurohormones and the different types of sleep disorders (EDS, RBD, RLS, SDB and insomnia) in early-stage PD.

In the present study, we aimed to investigate the associations between plasma neurotransmitter and neurohormone levels and sleep disorders and to determine the prevalence of sleep disturbances in patients with early-stage PD.

Subjects

We consecutively recruited 59 patients with early-stage PD from the Parkinson's Disease and Movement Disorder Clinic, Tianjin Huanhu Hospital, between January 2021 and October 2022. The inclusion criteria were as follows: diagnosis of clinically established PD according to the MDS Clinical Diagnostic Criteria for Parkinson's Disease; Hoehn and Yahr (H-Y) stage ≤ 2.5; and no or minimal cognitive disturbances (defined as a Mini-Mental State Examination (MMSE) score greater than 26/30). The exclusion criterion was a diagnosis of secondary, hereditary or atypical parkinsonism according to the aforementioned diagnostic criteria. Age-matched and sex-matched healthy controls ($n=30$) with no history of any neurological or sleep disorders (as assessed after the interview and clinical examination by a neurologist) were enrolled from the patients' spouses.

Assessment of clinical symptoms

All participants underwent examination by movement disorder specialists through face–to-face interviews and detailed questionnaires. Demographic information, including sex, onset age, disease duration, and the use of anti-Parkinson's drugs, antidepressants and sedatives, was recorded. Additionally, the levodopa equivalent daily dose (LEDD) was calculated via conversion factors and previously reported parameters by submitting daily doses of commonly used anti-Parkinson drugs (single or in combination) [14]. All PD patients completed the Chinese versions of the MDS-UPDRS part I, MDS-UPDRS part II (activities of daily living, ADL), and MDS-UPDRS part III (motor symptoms) [15]. Disease severity was evaluated using the Hoehn and Yahr (H-Y) stage. Motor subtypes [16] were defined via the MDS-UPDRS parts II and III, including the tremor dominant subtype (ratio ≥ 1.15), postural instability and gait disorders (PIGD) subtype (ratio ≤ 0.90) and indeterminate subtype ($0.9 <$ ratio < 1.15). Disease progression was assessed as follows: total disease progression was calculated by dividing the sum of the MDS-UPDRS Parts I, II, and III

scores by disease duration; motor progression was calculated by dividing the MDS-UPDRS Part III score by disease duration; and ADL progression was determined by dividing the MDS-UPDRS Part II score by disease duration. Non-motor symptoms were assessed via the Non-Motor Symptoms Scale (NMSS) [17], followed by the Montreal Cognitive Assessment (MoCA, education level-corrected) [18] for cognitive impairment, the Hamilton Depression Scale-24 (HAMD-24) [19] for depression, the Hamilton Anxiety Scale (HAMA) [20] for anxiety, the Scale of Autonomic Function in PD (SCOPA-AUT) [21] for autonomic dysfunction, the Fatigue Severity Scale (FSS) [22] for fatigue, the Pittsburgh Sleep Quality Index (PSQI) [23] for general sleep quality, and the REM Sleep Behaviour Disorder Questionnaire-Hong Kong (RBDQ-HK) [24] for parasomnia. Quality of life was assessed via the 39-item Parkinson's Disease Questionnaire (PDQ-39) [25]. All motor and non-motor symptom assessments were conducted in the OFF-medication condition.

Sleep assessment

All patients underwent night-time video-polysomnography at the Parkinson's Disease and Movement Disorder Impatient Clinic. The recordings included eight (F1/A2, C3/A2, O1/A2, T3/A2, F2/A2, C4/A2, T4/A2, and O2/A2) bipolar electroencephalogram (EEG) channels, two electrooculograms (EOGs), surface electromyograms (EMGs) of the chin and right tibialis anterior muscles, electrocardiogram (ECG), airflow via nasal pressure and naso-oral thermistor, respiratory effort (via thoracic and abdominal plethysmography), transcutaneous oxyhemoglobin, body position, and tracheal sounds (snoring detector), and synchronized infrared video and ambient sounds. Sleep neurologists scored sleep stages, arousal, RBD, periodic leg movements and respiratory events in accordance with international criteria. Sleep-disordered breathing (SDB) was defined as an apnoea-hypopnea index greater than 15/h. RBD, restless legs syndrome (RLS) and insomnia were diagnosed according to the criteria of the International Classification of Sleep Disorders, 3rd Edition [26]. Excessive daytime sleepiness (EDS) was defined as an ESS score of 10 or greater [27].

Detection of circadian levels of neurotransmitters and neurohormones in plasma

A total of 3 ml of venous blood was collected from all the subjects (patients and controls) at 1:00 AM and 9:00 AM on the same day under fasting conditions. The samples were centrifugated within 4 h and preserved at − 80 °C until testing. The concentrations of neurotransmitters and neurohormones, including dopamine (DA), epinephrine (E), aspartate (Asp), 5-hydroxytryptamine (5-HT), glutamic acid (Glu), acetylcholine (Ach), glutamine (Gln), melatonin (MT), and gamma-aminobutyric acid (GABA), were detected via high-performance liquid chromatography tandem mass spectrometry (HPLC–MS). The multireaction monitoring scanning mode was used for LC–MS/MS detection. A Waters Iclass-AB Sciex 6500 liquid–mass tandem mass spectrometry system with a Waters BEH C18 (model: 1.7 μm * 2.1 * 100 mm) chromatographic column was used as the analytical instrument. Mobile phase A was water + 0.1% formic acid, and mobile phase B was methanol + 0.1% formic acid. The flow rate was 0.35 mL/min, and the gradient settings were 0–2 min, 2% B, 2.5–15 min, and 20%–80% B.

