RESEARCH PAPER

Sleep and REM sleep behaviour disorder in Parkinson's disease with impulse control disorder

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ABSTRACT

Introduction Because the association between rapid eye movement sleep behaviour disorder (RBD) and impulse control disorders (ICDs) in Parkinson's disease (PD) has been debated, we assessed the sleep characteristics and the frequency of RBD using video-polysomnography (v-PSG) in patients with PD with versus without ICDs.

Methods Eighty non-demented patients with PD consecutively identified during routine evaluation at three movement disorders centres were enrolled in a case–control study. Forty patients (22 men; mean age: 62.6±9.7 years, Hoehn & Yahr: 2.1±0.6) with one or more current ICDs were age-matched and sex-matched with 40 patients with no history of ICDs (22 men, mean age: 64.9±7.8 years, Hoehn & Yahr: 2.2±0.6). They underwent a detailed sleep interview followed by a full-night in-lab v-PSG. Sleep was scored blindly to ICDs condition and RBD diagnosis included a clinical complaint of enacted dreams and/or documented behaviour during rapid eye movement (REM) sleep, with the presence of quantified REM sleep without atonia (RSWA).

Results Patients with ICDs had a higher arousal index and higher RSWA than those without ICDs (51.9%±28.2%vs 32.2±27.1%, p=0.004). In addition, RBD was more frequent in the ICD group (85%vs53%, p=0.0001). RBD was still associated with ICDs in a multivariate regression analysis including age of onset, PD duration and severity, treatment duration, levodopa-equivalent and dopamine agonist-equivalent daily doses and antidepressant use (OR: 4.9 (95% CI 1.3 to 18.5), p=0.02).

Conclusions This large, controlled series of patients with PD with ICDs assessed by v-PSG confirms the association between ICDs and RBD. Increased surveillance of symptoms of ICDs should be recommended in patients with PD with RBD.

INTRODUCTION

Impulse control disorders (ICDs) are potentially serious psychiatric complications in patients with Parkinson's disease (PD) treated with dopaminergic agents. They consist in compulsive and repetitive behaviours that are excessive and/or eventually harmful to oneself or others[1] and include compulsive gambling, sexual behaviour, buying and eating, as well as punding, excessive hobbyism and overuse of dopamine agents, known as dopamine dysregulation syndrome (DDS).[2] The estimated prevalence of ICDs in PD is about 14%[3] or higher according to other reports.[4] Several factors are associated with a higher risk of ICDs in PD, including young age, male sex, previous history of psychiatric disorders and high doses of dopamine agonists.

Subjective sleep disturbances, including reduced sleep efficiency and daytime sleepiness, have been reported in patients with PD with ICDs,[5–7] but no study has assessed video-polysomnographic (v-PSG) features in this population. Recently, we reported an association between ICDs and rapid eye movement sleep behaviour disorder (RBD), a parasomnia characterised by dream enactment behaviour during rapid eye movement (REM) sleep,[8] in a sample of 216 patients with PD assessed using a questionnaire.[9] However, two studies using either a questionnaire or standard criteria to diagnose both RBD and ICDs failed to observe this association.[10 11] The differences between these studies may be ascribed to insufficient power, an insufficient percentage of patients with ICDs, and incomplete age matching, sex matching and severity matching between groups.

We aimed to assess sleep features, including RBD and REM sleep without atonia (RSWA), in a large cohort of patients with PD with ICDs assessed by standard criteria, compared with age-matched and sex-matched patients with PD without a history of ICDs, in order to ascertain whether ICDs are associated with RBD in patients with PD.

PATIENTS AND METHODS

Forty-six non-demented patients diagnosed with idiopathic PD (26 men, mean age: 63.3±8.9 years) and with one or more current ICDs and related behaviours were recruited from consecutive patients with PD consulting at three movement disorder centres, namely the Neurology Service at the Centre Hospitalier Regional Universitaire Gabriel Montpied Hospital in Clermont-Ferrand (n=25), the Pitié-Salpêtrière Hospital in Paris (n=11) and the Department of Neurosciences, University of Turin (n=10) from June 2013 to December 2015. After undergoing v-PSG recording, n=3 patients were excluded due to lack of or insufficient (ie, less than 5 min) REM sleep time and n=3 patients were excluded for obstructive sleep apnoea syndrome. Forty patients were successfully enrolled and

matched for sex, age and severity with 40 non-demented patients with PD received consecutively at the same institutions (n=36 in Clermont-Ferrand and n=4 in Paris) without any history of ICDs.

