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Abstract

Objective. To assess the frequency of symptoms of impulse control disorders (ICD, namely pathological gambling, compulsive sexual behaviour, compulsive eating and compulsive shopping) and related behaviours (hobbyism, punding, walkabout and dopamine dysregulation syndrome) in patients with Parkinson's disease (PD) with and without probable rapid eye movement, sleep behaviour disorder (pRBD).

Methods. Two hundred and sixteen consecutive PD patients, attending two university-based movement disorders clinics, were screened for p-RBD using the RBD Single Question and the RBD Screening Questionnaire (RBDSQ). Current ICDs and related behaviours symptoms were assessed with the Questionnaire for Impulsive-Compulsive Disorders in PD (QUIP)-short form.

Results. PD-pRBD patients (n=106/216;49%) had a longer PD duration, a higher Hoehn & Yahr score, a greater levodopa-equivalent daily dose (LEDD), but no difference in dopamine agonist use, compared to PD-without pRBD. A higher proportion of one or more current ICDs and related behaviours symptoms was reported in PD-pRBD compared to PD-without RBD (53% vs28%; p=0.0002). In a multivariate regression analysis accounting for gender, age of onset, PD duration, PD severity, depression score and total and dopaminergic agonist-LEDD, RBD was associated to a relative risk of 1.84 for any ICD or related behaviours symptoms (p=0.01), and to a risk of 2.59 for any ICD symptoms only (p=0.001). Furthermore, PD-pRBD had a more than fourfold risk for symptoms of pathological gambling (relative risk (RR): 4.87; p=0.049) compared to PD-without pRBD.

Conclusions. The present study indicates that RBD is associated with an increased risk of developing symptoms of ICDs in PD. Identifying RBD in PD may help clinicians to choose the best therapeutic strategy.

Trial registration. AU1023 Institutional Ethics CommitteePublished by the BMJ Publishing Group Limited.

Introduction

REM sleep behaviour disorder (RBD) is a parasomnnia characterised by elaborate motor activity during REM sleep frequently associated to oneiric content. Clinical manifestations are due to the abnormal persistence of muscle tone and/or to increased phasic muscle activity during this sleep stage.[1] Pathophysiology of human RBD is believed to be related to a dysfunctional network involved in motor control during REM sleep mainly located in the brainstem and not completely elucidated.[2] Putative structures promoting REM sleep atonia, including the ventro-mesopontine junction, the pedunculo-pontine and tegmental laterodorsal nuclei (PPN-LTD), the sublaterodorsal nucleus, the Locus Coeuruleus (LC) and the peri-LC area, are thought to project to the spinal motoneuron directly or indirectly via the medullary magnocellular reticular formation. Supratentorial modulatory influences on the REM sleep atonia system are likely, via its reciprocal connections with substantia nigra, limbic areas including the ventral tegmental area and the amygdala, hypothalamus, thalamus, basal forebrain and frontal cortex.[2,3] Up to 50% of the patients with Parkinson's disease have concomitant RBD that may either predate, co-occur or follow the onset of motor symptoms.[4] Growing evidences indicate that patients with Parkinson's disease (PD) and with RBD are more severely impaired in motor and non-motor domains compared to patients with PD-without RBD, suggesting that RBD would be associated with a more widespread degenerative process.[5] Indeed, PD-RBDs were reported to have more rigid-akinetic, rather than tremor-dominant subtype forms, more axial symptoms, more severe L-dopa-induced dyskinesia,[6,7] and worst outcome to subthalamic nuclei deep brain stimulation compared to patients with PD-without RBD.[8] They also show worse cognitive performances,[9] a slower EEG activity,[10] an impairment in visuospatial functions,[11] an increased risk for dementia,[12] as well as a greater autonomic involvement,[13] when compared to PD-without RBD.

