Sleep fragmentation as an important clinical characteristic of sleep disorders in Parkinson's disease: a preliminary study

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Abstract

Background: Sleep disorders are one of the earliest non-motor symptoms of Parkinson's disease (PD). Sleep disorders could, therefore, have value for recognition and diagnosis in PD. However, no unified classification and diagnostic criteria exist to evaluate sleep disorders by polysomnography (PSG). Utilizing PSG to monitor sleep processes of patients with PD and analyze sleep disorder characteristics and their relationship with demographic parameters could aid in bridging this gap. This preliminary study aimed to evaluate the clinical characteristic of sleep disorders in PD using PSG.

Methods: PSG was used to evaluate sleep disorders in 27 patients with PD and 20 healthy volunteers between August 2015 and July 2018 in Fujian Medical University Union Hospital. Total sleep time (TST), sleep efficiency (SE), total wake time, and other parameters were compared between the two groups. Finally, the correlation between sleep disorders and age, disease duration, Unified Parkinson's Disease Rating Scale-III scores, Hoehn-Yahr stage, and levodopa dose were analyzed. The main statistical methods included Chi-square test, two independent samples t test, Fisher exact test, and Pearson correlation.

Results: Sleep fragmentation in the PD group was significantly increased (74.1%) while difficulty falling asleep and early awakening were not, as compared to healthy controls. No significant differences were found in time in bed, sleep latency (SL), non-rapid eye movement (NREM) stage 1 (N1), N1%, N2, N2%, N3%, and NREM% between PD and control groups; but TST (327.96 $\pm$ 105.26 min *vs.* 414.67 $\pm$ 78.31 min, $P = 0.003$), SE (63.26% $\pm$ 14.83% *vs.* 76.8% $\pm$ 11.57%, $P = 0.001$), R N3 (20.00 [39.00] min *vs.* 61.50 [48.87] min, $P = 0.001$), NREM (262.59 $\pm$ 91.20 min *vs.* 337.17 $\pm$ 63.47 min, $P = 0.003$), rapid-eye-movement (REM) (32.50 [33.00] min *vs.* 85.25 [32.12] min, $P < 0.001$), REM% (9.56 $\pm$ 6.01 *vs.* 15.50 $\pm$ 4.81, $P = 0.001$), REM sleep latency (157.89 $\pm$ 99.04 min *vs.* 103.47 $\pm$ 71.70 min, $P = 0.034$) were significantly reduced in PD group.

Conclusion: This preliminary study supported that sleep fragmentation was an important clinical characteristic of sleep disorders in PD. Whether sleep fragmentation is a potential quantifiable marker in PD needs to be further investigated in the future study.

Keywords: Parkinson's disease; Sleep fragmentation; Polysomnography; Clinical characteristic

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease, with clinical manifestations including dyskinesia symptoms, as well as non-motor symptoms such as autonomic and sensory symptoms, olfactory dysfunction, and cognitive impairment and sleep disorders. Researchers and clinicians have been primarily concerned with manifestations of dyskinesia, while non-motor disorders were typically ignored.

Currently, mental, cognitive, and sleep disorders are considered the three most common non-motor dysfunctions that cause morbidity and mortality in patients with PD with sleep disorders being the most common.[1,2] Investigation in a community-based patients with PD sample concluded that sleep disorders were prevalent in patients with PD, with incidence of >82%.[3] Therefore, sleep disorders are not rare in patients with PD, which require increased attention from researchers and clinicians.[4] In recent years, there have been major advances in our understanding of the relationship between sleep disorders and PD, yet many questions remain unanswered.[5,6] Sleep disorder-specific mechanisms in PD are unknown, but may be associated with latent neural degeneration, motor and non-motor dysfunction, and dopamine replacement therapy.[7] Sleep disorders in PD are complex and diverse, and include insomnia, nightmare, rapid-eye-movement (REM) sleep behavior disorder, periodic limb movement disorder, restless legs syndrome, sleep fragmentation (SF), excessive daytime sleepiness,

sleep apnea syndrome (SAS), and sleep attacks, all of which seriously impact quality of life in patient with PD.[6]

Nowadays, more and more attention has been paid to the study of sleep disorders in PD. REM sleep behavior disorder (RBD) is a biomarker of the early PD.[5] However, it is not known whether other types of sleep disorders are also sensitive markers of PD.