Statistical analysis

We used SPSS Statistics (version 25.0, SPSS Inc., Chicago, IL, USA) and R software (version 4.3.0) for statistical analysis. We evaluated differences in demography, clinical information, and neurotransmitter and neurohormone levels between PD patients and controls via the chi-square test for categorical variables and the Welch's t test and the Mann–Whitney U test for continuous variables. For PD patients, the chi-square test or Fisher's exact test was used for categorical variables, and one-way analysis of variance and the Mann–Whitney U test were used for numerical variables to compare three groups according to the number of sleep symptoms (0, 1, and ≥ 2). To determine which groups differed from each other, post hoc comparisons were performed using the pairwise least significant difference test and Mann–Whitney–Wilcoxon test (for numerical variables) or the pairwise Fisher's exact test (for categorical variables), followed by the Bonferroni correction. The same methods were used to compare the levels of plasma neurotransmitters and neurohormones between PD patients (with and without specific sleep disorders or different numbers of sleep disorders) and controls. To identify factors related to an increase in the number of sleep disturbances, we performed an ordinal logistic regression analysis that included disease course and scores of the MDS UPDRS part II, NMSS, SCOPA-AUT, PDQ-39, and PSQI as covariates. To compare every specific type of sleep disorder in PD patients, we identified important covariates with borderline significance in the univariate analysis, which were then verified in the multivariate logistic model via automatic forwards selection methods. Two-tailed p values of < 0.05 were considered to indicate statistical significance. We used the UpSetR v1.4.0 package based on the full dataset to build the figure of the presence of five sleep disturbances. The R patchwork package, ggpubr package, ggsci package and tidyverse package were used to display changes in MT levels in the RBD and 5-HT levels in the RLS. The ggpmisc package in the R software was used for Pearson's correlation

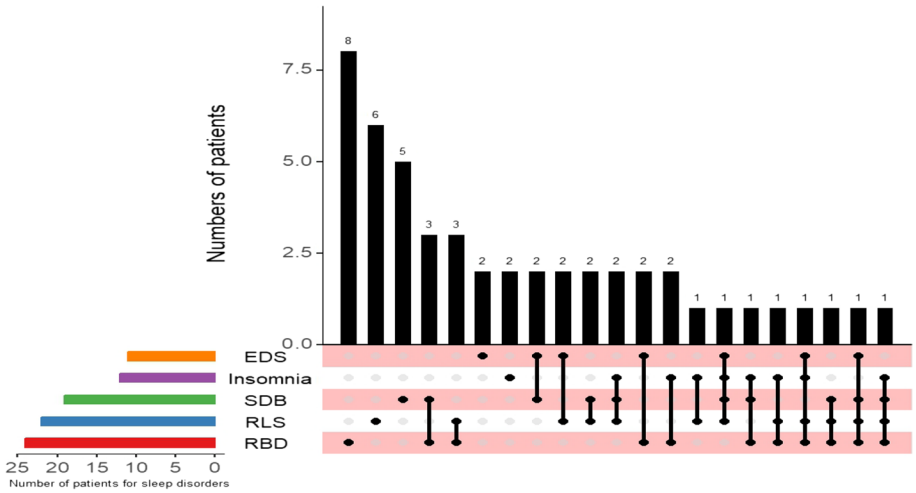

Fig. 1 Distribution of sleep disorders in PD patients

analysis, which was performed to evaluate the correlations between plasma neurotransmitter and neurohormone levels and the occurrence of each specific type of sleep disorder.

Results

Demographic and clinical characteristics of the participants

The demographic information and clinical characteristics of the 59 PD patients and 30 controls are presented in Table S1. There were no significant differences in age or sex between the two groups. Among the 59 early-stage PD patients, the mean onset age and disease duration were 61.25 ± 9.07 and 3.90 ± 3.06 years, respectively. The mean H–Y stage was 2.5 (2.0, 2.5). Thirty-six patients (61.0%) received anti-Parkinson's drugs. Six (10.2%) and 11 (18.6%) patients were taking antidepressants and benzodiazepines, respectively. The total LEDD was 418.54 ± 218.41 mg/24 h. The mean scores of the MDS-UPDRS parts I, II and III were 12.97 ± 6.89, 14.37 ± 8.54, and 25.61 ± 12.80, respectively. The scores on nonmotor symptom scales were as follows: HAMA, 15.05 ± 7.99; HAMD-24, 11.73 ± 8.35; MoCA, 22.81 ± 4.22; SCOPA-AUT, 13.40 ± 7.60; NMSS, 42.07 ± 26.21; and FSS, 2.70 ± 2.52.

Coexistence of sleep disorders in PD

PD patients were categorized into three groups: no sleep disorder, one sleep disorder, and combined sleep disorders (more than two sleep disturbances), accounting for 18.6%, 39.0%, and 42.4% of patients, respectively. Individual or cooccurring sleep disturbances in PD patients are shown in Fig. 1. The isolated RBD was the most common, followed by the isolated RLS and isolated SDB. The combinations of sleep disorders were relatively scattered—each sleep disorder could be associated with any other sleep disorder, and there was no preference in the combinations. The demographic and clinical characteristics of the three groups are shown in Table 1. PD patients with multiple sleep disorders had higher scores on the MDS-UPDRS part II, NMSS, PSQI, and PDQ-39 than did those with no sleep disorders. SCOPA-AUT scores were higher in the group with multiple sleep disorders than in the other two groups. Compared with patients with no sleep disorders, patients with one sleep disorder had higher NMSS scores. However, sex, onset age, disease duration, MDS-UPDRS part I and III scores, MoCA scores, HAMA scores, HAMD-24 scores, FSS scores, and disease progression were similar among the three groups. The ordinal logistic regression analysis using forwards selection revealed that the SCOPA-AUT score (OR = 1.16, 95% CI = 1.02–1.31, $p = 0.025$) was a contributing factor for multiple sleep disturbances (Table 2).

Factors associated with PD-RBD

Patients with PSG-confirmed RBD (24, 40.7%) had higher SCOPA-AUT scores than those without RBD. Binary logistic regression analysis revealed that RBD in PD patients was significantly associated with higher SCOPA-AUT scores (OR = 1.08, 95% CI = 1.00–1.17, $p = 0.040$), whereas it was not associated with motor symptoms, disease progression, depression, anxiety, cognition, fatigue, or other sleep disorders (Table S2).