Diagnosis of PD was performed according to the UK Brain Bank criteria[12] by a neurologist expert in movement disorder (AM, FD, JCC, MZ and LL). Exclusion criteria were the presence of clinical cognitive impairment (as defined by a Mini Mental State Examination score <26),[13] psychosis according to Diagnostic and Statistical Manual of Mental Disorder (DSM)-V criteria,[14] subthalamic nucleus- brain deep stimulation, continuous administration of either enteral levodopa/carbidopa gel (duodopa) or apomorphine. The patients were given a stable dose of dopaminergic drugs for at least 30 days before starting the study. Demographic and clinical data (sex, age, age at onset defined as the occurrence of the first motor symptoms, PD duration, PD severity as measured by both the Hoehn & Yahr scale[15] and the Unified Parkinson's Disease Rating Scale-III subscore,[16] duration of treatment and current treatment dose) were collected for all subjects. The total levodopa and the dopamine agonist-levodopa equivalent daily doses (LEDD and DA-LEDD, respectively) were calculated according to Tomlinson *et al*.[17] When available, sleep habits and history of sleep disorders, including possible parasomnia, were collected from the patient and the bed partner by a neurologist expert in Sleep Medicine (MLF, IA, MZ, AC).

Diagnosis of ICDs was performed after a detailed clinical interview and according to standard criteria[18] by a neurologist expert in movement disorders and psychobehavioural symptoms in PD. Furthermore, French-speaking subjects (n=72) were assessed using the recently validated Ardouin Scale of Behaviour in Parkinson's Disease (ASBPD),[19] a new instrument specifically designed for assessing hypodopaminergic and hyperdopaminergic mood and behaviours. The diagnosis of ICDs was supported by a score ≥2 (moderate severity) in at least one of the items assessing ICD-related hyperdopaminergic behaviours (ie, items 5, 6, 7, 8, 10, 11, 12 and 13 of part III).

All patients underwent one full-night in-lab v-PSG with digital polysomnography according to the recommendations of the American Academy of Sleep Medicine (AASM).[20] Besides the standard leads for sleep stage scoring, additional derivations included bilateral anterior tibialis surface electromyographic (EMG) channels, nasal airflow, thoracic and abdominal respiratory effort, oxygen blood saturation, electrocardiography and microphones.

Sleep stages, arousals, leg movements and respiratory events were scored according to AASM criteria, with allowance for chin EMG muscle tone during REM sleep.[20] Patients with apnoea/hypopnoea index >15 were excluded, in order to avoid excessive arousal-related increase of muscle tone during REM sleep that could potentially affect the quantification of RSWA. No patients were treated with nocturnal non-invasive ventilation or continuous positive airway pressure.

The diagnosis of RBD was performed according to the International Sleep Disorder Classification criteria 3rd edition,[21] namely a history of dream enactment or PSG-documented REM sleep motor behaviours plus a measure of RSWA, as defined by the AASM Manual for the Scoring of Sleep and Associated Events V.2.2.[20]

Scoring of RSWA was performed by a single neurologist and sleep specialist (MF) who was blind to both the presence of ICD and the history of RBD. REM sleep epochs were carefully examined for artefacts, and respiratory arousal-related increases in EMG tone were excluded. Patients who had spent less than 5 min in REM sleep were excluded, since REM duration was believed to be insufficient for a reliable assessment of RSWA. Furthermore, each video-recorded REM sleep period was analysed in order to detect motor behaviours and sleep vocalisations referable to RBD, such as violent and non-violent complex motor activity. The latter was scored according to the RBD Severity Scale[22] and the final RBD severity score was defined according to the most severe episode seen during the sleep recording.

To assess RSWA, each 30 s REM sleep epoch was divided into 3 s mini-epochs, according to the method published by the SINBAR group.[23] REM sleep epochs were carefully examined for artefacts, and increases in EMG tone caused by respiratory arousal were excluded. The percentage of mini-epochs showing any chin muscle activity lasting at least 0.1 s and with an amplitude exceeding twice the background was calculated. REM sleep EMG activity was considered to be abnormal when the percentage of any chin EMG activity was >18%0.[23] Furthermore, percentage of 30 s tonic epochs and of 3 s mini-epochs containing EMG phasic activity were assessed according to the same method.[23]

Standard protocol approvals, registrations and patient consents

The protocol was approved by the local hospital's ethical standards committee on human experiments. All the subjects gave their written informed consent to participate in the study.