This study adopted polysomnography (PSG) to monitor sleep structure and processes, analyzed manifestations and related influencing factors of their sleep disorders, and investigated potential other types of sleep disorders in patients with PD, aiming to improve clinicians' understanding of the clinical characteristics of sleep disorders in patients with PD.

Methods

Ethical approval

This study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Ethics Committee of the Fujian Medical University Union Hospital. Informed written consent was obtained from all participants prior to their enrollment in this study.

Clinical data and grouping

The 27 patients with primary PD (15 males and 12 females; age range: 49–85 years; mean course of disease: 6.8 ± 3.7 years, with range of 0.2–11.9 years) hospitalized in Department of Neurology of the Fujian Medical University Union Hospital between August 2015 and July 2018 were included. Among them, one patient had a Hoehn-Yahr stage of 1, five patients were stage 2, eight patients were stage 2.5, eight patients were stage 3, four patients were stage 4, and one patient was stage 5. One patient received deep brain stimulation surgery. None of the patients received benzodiazepines, hypnotics, or anti-anxiety/anti-depressant medications. In line with the UK PD Society Brain Bank Clinical Diagnostic Criteria,[8] the enrollment criteria were bradykinesia and one of the following: muscle rigidity, resting tremor (4–6 Hz), or postural balance disorder (not caused by visual, vestibular, cerebellar, or proprioceptive sensation). Exclusion criteria included: (1) essential tremor; (2) secondary Parkinson's syndromes and Parkinsonism-plus syndromes; or (3) patients with PD concurrently suffering from other mental disorders and severe cardiopulmonary diseases that influenced sleeping.

For the control group, 20 middle-aged and elderly individuals complaining of abnormal sleep, without obvious central nervous system disorders (as determined through head computed tomography or magnetic resonance imaging), other mental disorders or severe heart and lung diseases that influenced sleep were voluntarily included. Among them, there were 14 males and six females with age ranging from 49 to 74 years (mean age: 64.2 ± 7.7 years). No volunteers received benzodiazepines, hypnotics, or anti-anxiety/anti-depressant medications.

Patients with PD with sleep disorders were divided into early onset (≤50 years old) and late-onset groups (>50 years old) based on onset age; ≤5 years and >5 years groups based on course of disease; tremor dominant group, akinetic-rigid dominant group and postural instability and gait disorder (PIGD) dominant group based on clinical manifestations; and early-stage group and advanced stage group based on Hoehn-Yahr staging.

PSG evaluation

Cadwell Easy II™ digital PSG software (Cadwell Laboratories, Kennewick, WA, USA) was used for sleep scoring.

PSG sleep staging criteria: according to the Manual for the Scoring of Sleep and Associated Events Rules published by the American Academy of Sleep Medicine in 2007, sleep is divided into non-REM (NREM) and REM sleep. NREM includes sleep stages N1, N2, and N3. Stage W (waking period): within the record frame of 30 s, occipital α rhythm (8–13 Hz) accounts for more than 50% of the record frame; or occurrence of one of the following while the recording frame lacks α rhythm: (A) Eye blink frequency of 0.5 to 2.0 Hz; (B) eye movements in reading; (C) irregular conjugate REM accompanied by normal or enhanced sub-mental electroencephalogram (EEG). Sleep stage N1: Patients with α rhythm have a weakened rhythm and visible low-amplitude mixed-frequency EEG activity (>50% of one frame); in subjects without α rhythm, one of the following appears: (A) brain waves showed reduced EEG background frequency of ≥1 Hz compared with stage W; (B) vertex sharp waves; (C) slow eye movement. Sleep stage N2: EEG with sleep spindles and K-complexes; spindle frequency from 11 to 16 Hz, and sleep spindles >0.5 s and in the central area; K-complexes >0.5 s and in the forehead; stage N2 continues until awake, large body movement, stage N3 or REM. Sleep stage N3: δ wave (0.5–2.0 Hz) with high-amplitude (≥75 μV) appears in frontal lead EEG, accounting for at least 20% of one frame, sleep spindles sustainable; stage N3 continues to N2 stage, REM or awakening. REM sleep: visible low-amplitude mixed-frequency EEG activity presenting as low-voltage θ waves (3–7 Hz), "α waves with a low frequency" (1–2 Hz slower than stage W), observable sawtooth waves (2–6 Hz); sub-mental electro-myography (EMG) with nearly flat activity and REM; REM stage continues until stage N1 and N2, occurs in K-complexes without eye movement, or continues until awakening.