Factors associated with PD-RLS

Table S3 shows the results of univariate and multivariate regression analyses for PD patients with and without RLS. Univariate analysis revealed that the RLS score was

Table 1 Demographical and clinical characteristics by co-occurrence of sleep-related disorders in early-stage PD patients

Group	No sleep disorder[a] *N* = 11 (19%)	One sleep disorder[b] *N* = 23 (39%)	at least two sleep diorders[c] *N* = 25 (42%)	F/H/X²	*P*
Demography					
Onset age (years)	61.59 ± 10.74	58.83 ± 8.81	63.32 ± 8.34	1.51	0.23
Disease course (years)	2.06 ± 1.52	3.96 ± 3.20	4.67 ± 3.17	2.95	0.06
Male sex, N (%)	4 (36.4)	13 (56.5)	14 (56.0)	1.42	0.49
Global assessment of disease					
H-Y stage (on–OFF condition)	2.00 (1.00, 2.50)	2.50 (2.00, 2.50)	2.50 (2.00, 2.50)	3.99	0.14
MDS-UPDRS I (score)	10.82 ± 5.33	11.65 ± 6.95	15.12 ± 7.07	2.27	0.11
MDS-UPDRS II (score)	9.45 ± 2.70[c]	13.65 ± 8.44	17.20 ± 9.39[a]	3.56	**0.04**
MDS-UPDRS III (score)	19.36 ± 10.04	28.17 ± 12.43	26.00 ± 13.70	1.84	0.17
Non motor symptoms					
NMSS (score)	20.45 ± 8.56[b, c]	40.04 ± 20.83[a]	53.44 ± 29.65[a]	7.56	**0.001**
PSQI (score)	5.09 ± 2.95[c]	7.17 ± 4.14[c]	10.20 ± 5.12[a,b]	5.31	**0.008**
MoCA (score)	24.91 ± 3.59	23.14 ± 4.66	21.48 ± 3.78	2.81	0.07
HAMA (score)	11.18 ± 6.01	14.26 ± 8.34	17.48 ± 7.86	2.71	0.08
HAMD-24 (score)	8.27 ± 7.04	11.13 ± 8.73	13.80 ± 8.23	1.82	0.17
SCOPA-AUT (score)	7.27 ± 4.52[c]	11.34 ± 6.39[c]	17.58 ± 6.92[a, b]	11.56	**< 0.001**
FSS (score)	1.61 ± 1.19	2.70 ± 3.40	3.17 ± 1.85	1.49	0.23
Disease progression and life quality					
Total disease progression	33.77 ± 28.06	21.43 ± 16.57	20.15 ± 19.53	1.86	0.17
Motor progression	15.52 ± 15.26	10.95 ± 7.90	9.26 ± 9.50	1.43	0.25
ADL progression	8.22 ± 6.24	4.93 ± 3.75	5.09 ± 3.35	2.68	0.08
PDQ-39 (score)	19.45 ± 13.41[c]	30.17 ± 24.57	43.44 ± 27.79[a]	4.07	**0.02**
Treatment					
LEDD (mg/day)	170.45 ± 153.22	214.04 ± 244.26	314.04 ± 314.04	1.44	0.25
Dopamine agonist, N (%)	3 (27.3)	5 (21.7)	9 (36.0)	1.21	0.55

Data are shown as mean ± SD, median (quartile range) or N (%). Statistical significance was set at $p < 0.05$. Significant differences are shown in bold

Abbreviations: MDS UPDRS Movement Disorder Society-Unified Parkinson's Disease Rating Scale, *NMSS* non-motor symptom evaluation scale, *PSQI* Pittsburgh Sleep Quality Index, *MoCA* Montreal Cognitive Assessment, *HAMA* Hamilton Anxiety Scale, *HAMD-24* Hamilton Depression Scale −24, *SCOPA-AUT* scale of outcomes in PD for autonomic symptoms, *FSS* Fatigue Severity Scale, *LEDD* L-dopa equivalent daiyl dose, *ADL* activities of daily living, *PDQ-39* 39-item Parkinsons Disease Questionnaire

[a] For a pairwise difference with no sleep disturbance

[b] For a pairwise difference with one sleep disorder

[c] For a pairwise difference with at least two sleep disorders

Table 2 Logistic regression analyses for PD patients with only one, multiple types and without sleep disorders

Varibles	OR[a] (95%CI)	*P*-value	OR[b] (95%CI)	*P*-value
Disease course	1.21 (1.01–1.44)	0.039		
MDS UPDRS II	1.08 (1.02–1.16)	0.017		
NMSS	1.04 (1.02–1.07)	0.001		
SCOPA-AUT	1.20 (1.09–1.38)	< 0.001	1.16 (1.02–1.31)	0.025
PDQ-39	1.03 (1.01–1.05)	0.009		
PSQI	1.18 (1.05–1.32)	0.005		

Abbreviations: MDS UPDRS II Movement Disorder Society-Unified Parkinson's Disease Rating Scale part II, *NMSS* non-motor symptom evaluation scale, *SCOPA-AUT* scale of outcomes in PD for autonomic symptoms, *PDQ-39* 39-item Parkinsons Disease Questionnaire, *PSQI* Pittsburgh Sleep Quality Index

[a] Univariate ordinal logistic regression

[b] Multivariate ordinal logistic regression

significantly associated with the disease duration, LEDD, mNMSS score, PSQI score, FSS score, and motor progression. These covariates were further included in the multivariate analysis, and higher PSQI scores (OR = 1.92, 95% CI = 1.01–1.64, $p = 0.039$) were significantly correlated with RLS, indicating that higher PSQI scores may be independent risk factors for RLS. No differences in red blood cell count or haemoglobin, serum ferritin, folic acid or vitamin B12 levels were detected between patients with and without RLS (Table S7).

Factors associated with PD-SDB

Higher body mass index (OR = 1.21, 95% CI = 1.01–1.45, $p = 0.044$) and lower MoCA scores (OR = 0.84, 95% CI = 0.72–0.98, $p = 0.029$) were significantly correlated

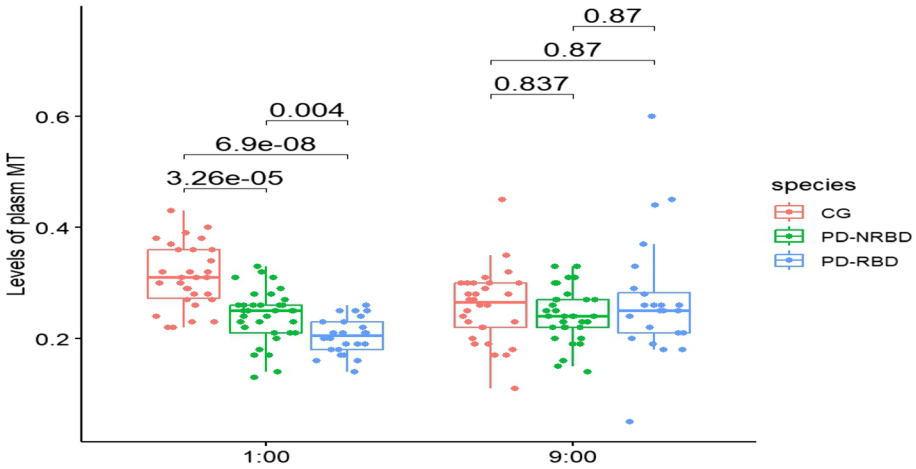

Figure2 Comparisons of plasma melatonin concentration between groups

with SDB according to both univariate and multivariate regression analyses (Table S4). No other differences in clinical factors were observed between PD patients with and without SDB.