Impulsive-Compulsive Behaviours (ICB) are behaviours that are performed repetitively, excessively and/or compulsively and that interfere in major areas of life functioning. ICBs in PD include Impulse Control Disorders (ICD), such as pathological gambling, hypersexuality, compulsive shopping and compulsive eating, as well as other compulsive related behaviours. The latter comprise an intense fascination with complex, excessive, repetitive, non-goal-oriented behaviours, such as punding, walkabout or hobbyism, and overuse of dopamine replacement therapy, also described as dopamine dysregulation syndrome.[14] The prevalence of a history of ICDs and related behaviours diagnosed

according to standard diagnostic criteria in PD is around 31%, whereas one or more active disorders are found in 14% of treated PD patients.[15,16]

Predisposing factors for ICDs in PD include young age, early onset, PD duration, a personal or familiar history of ICDs, substance abuse or bipolar disorder, impulsivity trait. Dopaminergic mesocorticolimbic system is known to play a key role in reward and in impulse control regulation. Changes in dopamine transmission at presynaptic and postsynaptic levels after chronic levodopa treatment may predispose to the emergence of ICDs via a sensitisation of an impaired ventral striatal circuitry.[14] Given the increased severity in motor and non-motor symptoms in patients with PD with RBD, we hypothesised that such patients with RBD may also have more severe alterations in dopaminergic mesocorticolimbic pathway that would make them more susceptible to develop ICDs, compared to those without RBD.

Hence, we aimed to assess the frequency of symptoms of ICDs and related behaviours in PD with probable RBD (PD-pRBD), compared to those without pRBD, in a large cohort of consecutive idiopathic PD patients, and to assess the risk associated with RBD to develop ICDs symptoms in PD.

Methods

Participants

Two hundred and sixteen consecutive patients with diagnosis of idiopathic PD were enrolled in the study. Patients were recruited at the Neurology Service at the CHRU Gabriel Montpied Hospital in Clermont-Ferrand, France (n=150), and at the Parkinson's and Movement Disorders Clinic, Department of Neurosciences, University of Turin, Italy (n=66).

Diagnosis of PD was made according to the UK Brain Bank criteria[17] by a neurologist expert in movement disorder. Patients with clinical cognitive impairment (as defined by a Mini Mental State Examination score <26),[18] with psychosis according to DSM-IV criteria,[19] with previous treatment with deep brain stimulation or continuous administration of enteral levodopa/carbidopa gel (duodopa) or apomorphine were excluded.

Standard protocol approvals, registration and patient consents

The protocol was approved by the local hospital's ethics committee, and all subjects gave written informed consent to participate to the study.

Study outcomes

Demographical and clinical data (sex, age, age of onset, duration of PD, severity of PD as measured by the H&Y scale, current treatment) were collected for all subjects.

In order to assess probable RBD, participants were asked to fill out both the RBD single question (RBD1Q), a recently validated one-question screening tool,[20] and the RBD Screening Questionnaire (RBDSQ).[21] The latter is comprised of 13 questions related to clinical symptoms of RBD and it has been widely employed in general population and in patients with PD.[22] Probable RBD was defined

by a positive answer to the RBD1Q and/or a score ≥6 on the RBDSQ. Participants were then asked to fulfil the short version of the Questionnaire for Impulsive-Compulsive Behaviors in PD (QUIP-current).[15] This is a self-report and self-completed screening instrument specifically developed and validated to detect the presence of current symptoms of ICDs (compulsive gambling, buying, sexual behaviour and eating) and related behaviours (punding, hobbyism, walkabout and dopamine dysregulation syndrome) lasting at least 4 weeks. The presence of any ICD and related behaviours symptoms was defined by any positive answer to the QUIP (QUIP score ≥1), while the presence of ICD symptoms only is defined by one or more positive answers to questions A to D assessing pathological gambling, compulsive sexual behaviour, compulsive eating and compulsive shopping, respectively. Finally, participants fulfilled the depression subscale of the Hospital Anxiety and Depression Scale (HADS)[23] and the Starkstein Apathy Scale,[24] in order to assess symptoms of depression and apathy, respectively. Total Levodopa Equivalent Daily Dose (LEDD) was calculated for every participant according to the formula described elsewhere,[25] as well as the number of dopamine agonists (DA) users and the DA-LEDD, which included pramipexole, ropinirole and rotigotine.