Physiological sleep parameters included: (1) Time in bed (TIB; min): total time between turning lights on and off. (2) Total sleep time (TST; min): sum of sleep time in stage N1, N2, N3, and REM. (3) Sleep efficiency (SE; %): Ratio of TST to recording time for sleep in laboratory examination (namely TST × 100/TIB), usually with >85% as normal clinical practice. (4) Total wake time (TWT; min): the number of waking minutes in bed. (5) Sleep latency (SL; min): the time of stage N1 sleep from lights off to 3 min after the first frame, which occurs between 10 and 30 min. (6) REM sleep latency (REM-SL; min): REM sleep time from lights off to the first frame. (7) N1%: percent time in NREM sleep stage N1 in TST; N2%: percent time in

NREM sleep stage N2 in TST; N3%: in NREM sleep stage N3 in TST; NREM%: percent time in NREM sleep in TST; REM%: percent time in REM sleep in TST.

SL >30 min in PSG was considered difficulty of falling asleep. More than three arousals exceeding 5 min at night was considered as SF; waking up 1 h before the end of PSG monitoring and failure to fall asleep again after waking up were considered as early awakening

Research methods

Neurologists collected all clinical data via face-to-face interview, examination, and evaluation. All rating scales were completed once and the questionnaire was conducted through patient and family recall. Recorded data included: age, gender, age of onset, disease course, type and dopamine dose, and average daily levodopa equivalent dose (LDE) as calculated by:

LDE = standard levodopa tablets × 1 + levodopa controlled-release tablets × 0.75 + pergolide mesylate tablets × 100 + bromocriptine mesilate tablets × 10 + (standard levodopa tablets × 1 + levodopa controlled-release tablets × 0.75) × 0.33 (entacapone tablets were administrated at the same time) + methanesulfonic acid alpha-dihydroergocryptine tablets × 1.7 + piribedil sustained-release tablets × 1 + pramipexole hydrochloride tablets × 100 + selegiline hydrochloride tablets × 10.[9-11]

The Unified Parkinson's Disease Rating Scale (UPDRS)-III was applied to evaluate dyskinesia in patients with PD. Hoehn-Yahr staging was used to evaluate motor function of patient with PD.

Overnight PSG was conducted, with EEG, electronystagmogram, electrocardiogram, snore, oronasal airflow, submental EMG, blood oxygen saturation, thoracic and abdominal breathing, leg movement, and body position monitored. Sleep behavior disorder and sleep staging were recorded with infrared video to determine the nature. TST, SE, TWT, SL, REM-SL, N1%, N2%, N3%, NREM%, and REM% of the two groups were compared and used to investigate manifestations of sleep disorders. One week before PSG, analeptic and hypnotic drugs were forbidden. Patients were required to go to sleep in the laboratory 1 h earlier than their regular sleep time, for acclimation to sleep monitoring and examination purposes. Upon

electrode placement and impedance was detected, PSG monitoring was monitored overnight (minimum 7 h). According to standard methods, EEG signals in F3–A2, F4–Cl, C3–A2, C4–A1, 01–A2, and 02–A1 were synchronously recorded using a surface disk electrode. Sub-mental EMG was recorded using two surface electrodes; eye movement was recorded, by placing an electrode 1 cm superior and inferior outside the right and left outer canthi; respiratory motion of the thorax and abdomen was recorded by impedence-type thoracic and abdominal motion sensor; oronasal airflow and snore were recorded with a pressure-type sensor placed in the nasal vestibule; limb movement was recorded by a displacement transducer fixed on both legs; posture of the body was recorded using a chest-fixed sensor; and blood oxygen saturation of the right index finger was monitored with a blood oxygen saturation sensor.

Statistical analysis

The data with normal distribution were expressed as mean ± standard deviation, and as median (interquartile range) for data with abnormal distribution. Differences in the PSG sleep parameters between PD group and control group were calculated by Chi-square test, Mann-Whitney U test or two independent samples t test. A Fisher exact probability test was applied to compare the incidence of different sleep disorders between PD and control groups. Correlations of partial sleep parameters obtained by PSG monitoring in the PD group were analyzed by Pearson correlation analysis. All data were analyzed with SPSS version 17.0 statistical software (SPSS Inc., Chicago, IL, USA). A $P < 0.05$ was considered as statistical significance.