Factors associated with PD-insomnia

Table S5 shows the clinical characteristics of PD patients with and without insomnia. In the univariate regression model, nonmotor scores (including scores on the MDS-UPDRS part I, mNMSS, HAMA, HAMD-24, MoCA, SCOPA-AUT and PSQI), antidepressant use, and scores on the PQD-39 and MDS-UPDRS part II were significantly correlated with insomnia. According to multivariate logistic regression analyses, higher scores on the MDS-UPDRS part I (OR = 2.05, 95% CI = 1.04–4.05, $p = 0.038$), HAMD-24 (OR = 1.88, 95% CI = 1.10–3.20, $p = 0.021$) and SCOPA-AUT (OR = 1.43, 95% CI = 1.07–1.92, $p = 0.016$) were significantly correlated with insomnia.

Factors associated with PD-EDS

Univariate regression analysis revealed that PD patients with EDS (10/59, 16.9%) had higher scores on the MDS-UPDRS part I, part II, SCOPA-AUT and PDQ-39. When these factors were included in the multivariate analyses, the results revealed that only autonomic dysfunction increased the risk of EDS by 1.17 times (95% CI = 1.05–1.31, $p = 0.006$) (Table S6).

Comparison of plasma neurotransmitter and neurohormone concentrations between PD patients and controls

In healthy controls, the plasma dopamine level at 1:00 am was significantly lower than that at 9:00 am, and the melatonin level at 1:00 am was significantly greater than that at 9:00 am, which is consistent with the findings of previous studies [28, 29]. Patients with PD had decreased plasma concentrations of Asp, Glu, GABA, MT and epinephrine at 1:00 am and decreased plasma concentrations of Asp, Glu, DA and epinephrine at 9:00 am. The peripheral level of Gln was increased at 9:00 am in the PD group (Table S8).

Peripheral melatonin and DA levels in PD-RBD patients

The plasma concentration of melatonin at 1:00 am was significantly lower in PD patients with RBD than in controls and PD patients without RBD (Fig. 2), whereas the levels of DA were elevated in PD patients with RBD compared with those in patients without RBD at this time point. However, no difference in DA levels was observed between the PD-RBD and control groups (Table S9). The plasma melatonin level at 1:00 am was negatively correlated with RBD ($r = -0.40$, $p = 0.0018$), and the DA level was positively correlated with RBD ($r = 0.29$, $p = 0.025$) (Fig. 3).

Peripheral 5-HT and glutamine levels in PD-RLS

At 1:00 am, PD patients with RLS had significantly lower levels of 5-HT than patients without RLS did (Figure S1). The glutamine level decreased significantly in the PD-RLS group at 9:00 am (Table S10). PD-RLS was negatively correlated with the levels of 5-hydroxytryptamine at 1:00 am ($r = -0.40$, $p = 0.0016$) and glutamine at 9:00 am ($r = -0.39$, $p = 0.0022$) (Fig. 3).

Peripheral acetylcholine levels in PD-SDB

PD patients with SDB had lower plasma acetylcholine concentrations than patients without SDB did at 1:00 am (Table S11). There was also a negative correlation