Statistical analysis

According to the literature, the proportion of patients with PD with RBD has been estimated at around 50%.[8] Sample size estimation was performed by considering that n=39 patients per group is sufficient to highlight a minimal absolute difference of 30% for a type I error at 5% and a statistical power at 80%. Thus, we decided to include 40 patients per group (with and without ICDs). Statistical analysis was performed using Stata (V.13, StataCorp, College Station, Texas, USA). The tests were two-sided, with a type I error set at $\alpha=0.05$. Demographic and clinical characteristics were presented for each group as mean±SD or as median (IQR) for continuous data (according to statistical distribution; data were assessed for normality using Shapiro-Wilk test), and as the number of patients and associated percentages for categorical parameters. Student's t-test was performed to assess between-group differences on quantitative variables that were normally distributed, while the Mann-Whitney U test was used when assumptions of t-test were not met. Between-group differences for categorical variables were assessed by the Fisher's exact or χ^2 tests. According to the statistical distribution, the Spearman correlation test was employed to study the relationship between the ASBPD subscores on hyperdopaminergic behaviours related to ICDs and RSWA measures.

Variables associated with the presence of ICDs in PD that were considered significant in univariate analyses, or clinically relevant according to the literature, were entered in a multivariate logistic regression analysis to assess the OR (and 95% CI) and ascertain the RBD in the two groups. Random-effects logistic regression was performed to take into account within and between-centre (Clermont-Ferrand, Turin and Paris) variability.

RESULTS

The demographic and clinical data of patients with and without ICDs are shown in table 1. The two groups did not differ in age or sex distribution. Patients with PD with ICDs were younger at PD onset, with a longer duration of disease and a higher total

Table 1 Demographic and clinical characteristics of patients with PD with and without impulse control disorders (ICD)

	With ICDs (n=40)	Without ICDs (n=40)	p
M/F (%M)	22/18 (55%)	22/18 (55%)	ns
Age (years)	62.6±9.7	64.9±7.8	ns
Age of onset (years)	51.4±9.9	58.1±7.7	0.001
Duration of PD (years)	10.2±4.6	6.6±3.7	0.0002
Hoehn and Yahr score	2.1±0.6	2.2±0.6	ns
UPDRS-III	17.3±11.4	17.5±9.8	ns
LEDD (mg)	1018.1±362.3	701.0±429.5	0.0006
Dopamine agonist use, N (%)	24/40 (60%)	28/40 (70%)	ns
Mean DA-LEDD (mg)	110.9±124.7	145.8±119.4	ns
History of RBD	37/40 (93%)	21/40 (53%)	<0.0001

DA-LEDD, dopamine agonist-levodopa equivalent daily dose; ICD, impulse control disorder; LEDD, levodopa equivalent daily dose; ns, not significant; PD, Parkinson's disease; RBD, rapid eye movement sleep behaviour disorder; UPDRS-III, Unified Parkinson's Disease Rating Scale-III (Motor Scale).

dose of dopaminergic treatment compared with patients with PD without ICDs. No between-group differences were observed in PD severity assessed by either the Hoehn & Yahr score or the Unified Parkinson's Disease Rating Scale-III score. This was also the case for the percentage of dopamine agonist users and the mean dopamine agonist-levodopa equivalent daily dose.

Data on dopaminergic and psychotropic medications are presented in table 2. There was no significant between-group difference in the use of dopamine agonists such as pramipexole, rotigotine and piribedil, while patients with PD-ICDs were taking less ropinirole compared with those with PD-noICD (p=0.04). Patients with PD-ICDs were taking more benzodiazepines compared with those with PD-noICD (p=0.03), but no between-group difference was observed in antidepressant and antiepileptic use.

Table 3 illustrates the number and type of ICDs and related behaviours in patients with PD-ICDs. Twenty-five patients had one ICD or related behaviour, while 15 had a combination of more than one ICD or related behaviours (n=9 had two concomitant ICDs, n=3 had three concomitant ICDs and n=3 had four ICDs).