Results

General data comparison

Forty-seven subjects were included in this study, including 27 patients with PD and 20 controls. No statistical differences were found in age or gender between the two groups ($P > 0.05$) [Table 1]. The clinical characteristics of patients with PD with sleep disorders were as follows: early-onset (≤50 years) in five patients (18.5%), and late-onset (>50 years) in 22 patients (81.5%); disease duration ≤5 years in nine patients (33.3%) and >5 years in 18 patients (66.7%); PIGD-dominant in eight patients (29.6%), akinetic-rigid-dominant in 12 patients (44.4%),

Table 1: Clinical characteristics of the PD group and the control group in this study.

Characteristics	Control group (n = 20)	PD group (n = 27)	Statistical value	P
Male/female, n	14/6	15/12	1.014[*]	0.314
Age (years), mean ± SD	64.2 ± 7.7	63.9 ± 9.3	–0.102[†]	0.919
Duration of diseases (years), mean ± SD	–	6.8 ± 3.7		
Age of onset (years), mean ± SD	–	57.6 ± 9.1		
UPDRS-III score, mean ± SD	–	36.7 ± 18.1		
LDE (mg/d), mean ± SD	–	533.1 ± 244.6		

[*]Chi-square test, [†]t test. PD: Parkinson's disease; SD: Standard deviation; UPDRS: Unified Parkinson's disease rating scale; LDE: Levodopa equivalent dose.

and tremor-dominant in seven patients (25.9%); Hoehn-Yahr stage ≤2.0 in six patients (22.2%) and >2.0 in 21 patients (77.8%).

Incidence of different sleep disorders between the PD group and the control group

Incidence of SF in PD group was higher than that of control group ($P = 0.019$) [Table 2]. However, the incidence of difficulty falling asleep and early awakening between the two groups was not significantly different ($P > 0.05$). No

Table 2: Comparison of the prevalence of sleep disorders with different types between the PD group and the control group.

Items	Control group (n = 20)	PD group (n = 27)	χ^2 value	P
Difficulty falling asleep	3 (15.0)	7 (25.9)	0.296	0.586
Sleep fragmentation	8 (40.0)	20 (74.1)	5.539	0.019
Early awakening	4 (20.0)	9 (30.0)	1.021	0.312

The data are shown as n (%). PD: Parkinson's disease.

statistical differences were found in age, gender, disease duration, age onset, UPDRS-III score and LDE between patients with PD with fragmented sleep or not ($P > 0.05$) [Table 3].

PSG sleep parameters in the PD group and the control group

No significant differences were found in TIB, SL, N1, N1%, N2, N2%, N3%, and NREM% between the two groups ($P > 0.05$) [Table 4]. Compared with the control group, TST, SE, REM-SL, N3, NREM, REM, and REM% decreased significantly in the PD group (all $P < 0.05$), while REM-SL and TWT increased significantly (all $P < 0.05$).

PSG sleep parameters in PD group with different disease courses

No significant differences in TIB, TST, SE, TWT, REM-SL, N1, N1%, N2, N2%, N3, NREM%, REM, or REM% between the diseases duration ≤5 years and >5 years groups were observed ($P > 0.05$) [Table 5]. Compared with

Table 3: Clinical characteristics of PD patients with sleep fragmentation or not.

Characteristics	Sleep fragmentation (n = 20)	No sleep fragmentation (n = 7)	Statistical value	P
Male/female, n	12/8	3/4		0.662[*]
Age (years), mean ± SD	65.7 ± 9.3	58.7 ± 7.7	1.773[†]	0.088
Duration of diseases (years), mean ± SD	6.8 ± 3.8	6.7 ± 3.9	0.080[†]	0.937
Age of onset (years), mean ± SD	59.2 ± 9.6	52.8 ± 5.5	1.643[†]	0.113
UPDRS-III score, mean ± SD	39.95 ± 17.80	27.29 ± 16.67	1.645[†]	0.113
LDE (mg/d), mean ± SD	564.69 ± 245.58	245.58 ± 235.72	1.140[†]	0.265

[*]Fisher exact test,[†]t test. PD: Parkinson's disease; SD: Standard deviation; UPDRS: Unified Parkinson's disease rating scale; LDE: Levodopa equivalent dose.

Table 4: Comparison of sleep parameters by polysomnography between the PD group and the control group.