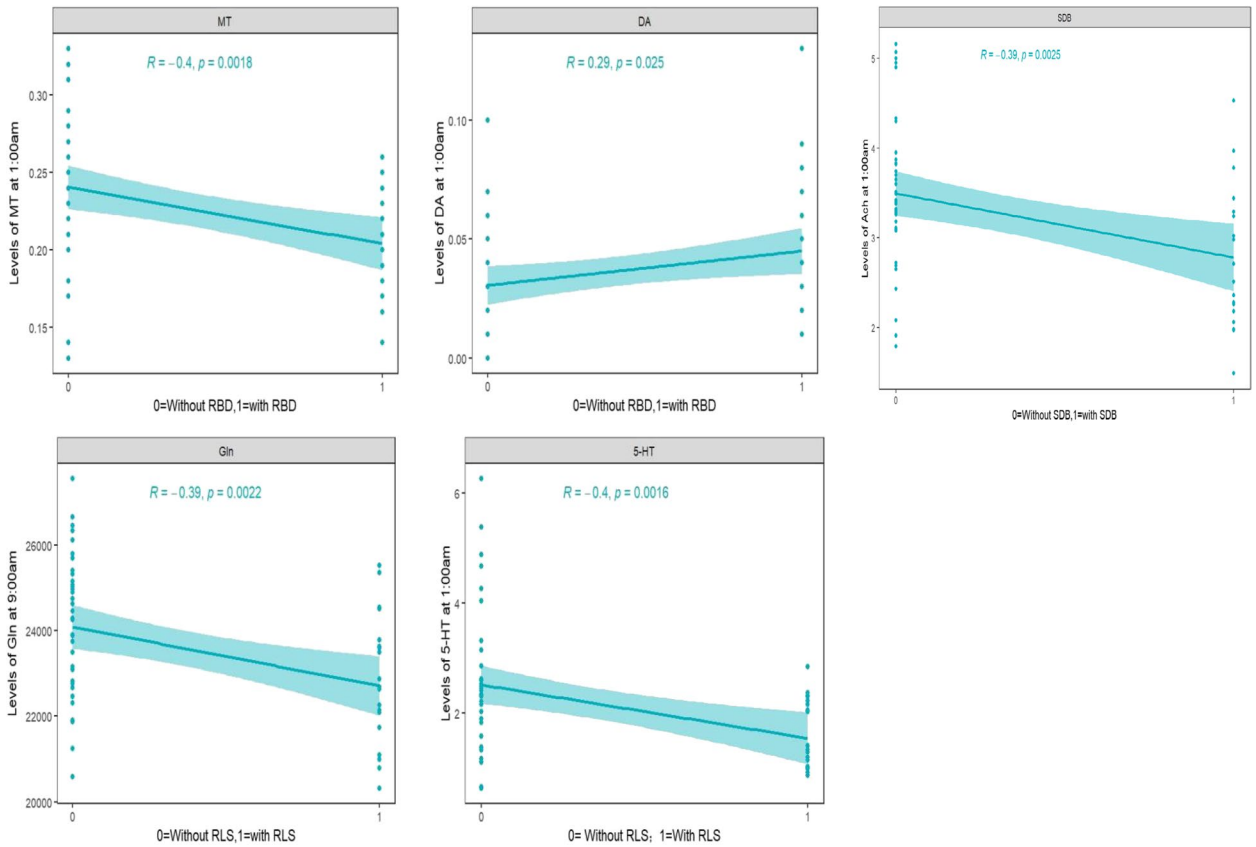

Fig. 3 Point-biserial correlation between the levels of plasma neurotransmitters and neurohormones and specific sleep disorders in PD patients

between SDB and acetylcholine levels at 1:00 am in PD patients ($r = -0.39$, $p = 0.0025$).

PD patients with EDS or insomnia did not exhibit significant changes in peripheral neurotransmitter or neurohormone levels (Tables S9 and S11).

Discussion

In the present study, we confirmed that the incidence of sleep disturbances was high and that multiple sleep disorders often coexisted in early-stage PD patients. RBD was the most common sleep disorder, followed by RLS, OSA, insomnia, and EDS. The incidence of insomnia (18.6%) was lower than that reported in a previous study [4]. Approximately 80% of PD patients had at least one type of sleep disturbance, and approximately 50% of patients had two or more sleep disturbances, similar to previously reported findings in the ICEBERG cohort [4]. The percentage of patients with combined sleep disorders in the PPMI cohort [30] was 11.5%, which was determined based on questionnaires that assessed a limited range of sleep disorders (RBD, EDS and PD-related sleep symptoms). The number of combined sleep disorders increased with the severity of dysautonomia, possibly related to the presence of RBD, EDS, and insomnia, and PD patients with RBD, EDS, and insomnia had higher scores for dysautonomia than did those without sleep disorders.

The current findings revealed that RBD diagnosed via PSG accounted for the highest proportion (40.7%) of early-stage PD patients with sleep disorders and was associated with dysautonomia. There is evidence indicating that autonomic dysfunction and RBD share common neuropathology [31]. Patients presenting with pure autonomic failure (PAF) and isolated RBD (iRBD) are reported to be at high risk of converting to α-synucleinopathy [32, 33]. Compared with healthy controls, iRBD patients exhibit more prominent autonomic dysfunction [34], suggesting a correlation between PAF and iRBD. Substantial evidence suggests that PD patients with RBD may have a distinct phenotype compared with PD patients without RBD, including autonomic dysfunction [4, 35, 36]. RBD is considered to constitute a key marker of diffuse–malignant PD subtypes with cognitive loss, severe autonomic dysfunction, fast motor progression and loss of independent living and mortality. Our study revealed a lower level of plasma melatonin

in PD patients with RBD than in patients without RBD and healthy controls at 1:00 AM. In addition, the plasma melatonin level at this time was negatively correlated with RBD, suggesting that the decrease in the peripheral melatonin level in the early morning might be involved in RBD development. Previous studies using animal experiments reported that α-synuclein reduces acetylserotonin O-methyltransferase-mediated melatonin biosynthesis [37, 38]. Two previous studies reported that patients with PD presented reduced circulating melatonin levels [6, 11]. Furthermore, based on comprehensive clinical observations, 59.9% of 137 RBD patients reported improvements with melatonin treatment across various outcome measures in published studies [39–42]. Thus, melatonin has been proposed as a preferable treatment for RBD. These results are consistent with previous findings and support the role of melatonin in the incidence of RBD. We also found that plasma dopamine levels at 1:00 AM were higher in PD patients with RBD than in those without RBD, possibly resulting from a higher L-DOPA requirement induced by worsening motor symptoms.

In the present study, RLS was the second most common sleep disorder in early-stage PD, with a frequency of 35.6%, which was higher than that reported in previous studies (4.6%–16.3%) [43, 44]. In the current study population, PD patients with RLS exhibited poorer sleep quality than those without RLS, which was similar to findings reported in previous investigations [10, 45, 46]. RLS can have a negative impact on sleep quality by decreasing sleep time and efficiency [4, 47]. Our study revealed that PD patients with RLS presented abnormal neurotransmitter levels, including reduced plasma levels of 5-hydroxytryptamine (5-HT) at 1:00 AM and reduced plasma levels of glutamine at 9:00 AM, which were negatively correlated with RLS. Piao et al. [10] reported a similar 5-HT change in cerebrospinal fluid. Another study reported that sleep dysfunction in PD is associated with reduced serotonergic function in the midbrain raphe, basal ganglia and hypothalamus according to $^{[11}$C]DASB positron emission tomography findings [48]. A possible mechanism underlying this phenomenon is that 5-HT may interact with dopamine pathway activity or disturb iron metabolism [49, 50]. One previous study confirmed that glutaminergic neurotransmitters in the thalamus are involved in the development of RLS by increasing arousal [51], although it is unclear how glutaminergic neurotransmitters are involved in the development of PD-RLS.

SDB was previously reported to be more prevalent in early-stage PD patients than in the general population [52]. In the present study, SDB was associated with increased body mass index and cognitive dysfunction in PD patients, and these outcomes are in accordance with several previous reports [53–55]. Sleep-related hypoxemia disorders can affect cognitive function and result in a worse prognosis for PD patients, and longitudinal studies have reported that continuous positive airway pressure (CPAP) can improve global cognitive function over a 12-month period in PD patients with OSA [56, 57]. Compared with those in patients without SDB and controls, the plasma levels of acetylcholine at 1:00 AM were significantly lower in PD patients with SDB. Hilker et al. [58] reported that compared with PD patients without dementia, PD patients with dementia presented significantly reduced neocortical acetylcholinesterase (AChE) activity. Therefore, the current findings indicate that cholinergic denervation may account for cognitive impairment in PD-SDB patients.