Sleep characteristics of patients with and without ICD are shown in table 4. No between-group differences were found in

Table 2 Dopaminergic and psychotropic medications

	PD-ICDs n=40	PD-noICDs n=40	p
Pramipexole, n (%)	12 (30%)	10 (25%)	0.81
Ropinirole, n (%)	3 (7.5%)	10 (25%)	0.04*
Rotigotine, n (%)	7 (17.5%)	6 (15%)	0.77
Piribedil, n (%)	2 (5%)	1 (2.5%)	1.00
Antidepressants § n (%)	13 (32.5%)	7 (17.5%)	0.18
Benzodiazepines†, n (%)	10 (25%)	2 (5%)	0.03*
Antiepileptics‡, n (%)	2 (5%)	2 (5%)	–

*α=0.05
§Including mianserine (n=5), venlafaxine (n=4), paroxetine (n=4), sertraline (n=3), citalopram (n=1), escitalopram (n=1), duloxetine (n=1), fluoxetine (n=1) and bupropion (n=1).
†Including clonazepam (n=6), alprazolam (n=3), lorazepam (n=1), clorazepate (n=1), bromazepam (n=1).
‡Including levetiracetam (n=1), topiramate (n=1), pregabalin (n=1) and gabapentin (n=1).
ICD, impulse control disorders; PD, Parkinson's disease.

Table 3 Number and type of ICDs and related behaviours

Type of ICDs	PD-ICDs (no. of patients)*	PD-noICDs (no. of patients)*	p
Pathological gambling (no. of cases)	11	–	–
Excessive hobbyism or creativity	19	–	–
Punding	10	–	–
Compulsive buying	7	–	–
Compulsive eating	13	–	–
Compulsive sex	3	–	–
Dopamine dysregulation syndrome	1	–	–
ASBPD hyperdopaminergic behaviour subscore (items 5, 6, 7, 8, 10, 11, 12 and 13)	5.2±2.5 (n=32)	0.4±0.7 (n=40)	<0.0001

*n=25 PD-ICD had only one ICD or related behaviours while n=15 had a combination of more than one ICD or related behaviours (n=9 patients had two ICDs, n=3 had three ICDs and n=3 had four ICDs).
ASBPD, Ardouin Scale of Behaviour in Parkinson's Disease; ICD, impulse control disorders; PD, Parkinson's disease.

sleep architecture, except for the overall arousal index which was higher in the ICDs group. The proportion of patients with bed partner did not differ between the two groups (22/40 PD-ICDs vs 20/40 PD-noICDs, p=0.82). Thirty-seven patients (93%) with PD with ICD versus 16 (40%) without ICD reported a history of dream-enacting behaviours (n=35) or screaming and/or vocalisation (n=2), suggesting a clinical RBD (p=0.0001). After v-PSG, 34 (85%) patients with ICD versus 21 (53%) without ICD were diagnosed with RBD based on the presence of a history of dream-enactment behaviours and/or video-documented behaviours and abnormal RSWA (p=0.002). In patients with vPSG-diagnosed RBD, the mean RBD severity score was higher in PD-ICD compared with PD-noICD (p=0.039). Furthermore, mean RSWA, expressed either as a percentage of 3 s mini-epochs containing any chin EMG activity, or as a percentage of 30 s tonic epochs, was significantly higher in PD-ICDs compared with PD-noICDs (p=0.009 and p=0.03, respectively). No between-group difference was found in the pe of 3 s mini-epochs containing EMG chin phasic activity alone.

Six (15%) patients with ICD failed to satisfy the PSG quantitative criteria for RSWA required to diagnose RBD. However, three of them reported a typical history of dream-enacting behaviours and two of them exhibited brief typical behavioural episodes during video-PSG. According to International Classification of Sleep Disorder-3 (ICSD-3), in these three patients, RBD may be provisionally diagnosed, based on clinical judgement.[21] Conversely, among the 19 patients without a history of ICD who did not fulfil PSG criteria for the RBD diagnosis, none had a history of dream-enacting behaviours or behavioural episodes of RBD observed at the v-PSG.