Items	Control group (n = 20)	PD group (n = 27)	Statistical values	P
TIB (min)	540.72 ± 77.60	519.87 ± 108.67	−0.730	0.469
TST (min)	414.67 ± 78.31	327.96 ± 105.26	−3.100	0.003
SE (%)	76.8 ± 11.57	63.26 ± 14.83	−3.386	0.001
TWT (min)	126.00 ± 67.85	191.91 ± 81.57	2.936	0.005
SL (min)	21.25 (20.50)	21.50 (32.00)	−0.968	0.333
REM-SL (min)	103.47 ± 71.70	157.89 ± 99.04	2.185	0.034
N1 (min)	66.02 ± 34.00	56.41 ± 26.67	−1.087	0.283
N1%	16.65 ± 9.58	17.89 ± 9.17	0.449	0.655
N2 (min)	216.37 ± 70.82	177.65 ± 93.50	−1.550	0.128
N2%	51.55 ± 11.75	53.26 ± 18.55	0.361	0.720
N3 (min)	61.50 (48.87)	20.00 (39.00)	−3.303	0.001
N3%	13.75 (9.25)	8.00 (13.00)	−1.852	0.064
NREM (min)	337.17 ± 63.47	262.59 ± 91.20	−3.134	0.003
NREM%	81.52 ± 6.03	80.87 ± 13.96	−0.217	0.829
REM (min)	85.25 (32.12)	32.50 (33.00)	−3.895	<0.001
REM%	15.50 ± 4.81	9.56 ± 6.01	−3.639	0.001

Data are presented as mean ± standard deviation or median (interquartile range). Differences were compared using two independent samples t test for mean values and Mann-Whitney U test for median values. PD: Parkinson's disease; TIB: Time in bed; TST: Total sleep time; SE: Sleep efficiency; TWT: Total wake time; SL: Sleep latency; REM-SL: REM sleep latency; N1: NREM stage 1; N2: NREM stage 2; N3: NREM stage 2; NREM: Non-rapid eye movement; REM: Rapid eye movement.

with the duration of disease >5 years group, SL in the duration of disease ≤5 years group was significantly lower (P < 0.05).

PSG sleep parameters among PD groups with different types of dyskinesia

According to the UPDRS-III, movement disorders were classified into tremor, akinetic-rigid and PIGD dominant types. Among them, tremor score was the sum of the 20th and 21st item scores; the score of akinetic-rigid

score was the sum of 18th, 19th, 22nd to 25th, and 31st item scores; PIGD score was the sum of the 26th to 30th item scores.[12,13]

Pairwise comparison among the three-movement disorder groups revealed no significant difference in TIB, TST, SE, TWT, SL, REM-SL, N1, N2, N2%, N3, N3%, NREM, NREM%, REM, or REM% (P > 0.05) [Table 6]. In addition, comparison between the akinetic-rigid dominant and PIGD dominant type groups as well as the tremor dominant and PIGD dominant type groups

Table 5: Comparison of sleep parameters by polysomnography in the PD group with different durations.

Items	Disease duration ≤5 years (n = 9)	Disease duration >5 years (n = 18)	Statistical values	P
TIB (min)	546.61 ± 120.74	506.50 ± 103.12	0.901	0.376
TST (min)	367.44 ± 135.37	308.22 ± 84.16	1.404	0.173
SE (%)	66.56 ± 15.82	61.61 ± 14.50	0.811	0.425
TWT (min)	179.17 ± 82.41	198.28 ± 82.77	−0.566	0.576
SL (min)	18.94 ± 13.71	41.75 ± 37.26	−2.303	0.030
REM-SL (min)	112.94 ± 67.74	180.36 ± 106.01	−1.730	0.096
N1 (min)	69.39 ± 35.98	49.91 ± 18.55	1.873	0.073
N1%	21.33 ± 14.60	16.17 ± 4.34	1.406	0.172
N2 (min)	199.39 ± 115.31	166.78 ± 82.08	0.850	0.404
N2%	52.67 ± 21.00	53.56 ± 17.84	−0.115	0.909
N3 (min)	12.50 (46.00)	31.25 (30.25)	−1.004	0.316
N3%	3.00 (16.50)	10.50 (11.75)	−1.185	0.236
NREM (min)	294.06 ± 100.20	246.86 ± 84.91	1.283	0.211
NREM%	81.64 ± 12.00	80.48 ± 15.15	0.201	0.842
REM (min)	37.89 ± 25.98	30.94 ± 24.62	0.679	0.504
REM%	9.56 ± 4.19	9.56 ± 6.86	0.000	1.000

Data are presented as mean ± standard deviation or median (interquartile range). Differences were compared using two independent samples t test for mean values and Mann-Whitney U test for median values. PD: Parkinson's disease; TIB: Time in bed; TST: Total sleep time; SE: Sleep efficiency; TWT: Total wake time; SL: Sleep latency; REM-SL: REM sleep latency; N1: NREM stage 1; N2: NREM stage 2; N3: NREM stage 2; NREM: Non-rapid eye movement; REM: Rapid eye movement.