In the current study cohort, approximately one-fifth of the PD subjects had EDS. Patients with EDS experienced severe autonomic dysfunction, which was consistent with the findings of previous studies [59–61]. Videnovic et al. [11] reported that PD participants with EDS had a significantly lower amplitude of melatonin rhythm and 24-h melatonin area under the curve (AUC) than PD participants without EDS. In the present study, the absence of a change in the levels of melatonin among PD patients with or without EDS may have occurred because the patients were enrolled in the early stage of PD when circadian rhythm disruption was less severe than it was in the advanced stage.

The frequency of insomnia in this study was lower than that reported in a previous study (21%–41%) [4], possibly because the patients enrolled in the current study were in the early stage of PD, whereas insomnia was more prevalent in advanced PD patients [52]. Although the current findings suggest that insomnia may be related to depression, dysautonomia, and poorer ADLs in patients with early-stage PD [30, 62], we observed no significant changes in peripheral neurotransmitter or neurohormone levels in the PD-insomnia subgroup, thus indicating the heterogeneous nature of insomnia in PD patients [63].

Several limitations of our study should be noted. First, the sample size of 89 patients was modest. However, this sample still allowed a comprehensive analysis of sleep disturbances in early-stage PD patients, and all participants underwent comprehensive motor, nonmotor, and sleep assessments. Second, patients were medicated rather than drug naïve, which could have an impact on sleep disturbances. However, there were no significant differences in daily doses of levodopa or dopamine receptor agonists among the sleep disorder subgroups. Finally, blood samples were collected at only two time points, although the sampling was conducted at two representative times: morning and

midnight. Circadian peripheral changes in these bioactive substances should be considered in future studies.

Conclusion

Comorbid sleep disturbances were found to be common in early-stage PD patients. Dysautonomia is closely related to the presence of combined and specific sleep disorders, including RBD, EDS and insomnia. Changes in peripheral neurotransmitters and neurohormones may be involved in the development of sleep disturbances. Therefore, a better understanding of the role of these endogenous compounds could be helpful for optimizing treatments for PD-related sleep disorders in the future.

Abbreviations

PD	Parkinson's disease
RBD	Rapid eye movement sleep behaviour disorder
RLS	Restless legs syndrome
EDS	Excessive daytime sleepiness
SDB	Sleep-disordered breathing
MMSE	Mini-Mental State Examination
LEDD	Levodopa equivalent daily dose
ADL	Activities of daily living
PIGD	Postural instability and gait disorders
NMSS	Non-Motor Symptoms Scale
MoCA	Montreal Cognitive Assessment
HAMD	Hamilton Depression Scale
HAMA	Hamilton Anxiety Scale
SCOPA-AUT	Scale of Autonomic Function
FSS	Fatigue Severity Scale
PSQI	Pittsburgh Sleep Quality Index
RBSQ-HK	REM Sleep Behaviour Disorder Questionnaire-Hong Kong
PDQ-39	39-Item Parkinson's Disease Questionnaire
DA	Dopamine
E	Epinephrine
Asp	Aspartate
5-HT	5-Hydroxytryptamine
Glu	Glutamic acid
Ach	Acetylcholine
Gln	Glutamine
MT	Melatonin
GABA	Gamma-aminobutyric acid
HPLC–MS	High-performance liquid chromatography tandem mass spectrometry

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12964-025-02153-8.

Additional file 1.

Additional file 2.

Acknowledgements
Not appliable.

Authors' contributions
Contributions: (I) Conception, design and collection and assembly of data: Cui-Hong Ma; (II) Administrative support: Lei Chen; (III) Provision of study materials or patients: Ning Ren; (IV)Data analysis and interpretation: Cui-hong Ma, Jing Xu; (V) Manuscript writing: Cui-hong Ma; (VI) Final approval of manuscript: All authors.

Funding
This study was funded by Tianjin Key Medical Discipline (Specialty) Construction Project (No. TJYXZDXK-052B).

Data availability
The data that support the findings of this study are available on request from the Parkinson's Disease and Movement Disorder Clinic, Tianjin Huanhu Hospital.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the Declaration of Helsinki. This study was approved by the ethics committee of Huanhu Hospital, and written informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Neurology, Huanhu Hospital Affiliated to Tianjin Medical University, 6 Jizhao Road, Jinnan District, Tianjin 300350, China. [2]Department of Neurology, Chengde Central Hospital, Chengde 067000, China. [3]Department of Neurology, Chengde Medical University, Chengde 067000, China.

Received: 27 July 2024 Accepted: 11 March 2025
Published online: 18 March 2025

References

1. Schapira AHV, Chaudhuri KR, Jenner P. Non-motor features of Parkinson disease. Nat Rev Neurosci. 2017;18:435–50.
2. Stefani A, Högl B. Sleep in Parkinson's disease. Neuropsychopharmacology. 2020;45:121–8.
3. Berg D, Borghammer P, Fereshtehnejad SM, Heinzel S, Horsager J, Schaeffer E, et al. Prodromal Parkinson disease subtypes - key to understanding heterogeneity. Nat Rev Neurol. 2021;17:349–61.
4. Dodet P, Houot M, Leu-Semenescu S, Corvol JC, Lehéricy S, Mangone G, et al. Sleep disorders in Parkinson's disease, an early and multiple problem. NPJ Parkinsons Dis. 2024;10:46.
5. Yu SY, Sun L, Liu Z, Huang XY, Zuo LJ, Cao CJ, et al. Sleep disorders in Parkinson's disease: clinical features, iron metabolism and related mechanism. PLoS ONE. 2013;8:e82924.
6. Breen DP, Vuono R, Nawarathna U, Fisher K, Shneerson JM, Reddy AB, et al. Sleep and circadian rhythm regulation in early Parkinson disease. JAMA Neurol. 2014;71:589–95.
7. Jellen LC, Lewis MM, Du G, Wang X, Galvis MLE, Krzyzanowski S, et al. Low plasma serotonin linked to higher nigral iron in Parkinson's disease. Sci Rep. 2021;11:24384.
8. Factor SA, McDonald WM, Goldstein FC. The role of neurotransmitters in the development of Parkinson's disease-related psychosis. Eur J Neurol. 2017;24:1244–54.
9. Tuura RLO, Baumann CR, Baumann-Vogel H. Beyond dopamine: GABA, glutamate, and the axial symptoms of Parkinson disease. Front Neurol. 2018;9:806.
10. Piao YS, Lian TH, Hu Y, Zuo LJ, Guo P, Yu SY, et al. Restless legs syndrome in Parkinson disease: clinical characteristics, abnormal iron metabolism and altered neurotransmitters. Sci Rep. 2017;7:10547.
11. Videnovic A, Noble C, Reid KJ, Peng J, Turek FW, Marconi A, et al. Circadian melatonin rhythm and excessive daytime sleepiness in Parkinson disease. JAMA Neurol. 2014;71:463–9.
12. James FO, Boivin DB, Charbonneau S, Bélanger V, Cermakian N. Expression of clock genes in human peripheral blood mononuclear cells throughout the sleep/wake and circadian cycles. Chronobiol Int. 2007;24:1009–34.