The results of the univariate and multivariate analyses are given in table 5. The multivariate analysis showed that patients with PD with ICDs had an increased probability of having RBD (OR: 4.6, p=0.02, 95% CI 1.3 to 16.5), after adjusting for centres (Clermont-Ferrand, Paris, Turin) as a random effect, and for age of onset, duration and severity of PD, duration of treatment, total LEDD, DA-LEDD and antidepressant use as covariates. No correlation was found between the ASBPD subscore related to ICDs, or the tonic and phasic measures of RSWA.

Table 4 Polysomnographic features and RBD-related variables in patients with PD with ICD (PD-ICD) and without ICD (PD-noICD)

	PD-ICDs (n=40)	PD-noICDs (n=40)	p
Time in bed	473.8±60.3	451.5±67.0	ns
Total sleep time	338.5±93.4	323.9±74.0	ns
Sleep efficiency	72.1±19.1	72.6±19.6	ns
Number of awakenings	27.9±18.1	29.2±21.6	ns
Wake after sleep onset	112.5±86.6	88.2±54.6	ns
% N1	9.6±6.9	10.3±6.2	ns
% N2	54.6±12.7	57.9±12.8	ns
% N3	23.4±14.3	19.8±10.1	ns
% REM sleep	12.5±8.0	12.0±7.8	ns
REM sleep duration (min)	46.0±36.2	39.3±27.8	ns
PLMS index	25.0±25.2	29.4±37.6	ns
AHI	3.0±3.6	3.7±6.1	ns
Arousal Index (AI)	12.6±10.6	8.4±4.8	0.04
AI during NREM sleep	13.3±11.8	9.4±8.0	ns
AI during REM sleep	5.4±3.5	4.2±2.1	ns
History of DEB	37/40 (93%)	16/40 (40%)	<0.0001
v-PSG-confirmed RBD	34/40 (85%)	21/40 (53%)	0.002
RBDSS mean score	1.6±1.1 (n=34)	1.0±0.9 (n=16)	0.039
Mean RSWA			
% of 3 s mini-epochs with any chin EMG activity	42.5±22.2	28.6±22.9	0.009
% of 30 s tonic epoch	51.9±28.2	37.0±30.5	0.03
% of 3 s mini-epochs with chin EMG phasic activity	9.5±6.7	8.3±8.1	ns

AHI, Apnea-Hypopnea Index; DEB, dream-enacting behaviour; EMG, electromyographic; ICD, impulse control disorder; PD, Parkinson's disease; PLMS, Periodic Leg Movements Index; RBD, REM sleep behaviour disorder; RBDSS, REM sleep Behaviour Disorder Severity Scale, according to the most severe episode seen during the sleep recording; REM, rapid eye movement; NREM, NonREM sleep; RSWA, REM sleep without atonia; v-PSG, video-polysomnographic; ns, not significant

DISCUSSION

We found that patients with PD with ICDs, compared with those without ICDs, had increased arousal indexes and RSWA, as well as more frequent v-PSG-confirmed RBD. Indeed, v-PSG-confirmed RBD was found in 85% of patients with PD with ICDs and in only 53% of patients with PD without ICDs. The association between RBD and ICD remained significant after adjusting for variables that were found to differ between the two groups on the basis of univariate analysis (age of onset, PD duration, LEDD) or to be clinically relevant (severity of PD, duration of treatment, DA-LEDD, antidepressant use). Furthermore, three out of the six patients with ICDs who failed to show RSWA at v-PSG (8% of the total group) reported a typical history of dream-enacting behaviours, with two of them presenting brief REM sleep behavioural events during v-PSG, suggesting a 'minor' RBD, which is not uncommon in patients with PD.[8] This condition was recently shown to represent a 'prodromal RBD' in a cohort of patients with PD prospectively assessed over a 2-year period.[24] Thus, when pooling patients with v-PSG-confirmed RBD (n=34) and those with 'minor' RBD, the cumulative frequency of RBD in patients with ICDs rose to 93%. On the other hand, the percentage of RBD found in patients with PD without ICDs was close to that observed in other samples of consecutive patients with PD.[8] Thus, the results of the present study confirm our previous observation of an association between ICDs and RBD.[9]