Table 6: Comparison of sleep parameters by polysomnography in the PD group with different types of dyskinesia.

Items	Tremor-dominant group (n = 7)	Akinetic-rigid-dominant group (n = 12)	PIGD-dominant group (n = 8)	Tremor dominant vs. akinetic-rigid dominant		Akinetic-rigid dominant vs. PIGD dominant		Tremor dominant vs. PIGD dominant	
				Statistical values	P	Statistical values	P	Statistical values	P
TIB (min)	493.21 ± 129.29	528.67 ± 88.57	530.00 ± 127.46	−0.712	0.486	−0.028	0.978	−0.554	0.589
TST (min)	296.14 ± 89.95	355.63 ± 124.30	314.31 ± 86.02	−1.103	0.285	0.815	0.425	−0.400	0.696
SE (%)	60.71 ± 11.73	66.83 ± 17.17	60.12 ± 14.02	−0.832	0.417	0.917	0.371	0.087	0.932
TWT (min)	197.07 ± 77.89	173.04 ± 86.37	215.69 ± 80.66	0.605	0.553	−1.110	0.282	−0.453	0.658
SL (min)	35.50 (36.00)	19.75 (34.38)	22.00 (71.38)	−0.930	0.352	−0.617	0.537	−0.579	0.563
REM-SL (min)	167.50 ± 111.10	183.25 ± 102.12	111.44 ± 76.19	−0.314	0.757	1.694	0.108	1.153	0.270
N1 (min)	63.50 ± 29.16	51.50 ± 30.08	57.56 ± 19.91	0.848	0.408	−0.499	0.623	0.466	0.649
N1%	23.71 ± 15.18	14.50 ± 5.68	17.88 ± 3.18	1.544	0.167	−1.520	0.146	0.998	0.354
N2 (min)	134.71 ± 70.88	225.46 ± 108.71	143.50 ± 49.95	−1.966	0.066	2.276	0.037	−0.281	0.784
N2%	45.29 ± 16.62	61.75 ± 18.95	47.50 ± 15.87	−1.906	0.074	1.753	0.097	−0.264	0.796
N3 (min)	20.00 (52.00)	18.50 (36.22)	37.50 (35.38)	−0.423	0.672	−1.583	0.113	−0.811	0.417
N3%	6.00 (14.00)	5.50 (11.50)	13.50 (14.30)	−0.551	0.582	−1.546	0.122	−1.046	0.295
NREM (min)	225.86 ± 82.67	299.08 ± 107.09	240.00 ± 52.88	−1.553	0.139	1.635	0.120	−0.400	0.695
NREM%	78.27 ± 20.57	83.98 ± 9.75	78.48 ±1 3.47	−0.826	0.420	1.062	0.302	−0.023	0.982
REM (min)	30.50 (24.00)	31.75 (27.62)	34.00 (41.63)	−0.592	0.554	0.000	1.000	−0.290	0.772
REM%	10.00 (8.00)	10.00 (7.50)	9.50 (15.50)	−0.043	0.966	0.000	1.000	−0.116	0.908

Data are presented as mean ± standard deviation or median (interquartile range). Differences were compared using two independent samples t test for mean values and Mann-Whitney U test for median values. PD: Parkinson's disease; PIGD: Postural instability and gait disorder; TIB: Time in bed; TST: Total sleep time; SE: Sleep efficiency; TWT: Total wake time; SL: Sleep latency; REM-SL: REM sleep latency; N1: NREM stage 1; N2: NREM stage 2; N3: NREM stage 2; NREM: Non-rapid eye movement; REM: Rapid eye movement.

revealed no significant differences in N2 ($P > 0.05$), but compared with the akinetic-rigid dominant group, N2 was significantly lower in the PIGD-dominant group ($P < 0.05$).

PSG sleep parameters in different staged of PD group

PSG sleep parameters, including TIB, TST, SE, TWT, SL, REM-SL, N1, N1%, N2, N2%, N3, N3%, NREM, NREM%, REM, and REM%, were not significantly different between the early and advanced stage group ($P > 0.05$) [Table 7].