13. Boivin DB, James FO, Wu A, Cho-Park PF, Xiong H, Sun ZS. Circadian clock genes oscillate in human peripheral blood mononuclear cells. Blood. 2003;102:4143–5.
14. Jost ST, Kaldenbach MA, Antonini A, Martinez-Martin P, Timmermann L, Odin P, et al. Levodopa dose equivalency in Parkinson's disease: updated systematic review and proposals. Mov Disord. 2023;38:1236–52.
15. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement disorder society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord. 2008;23:2129–70.
16. Stebbins GT, Goetz CG, Burn DJ, Jankovic J, Khoo TK, Tilley BC. How to identify tremor dominant and postural instability/gait difficulty groups with the movement disorder society unified Parkinson's disease rating scale: comparison with the unified Parkinson's disease rating scale. Mov Disord. 2013;28:668–70.
17. Chaudhuri KR, Martinez-Martin P, Brown RG, Sethi K, Stocchi F, Odin P, et al. The metric properties of a novel non-motor symptoms scale for Parkinson's disease: results from an international pilot study. Mov Disord. 2007;22:1901–11.
18. Mazancova AF, Růžička E, Jech R, Bezdicek O. Test the best: classification accuracies of four cognitive rating scales for Parkinson's disease mild cognitive impairment. Arch Clin Neuropsychol. 2020;35:1069–77.
19. Mueller C, Rajkumar AP, Wan YM, Velayudhan L, Ffytche D, Chaudhuri KR, et al. Assessment and management of neuropsychiatric symptoms in Parkinson's disease. CNS Drugs. 2018;32:621–35.
20. Dissanayaka NN, Torbey E, Pachana NA. Anxiety rating scales in Parkinson's disease: a critical review updating recent literature. Int Psychogeriatr. 2015;27:1777–84.
21. Visser M, Marinus J, Stiggelbout AM, Van Hilten JJ. Assessment of autonomic dysfunction in Parkinson's disease: the SCOPA-AUT. Mov Disord. 2004;19:1306–12.
22. Martinez-Martin P, Wetmore JB, Arbelo JM, Catalán MJ, Valldeoriola F, Rodriguez-Blazquez C. Validation study of the Parkinson's fatigue scale in advanced Parkinson's disease. Patient Relat Outcome Meas. 2019;10:141–52.
23. Tsai PS, Wang SY, Wang MY, Su CT, Yang TT, Huang CJ, et al. Psychometric evaluation of the Chinese version of the Pittsburgh Sleep Quality Index (CPSQI) in primary insomnia and control subjects. Qual Life Res. 2005;14:1943–52.
24. Skorvanek M, Feketeova E, Kurtis MM, Rusz J, Sonka K. Accuracy of rating scales and clinical measures for screening of rapid eye movement sleep behavior disorder and for predicting conversion to Parkinson's disease and other synucleinopathies. Front Neurol. 2018;9:376.
25. Neff C, Wang MC, Martel H. Using the PDQ-39 in routine care for Parkinson's disease. Parkinsonism Relat Disord. 2018;53:105–7.
26. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. Chest. 2014;146:1387–94.
27. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14:540–5.
28. Sowers JR, Vlachakis N. Circadian variation in plasma dopamine levels in man. J Endocrinol Invest. 1984;7:341–5.
29. Li S, Wang Y, Wang F, Hu LF, Liu CF. A new perspective for Parkinson's disease: circadian rhythm. Neurosci Bull. 2017;33:62–72.
30. Suzuki K, Okuma Y, Uchiyama T, Miyamoto M, Sakakibara R, Shimo Y, et al. Impact of sleep-related symptoms on clinical motor subtypes and disability in Parkinson's disease: a multicentre cross-sectional study. J Neurol Neurosurg Psychiatry. 2017;88:953–9.
31. Coon EA, Cutsforth-Gregory JK, Benarroch EE. Neuropathology of autonomic dysfunction in synucleinopathies. Mov Disord. 2018;33:349–58.
32. Kaufmann H, Norcliffe-Kaufmann L, Palma JA, Biaggioni I, Low PA, Singer W, et al. Natural history of pure autonomic failure: a United States prospective cohort. Ann Neurol. 2017;81:287–97.
33. Norcliffe-Kaufmann L, Kaufmann H, Palma JA, Shibao CA, Biaggioni I, Peltier AC, et al. Orthostatic heart rate changes in patients with autonomic failure caused by neurodegenerative synucleinopathies. Ann Neurol. 2018;83:522–31.
34. Chiaro G, Calandra-Buonaura G, Cecere A, Mignani F, Sambati L, Loddo G, et al. REM sleep behavior disorder, autonomic dysfunction and synuclein-related neurodegeneration: where do we stand? Clin Auton Res. 2018;28:519–33.
35. Baschieri F, Sambati L, Guaraldi P, Barletta G, Cortelli P, Calandra-Buonaura G. Neurogenic orthostatic hypotension in early stage Parkinson's disease: new insights from the first 105 patients of the BoProPark study. Parkinsonism Relat Disord. 2021;93:12–8.
36. Riboldi GM, Russo MJ, Pan L, Watkins K, Kang UJ. Dysautonomia and REM sleep behavior disorder contributions to progression of Parkinson's disease phenotypes. NPJ Parkinsons Dis. 2022;8:110.
37. Ahmad SB, Ali A, Bilal M, Rashid SM, Wani AB, Bhat RR, et al. Melatonin and health: insights of melatonin action, biological functions, and associated disorders. Cell Mol Neurobiol. 2023;43:2437–58.
38. Jia C, Tian L, Cheng C, Zhang J, Al-Nusaif M, Li T, et al. α-Synuclein reduces acetylserotonin O-methyltransferase mediated melatonin biosynthesis by microtubule-associated protein 1 light chain 3 beta-related degradation pathway. Cell Mol Life Sci. 2024;81:61.
39. Gilat M, Jackson AC, Marshall NS, Hammond D, Mullins AE, Hall JM, et al. Melatonin for rapid eye movement sleep behavior disorder in Parkinson's disease: a randomised controlled trial. Mov Disord. 2020;35:344–9.
40. Gilat M, Marshall NS, Testelmans D, Buyse B, Lewis SJG. A critical review of the pharmacological treatment of REM sleep behavior disorder in adults: time for more and larger randomized placebo-controlled trials. J Neurol. 2022;269:125–48.
41. Kunz D, Mahlberg R. A two-part, double-blind, placebo-controlled trial of exogenous melatonin in REM sleep behaviour disorder. J Sleep Res. 2010;19:591–6.
42. Jun JS, Kim R, Byun JI, Kim TJ, Lim JA, Sunwoo JS, et al. Prolonged-release melatonin in patients with idiopathic REM sleep behavior disorder. Ann Clin Transl Neurol. 2019;6:716–22.
43. Yang X, Liu B, Shen H, Li S, Zhao Q, An R, et al. Prevalence of restless legs syndrome in Parkinson's disease: a systematic review and meta-analysis of observational studies. Sleep Med. 2018;43:40–6.
44. Moccia M, Erro R, Picillo M, Santangelo G, Spina E, Allocca R, et al. A four-year longitudinal study on restless legs syndrome in Parkinson disease. Sleep. 2016;39:405–12.
45. You S, Jeon SM, Do SY, Cho YW. Restless legs syndrome in Parkinson's disease patients: clinical features including motor and nonmotor symptoms. J Clin Neurol. 2019;15:321–7.
46. Suzuki K, Okuma Y, Uchiyama T, Miyamoto M, Sakakibara R, Shimo Y, et al. Characterizing restless legs syndrome and leg motor restlessness in patients with Parkinson's disease: a multicenter case-controlled study. Parkinsonism Relat Disord. 2017;44:18–22.
47. Zhang H, Zhang Y, Ren R, Yang L, Shi Y, Vitiello MV, et al. Polysomnographic features of idiopathic restless legs syndrome: a systematic review and meta-analysis of 13 sleep parameters and 23 leg movement parameters. J Clin Sleep Med. 2022;18:2561–75.
48. Wilson H, Giordano B, Turkheimer FE, Chaudhuri KR, Politis M. Serotonergic dysregulation is linked to sleep problems in Parkinson's disease. Neuroimage Clin. 2018;18:630–7.
49. Alex KD, Pehek EA. Pharmacologic mechanisms of serotonergic regulation of dopamine neurotransmission. Pharmacol Ther. 2007;113:296–320.
50. Jhoo JH, Yoon IY, Kim YK, Chung S, Kim JM, Lee SB, et al. Availability of brain serotonin transporters in patients with restless legs syndrome. Neurology. 2010;74:513–8.
51. Allen RP, Barker PB, Horská A, Earley CJ. Thalamic glutamate/glutamine in restless legs syndrome: increased and related to disturbed sleep. Neurology. 2013;80:2028–34.
52. Sobreira-Neto MA, Pena-Pereira MA, Sobreira EST, Chagas MHN, Fernandes RMF, Tumas V, et al. High frequency of sleep disorders in Parkinson's disease and its relationship with quality of life. Eur Neurol. 2017;78:330–7.
53. Sobreira-Neto MA, Pena-Pereira MA, Sobreira EST, Chagas MHN, Almeida CMO, Fernandes RMF, et al. Obstructive sleep apnea and Parkinson's disease: characteristics and associated factors. Arq Neuropsiquiatr. 2019;77:609–16.
54. Shen Y, Shen Y, Dong ZF, Pan PL, Shi HC, Liu CF. Obstructive sleep apnea in Parkinson's disease: a study in 239 Chinese patients. Sleep Med. 2020;67:237–43.
55. Mery VP, Gros P, Lafontaine AL, Robinson A, Benedetti A, Kimoff RJ, et al. Reduced cognitive function in patients with Parkinson disease and obstructive sleep apnea. Neurology. 2017;88:1120–8.
56. Neikrug AB, Liu L, Avanzino JA, Maglione JE, Natarajan L, Bradley L, et al. Continuous positive airway pressure improves sleep and daytime