Conflicting results have been reported concerning the prevalence of ICDs in patients with PD with RBD. In a recent study aimed at evaluating motor and non-motor features associated with questionnaire-assessed RBD for 475 patients with PD, participants with probable RBD were more likely to report symptoms of punding (4.0% vs 10.0%, p=0.02) and of DDS (2.4% vs 7.8%, p=0.01) when using a more stringent cut-off that increased the specificity of the RBD screening questionnaire.[25] Another study conducted with a cohort of 944 patients with PD found an increased frequency of ICDs in PD with probable RBD compared with those without RBD, but the difference was not significant after adjusting for age and disease duration.[10] However, in this study, ICDs were assessed using a modified version of the Minnesota Impulsivity Disorders Inventory, instead of standard diagnostic criteria which do not take into account the whole spectrum of ICDs, leading to their possible underestimation. On the other hand, the only v-PSG study assessing RBD and ICDs in 98 patients with PD failed to find an association between ICDs and RBD.[11] Nevertheless, an overall low rate of RBD was found in this cohort (31%) compared with other studies,[26–28] and only 21 patients with ICDs were included.

To the best of our knowledge, this is the largest cohort of patients with PD with ICDs assessed by v-PSG so far. A few

Table 5 Results of univariate and multivariate analysis in PD with and without ICDs

	PD-RBD (n=55)	PD-noRBD (n=25)	Univariate OR (95% CI)	p	Multivariate OR (95% CI)[1]	p
Sex (M,%)	31 (56%)	13 (52%)	0.84 (0.32 to 2.17)	0.72	0.79 (0.25 to 2.47)	0.69
Age at PD onset	55.0±9.0	56.0±10.3	0.99 (0.94 to 1.04)	0.64	1.04 (0.97 to 1.10)	0.30
PD duration	8.7±4.5	6.5±4.0	1.14 (1.00 to 1.29)	0.04	1.47 (0.93 to 2.34)	0.10
UPDRS-III	17.7±10.2	17.2±9.4	1.01 (0.96 to 1.06)	0.84	1.00 (0.95 to 1.06)	0.91
LEDD ≥730 mg (n,%)§	898 (654; 1248) 37 (67.2 %)	793 (440; 959) 13 (52 %)	1.01 (1.00 to 1.02) 1.90 (0.72 to 4.98)	0.06 0.19	1.48 (0.46 to 4.84)	0.51
DA-LEDD ≥120 mg (n,%)§	105 [0; 210] 27 (49.1%)	180 (0; 240) 15 (60%)	1.00 (0.99 to 1.01) 0.64 (0.25 to 1.68)	0.34 0.36	0.84 (0.27 to 2.67)	0.77
Duration of treatment	7.5±4.5	5.9±3.8	1.10 (0.97 to 1.24)	0.13	0.72 (0.46 to 1.14)	0.16
Antidepressant use	16 (29%)	4 (16%)	2.15 (0.64 to 7.28)	0.22	1.74 (0.42 to 7.27)	0.45
ICDs (n,%)	34 (62%)	6 (24%)	5.12 (1.76 to 14.90)	0.003	4.57 (1.27 to 16.53)	0.02*

*α=0.05
§Median value.
DA-LEDD, dopamine agonist-levodopa equivalent daily dose; ICD, impulse control disorder; LEDD, levodopa equivalent daily dose; PD, Parkinson's disease; RBD, rapid eye movement sleep behaviour disorder; UPDRS-III, Unified Parkinson's Disease Rating Scale-III (Motor Scale).

studies have evaluated sleep in PD with ICDs with several questionnaires showing an increased frequency of sleep disturbances in this population.[5–7] Relationships between sleep disturbances and ICDs are complex and bidirectional.[29] On the one hand, nocturnal hyperactivity, as well as anxiety and depression, may contribute to poorer sleep in patients with ICDs. Also, it has been suggested that behavioural addiction in itself may influence sleep–wake cycle regulation by modulating the expression of the so-called clock genes.[30] On the other hand, sleep deprivation may increase impulsivity and enhance emotional reactivity via a dysfunction of the prefrontal cortex–amygdala interactions.[31 32] Interestingly, in the present study, we did not find any difference between patients with and without ICDs, in terms of sleep architecture variables. This is quite surprising given the fact that patients with PD with ICDs were taking higher doses of dopaminergic therapy, and that both dopamine and dopaminergic agonists may promote wakefulness,[33] restlessness and nightmares.[34] However, in our study, DA-LEDD was similar in patients with and without ICDs. This may suggest that a higher dopamine agonist dose, rather than total LEDD, might have been responsible for the subjective sleep disturbances reported by other studies. On the other hand, altered sleep scores did not correlate to the total dose of dopaminergic drugs in a study involving 30 patients with PD with ICDs.[6] Besides, in our study, only the arousal index was higher in patients with ICD compared with those without ICD, suggesting that the fragmentation of sleep microstructure rather than macrostructure alterations may be responsible for the poor subjective sleep quality reported in patients with PD with ICDs.