PD partial sleep parameter correlation

Correlations between PSG-obtained partial sleep parameters (including TST, SE, TWT, REM, and REM%) and factors (including age, course of disease, UPDRS-III score, Hoehn-Yahr stage, and LDE) were analyzed in the PD group, but no apparent correlations were observed [Table 8].

Discussion

Internationally, PSG is recognized as the gold standard for sleep disorder diagnosis and an important means for the differential diagnosis of various sleep disorders. As such, it has been widely applied in clinical and scientific research on the subject. Through monitoring a variety of sleep-associated physiological parameters, PSG has great significance in clinical diagnosis and analysis in various sleep disorders in patients with PD. Relevant studies in recent years suggested sleep disorders are one of the most common non-motor symptoms of PD,[14] and its manifestations in PD are complex and diverse. The prevalence of insomnia in PD is 30.0% to 86.8% in China.[4] Key factors related with insomnia of PD include female gender, disease duration of PD, depression, anxiety, and others, which may lead to SF. More than three arousals exceeding 5 min at night is considered as SF. Main causes related to SF include night motor dysfunction and nocturia.[7] Prior PSG studies have concluded that the characteristics of sleep structure in patients with PD were divergent,[15-17] and most findings suggested that sleep disorders were characterized by prolonged SL, reduced SE, difficult sleep

Table 7: PSG sleep parameters in the PD patients with different stages in this study.

Items	Early stage groups (n = 6)	Advanced stage groups (n = 21)	Statistical values	P
TIB (min)	533.00 ± 92.70	516.12 ± 114.62	0.330	0.744
TST (min)	355.33 ± 94.89	320.14 ± 108.92	0.715	0.481
SE (%)	66.67 ± 14.49	62.29 ± 15.14	0.630	0.534
TWT (min)	177.67 ± 78.79	195.98 ± 83.78	−0.048	0.637
SL (min)	18.25 (26.25)	22.50 (32.75)	−0.671	0.502
REM-SL (min)	200.17 ± 71.36	145.81 ± 103.87	1.195	0.243
N1 (min)	64.92 ± 24.11	53.98 ± 27.40	0.883	0.386
N1%	21.33 ± 15.51	16.90 ± 6.67	1.046	0.306
N2 (min)	185.83 ± 124.11	175.31 ± 86.53	0.239	0.813
N2%	48.83 ± 25.48	54.52 ± 16.65	−0.656	0.518
N3 (min)	16.25 (35.37)	29.50 (37.25)	−0.642	0.521
N3%	4.00 (10.23)	11.00 (14.00)	−1.023	0.306
NREM	273.08 ± 93.00	259.60 ± 92.77	0.314	0.756
NREM%	77.13 ± 15.26	81.93 ± 13.77	−0.736	0.468
REM	30.67 ± 21.57	34.00 ± 26.09	−0.285	0.778
REM%	8.33 ± 4.68	9.90 ± 6.40	−0.557	0.583

Data are presented as mean ± standard deviation or median (interquartile range). Differences were compared using two independent samples t test for mean values and Mann-Whitney U test for median values. PSG: Polysomnography; PD: Parkinson's disease; TIB: Time in bed; TST: Total sleep time; SE: Sleep efficiency; TWT: Total wake time; SL: Sleep latency; REM-SL: REM sleep latency; N1: NREM stage 1; N2: NREM stage 2; N3: NREM stage 2; NREM: Non-rapid eye movement; REM: Rapid eye movement.

Table 8: Pearson analysis between the polysomnography-obtained partial parameters and factors in the PD group.

Parameters	Age		Disease duration		UPDRS-III score		Hoehn-Yahr stage		LDE	
	r	P	r	P	r	P	r	P	r	P
TST	−0.108	0.592	−0.161	0.423	−0.255	0.199	−0.147	0.463	−0.156	0.437
SE	−0.279	0.158	−0.148	0.461	−0.254	0.202	−0.215	0.281	−0.081	0.690
TWT	0.338	0.085	0.177	0.376	0.246	0.217	0.235	0.239	−0.014	0.944
REM	0.114	0.571	−0.140	0.487	0.206	0.303	0.219	0.272	−0.004	0.986
REM%	0.204	0.308	−0.053	0.793	0.449	0.019	0.405	0.036	0.072	0.723

PD: Parkinson's disease; UPDRS: Unified Parkinson's disease rating scale; LDE: Levodopa equivalent dose; TST: Total sleep time; SE: Sleep efficiency; TWT: Total wake time; REM: Rapid eye movement.

maintenance, decreased slow-wave sleep, and increased limb movement during night-time sleep, etc.