sleepiness in patients with Parkinson disease and sleep apnea. Sleep. 2014;37:177–85.
57. Kaminska M, Mery VP, Lafontaine AL, Robinson A, Benedetti A, Gros P, et al. Change in cognition and other non-motor symptoms with obstructive sleep apnea treatment in Parkinson disease. J Clin Sleep Med. 2018;14:819–28.
58. Hilker R, Thomas AV, Klein JC, Weisenbach S, Kalbe E, Burghaus L, et al. Dementia in Parkinson disease: functional imaging of cholinergic and dopaminergic pathways. Neurology. 2005;65:1716–22.
59. Xiang YQ, Xu Q, Sun QY, Wang ZQ, Tian Y, Fang LJ, et al. Clinical features and correlates of excessive daytime sleepiness in Parkinson's disease. Front Neurol. 2019;10:121.
60. Simuni T, Caspell-Garcia C, Coffey C, Chahine LM, Lasch S, Oertel WH, et al. Correlates of excessive daytime sleepiness in de novo Parkinson's disease: a case control study. Mov Disord. 2015;30:1371–81.
61. Amara AW, Chahine LM, Caspell-Garcia C, Long JD, Coffey C, Högl B, et al. Longitudinal assessment of excessive daytime sleepiness in early Parkinson's disease. J Neurol Neurosurg Psychiatry. 2017;88:653–62.
62. Tholfsen LK, Larsen JP, Schulz J, Tysnes OB, Gjerstad MD. Changes in insomnia subtypes in early Parkinson disease. Neurology. 2017;88:352–8.
63. Sobreira-Neto MA, Pena-Pereira MA, Sobreira EST, Chagas MHN, De Almeida CMO, Fernandes RMF, et al. Chronic insomnia in patients with Parkinson disease: which associated factors are relevant? J Geriatr Psychiatry Neurol. 2020;33:22–7.

Publisher's Note