Together with sleep fragmentation, nocturnal hyperactivity is frequently observed in patients with ICD, as they may feel the urge to engage themselves in behaviours such as hobbyism, creative activities, internet use or punding, often resulting in severe sleep deprivation. Therefore, the laboratory assessment may have prevented the patients from indulging in their usual nocturnal activities and thus it is possible that the in-lab vPSG was not representative of their typical sleep habits. Nevertheless, it should be pointed out that in this study, no systematic assessment of subjective sleep by sleep questionnaire was performed, and therefore we could not determine whether patients with PD with ICDs have poorer subjective sleep quality compared with those without ICDs. Further studies assessing subjective and objective sleep quality in patients with PD with ICDs may help to elucidate this issue.

The present study has two main strengths. First, the diagnosis of ICDs in PD is difficult, because the severity of the symptoms may fluctuate over time in association with changes in dopaminergic treatment. Thus, subclinical forms of ICDs commonly found in the course of the disease may be difficult to differentiate from clear-cut ICDs. In our study, the diagnosis of ICDs was performed via a semistructured interview according to standard criteria, and it was corroborated in most patients by the use of the ABPDS, a new tool specifically designed to assess behavioural disturbances, including ICDs, and their severity in the PD population.[19] Therefore, only patients with ICDs who had a score ≥2 indicating moderate severity in at least one item related to ICDs were included. In addition, the diagnosis of RBD was performed using the latest diagnostic criteria including quantitative measures of RSWA. Finally, the RSWA scores were determined by a sleep specialist blinded to both ICDs and RBD history in order to minimise any possible bias related to the v-PSG interpretation.

Recently, longitudinal studies point to non-motor symptoms (NMS) as important markers of prognosis and key-defining features of PD subtypes.[35] Among NMS, RBD affects up to 60% of patients with PD and tends to be associated with more severe motor and NMS so that its role as a marker of a more aggressive form of PD is increasingly recognised.[36 37] The pathogenesis of ICDs is not fully understood. The mesocorticolimbic dopaminergic pathway, which includes the ventral tegmental area (VTA), the ventral striatum, the amygdala, the hippocampus and the ventromedial and the orbito-frontal regions of the prefrontal cortex, is known to play a crucial role in reward and impulse control. Changes in dopamine transmission at presynaptic and postsynaptic levels induced by chronic levodopa treatment may predispose to the emergence of ICDs in PD via a sensitisation of an impaired ventral striatal circuitry.[38 39] Hence, it is conceivable that patients with PD with RBD may have more severe alterations in the mesocorticolimbic pathway which would favour the development of ICDs. On the other hand, hyperactivity of the reward system, and particularly of the VTA, is observed during normal REM sleep, probably related to the motivational and hedonic component of the dreams. Furthermore, excitatory projections from VTA to the sublaterodorsal nucleus, a key area for REM sleep state generation and REM sleep atonia, have been identified in animals, suggesting that VTA may participate in the modulation of REM sleep.[40]

To sum up, the present study shows an association between ICDs and vPSG-diagnosed RBD in PD, thus confirming our previous results. This result may have implications for the management of patients with PD and RBD, in which dopamine agonists should be avoided or at least used with caution. Future investigations are warranted in order to elucidate the pathophysiology underlying this association.

Contributors MLF conceptualised the study, interpreted the data and drafted the manuscript. MF analysed and interpreted the data and revised the manuscript for intellectual content; IA interpreted the data and revised the manuscript for intellectual content; MZ participated in the design of the study and revised the manuscript for intellectual content; PB designed the study, analysed the data and revised the manuscript for intellectual content; BP and MP participated in collecting data and revised the manuscript for intellectual content. JCC, AC and LL revised the manuscript for intellectual content; FCD, LL and EB participated in collecting and analysing the data; AM and FD conceptualised the study, interpreted the data and revised the manuscript for intellectual content.

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