This study evaluated the types of sleep disorders in patients with PD using PSG, and found that there was no obvious difference in the difficulty of falling asleep or early awakening between the PD group and the control group, while there was a higher incidence of SF in the PD group than the control group [Table 2]. Patients with PD rarely complained of SF, but this symptom was common in PSG. SF can occur in any sleep phase, and it is more common during the shallow sleep (NREM sleep stage 1 and 2), which is in line with a report by Askenasy et al[18] on the treatment of sleep disorders in PD. This study showed that patients with PD suffered from frequent sleep disruption, which affected sleep quality. Norlinah et al[19] found that factors influencing SF at night in patients with PD were numerous, including cramps, night-time limb movement disorder, increased muscle tension and SAS, as well as age and course of disease. These influenced result in prolonged awake time after sleep and consequent daytime fatigue and sleepiness.[14] Concerning sleep structure changes, TST, SE, N3, NREM, REM, and REM% in the PD group were significantly reduced, while TWT was elevated [Table 4]. These findings were consistent with most reports,[20,21] suggesting that patient with PD sleep abnormalities might result from nerve nuclei degeneration and a subsequent imbalance in neurotransmitters, which further disrupts the physiological sleep-wake cycle. Also, decreased slow-wave sleep may be related to reduced high-amplitude low-frequency δ waves in night-time sleep EEGs caused by the disease. Considering the relatively long disease course of patients with PD included in this study, decreased REM and REM% might be related with large doses of dopaminergic drugs. Therefore, attention to the effect of dopaminergic drugs on sleep structure is required to adequately choose therapeutic drugs according to patients' clinical symptoms. Although no significant differences in SL of REM sleep between the two groups were observed, mean REM-SL in the PD group exceeded normal REM-SL values,[22] and the mean REM-SL in control group was in the normal range. Therefore, prolonged SL in REM sleep is a likely characteristic of PD, and has a certain diagnostic value.

PSG results helped in dividing PD patients with sleep disorders into early and late onset groups, disease course ≤5 years and >5 years groups, different types of dyskinesia, and early and advanced stage groups based on Hoehn-Yahr staging. Sleep parameter analysis revealed that N3% in late-onset group was significantly lower than that of the early onset group, suggesting N3 stage sleep (slow-wave sleep) might be the most affected by age. Moreover, age greatly influences sleep; therefore, reduced N3% in relatively older patients may have little clinical significance. Compared with disease course >5 years group, N3% in the ≤5 years group significantly decreased, while NREM markedly increased. There were no significant differences in PSG sleep parameters between different types of patients with PD in the incidence and manifestation of sleep disorders, which was inconsistent with

previous research.[23] This might be due to subject heterogeneity, or grouping methods for dyskinesia and determining methods for sleep disorders in these two studies. Furthermore, there were significant in correlations of REM% with UPDRS-III score and Hoehn-Yahr stage, which supported the findings of prior reports. It might be related to neuropathological changes in PD.[11,24]

It is well known that RBD is a biomarker of PD. However, it is not known whether SF is also a sensitive marker of PD. This research found that SF was an important clinical characteristic of sleep disorders in PD, which could be quantitatively assessed by PSG.

Sleep disturbance including SF is a risk factor for a range of psychiatric conditions,[25-27] including anxiety, depression, cognitive decline, and drug addiction. SF in PD might be associated with anxiety, depression, impulse control disorders, and other psychiatric symptoms. However, the molecular, cellular, and circuit mechanisms of sleep disorder including SF are not well understood. Lower cortical gray matter volume in the lateral orbitofrontal cortex and inferior frontal gyrus pars orbitalis was associated with greater SF in older adults.[28] Ge et al[29] showed medial habenula cholinergic output neurons were sensitive to chronic SF, and also identified a key molecular substrate TWIK-like acid-sensitive K+ channel 3 (TASK-3, also named KCNK9) activity reduced following sleep fragmentation

In conclusions, SF is high rate in patients with PD. This preliminary study supported that SF was an important clinical characteristic of sleep disorders in PD. Sleep fragmentation might be a potential quantifiable marker in PD but still there are issues to be overcome in the future study. As the work here will be used to expand the sample size in multi-center, SF may be a marker in assessment of progression of PD, through the sleep disorders of detection with PSG. Further work is needed to clarify whether this is a consequence of or contributor to SF.

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Conflicts of interest

None.

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