Statistical analysis

Statistical analysis was performed using SPSS software package, V.19 (SPSS, Chicago, Illinois, USA). The tests were two-sided, with a type I error set at α=0.05. Demographical and clinical characteristics were presented as the mean±SD for each group (PD-pRBD and PD-without pRBD) for continuous data, and as the number of patients and associated percentages for categorical parameters. Data were assessed for normality (Shapiro–Wilk test), and Student t tests were performed to assess between-group differences on quantitative variables that were normally distributed, while Mann–Whitney U test was employed when variables were not normally distributed. Between-group differences in categorical variables were assessed by means of χ^2 tests. Spearman correlation test was employed to assess correlation between the RBDSQ and the QUIP scores in all the samples. In order to assess the relative risk (RR) to develop ICD and related behaviour symptoms in the two groups, variables associated with the presence of ICDs in PD that were considered significant in univariate analysis, or clinically relevant according to literature, were entered in a multivariate, robust, Poisson, generalised linear model regression analysis.[26]

Results

The whole sample comprised 216 patients (130 M, mean age: 66.9±10.8 years). There were no difference between the two patient populations (French vs Italian) in terms of sex distribution, H&Y score, mean age of onset and DA-LEDD. However, the French sample had an older age (68.0±10.0 years vs 64.4±12.2 years; p=0.04), a longer duration of PD (8.0±4.9 years vs 5.6±3.8 years, p<0.001) and a higher total LEDD (775.3±483.4 mg/d vs 621.6±370.2 mg/d, p=0.01) compared to the Italian sample. A total of 106 patients (49%, 63 M) were found to have probable RBD (pRBD). Clinical and demographic characteristics of patients with PD-pRBD and of PD-without pRBD are illustrated in table 1.

Table 1. Demographical and clinical characteristics of PD-pRBD and PD-noRBD patients.

	PD-pRBD (n=106)	**PD-without pRBD (n=110)**	**p Value**
M/F (%M)	63/43 (59)	67/43 (61)	ns
Age (years)	67.3±9.9	66.4±11.6	ns
Age of onset (years)	59.3±10.9	60.0±11.0	ns
Duration of PD (years)	8.1±5.0	6.4±4.4	0.006
H&Y	2.1±0.7	1.8±0.8	0.002
LEDD (mg)	827.8±451.0	632.5±443.1	0.002
Dopamine agonists users, N (%)	63 (58.5)	61 (55.5)	ns
Mean DA-LEDD (mg)	116.2±127.0	105.9±127.4	ns
HADRS-Depression Score	6.8±4.0	5.0±3.4	0.0006
Starkstein Apathy Scale	14.1±5.6	13.0±4.9	ns

DA-LEDD, dopaminergic agonists-Levodopa Equivalent Daily Dose; H&Y, Hoen and Yahr score; HADR-Depression, Hospital Anxiety and Depression Rating Scale-Depression subscale; LEDD, Levodopa Equivalent Daily Dose; PD, Parkinson's disease; pRBD, probable REM sleep behaviour disorder.

PD-pRBD patients had a longer PD duration, a higher Hoehn & Yahr score, a greater LEDD and a higher depression score compared to PD-without pRBD. No between-group differences were observed in sex distribution, age, age of PD onset, percentage of dopaminergic agonist (DA) users, mean DA-LEDD and apathy score.

PD-pRBD showed a higher QUIP score compared to PD-without pRBD patients (1.5±1.9 vs 0.6±1.2; p=0.0001). Particularly, one or more ICDs or compulsive-related behaviours symptoms (QUIP score >1) were found in 56/106 (52.8%) PD-pRBD patients, and in 31/110 (28.2%) PD-without pRBD patients (χ^2: 13.634; p=0.0002). The frequencies of impulse control and related behaviours symptoms for patients with PD-pRBD and with PD-without pRBD are illustrated in figure 1, and are as follows: compulsive gambling (10.4% vs 1.8%; p=0.008), compulsive sexual behaviours (11.3% vs 5.4%; p=0.14), compulsive buying (15.1% vs 3.6%, p=0.003), compulsive eating (19.8% vs 11.8%, p=0.10), hobbyism (22.6% vs 11.8%, p=0.03), punding (17.9% vs 10.0%, p=0.11), walkabout (4.7% vs 5.4%, p=0.79), dopamine dysregulation syndrome (13.2% vs 1.8%, p=0.001).

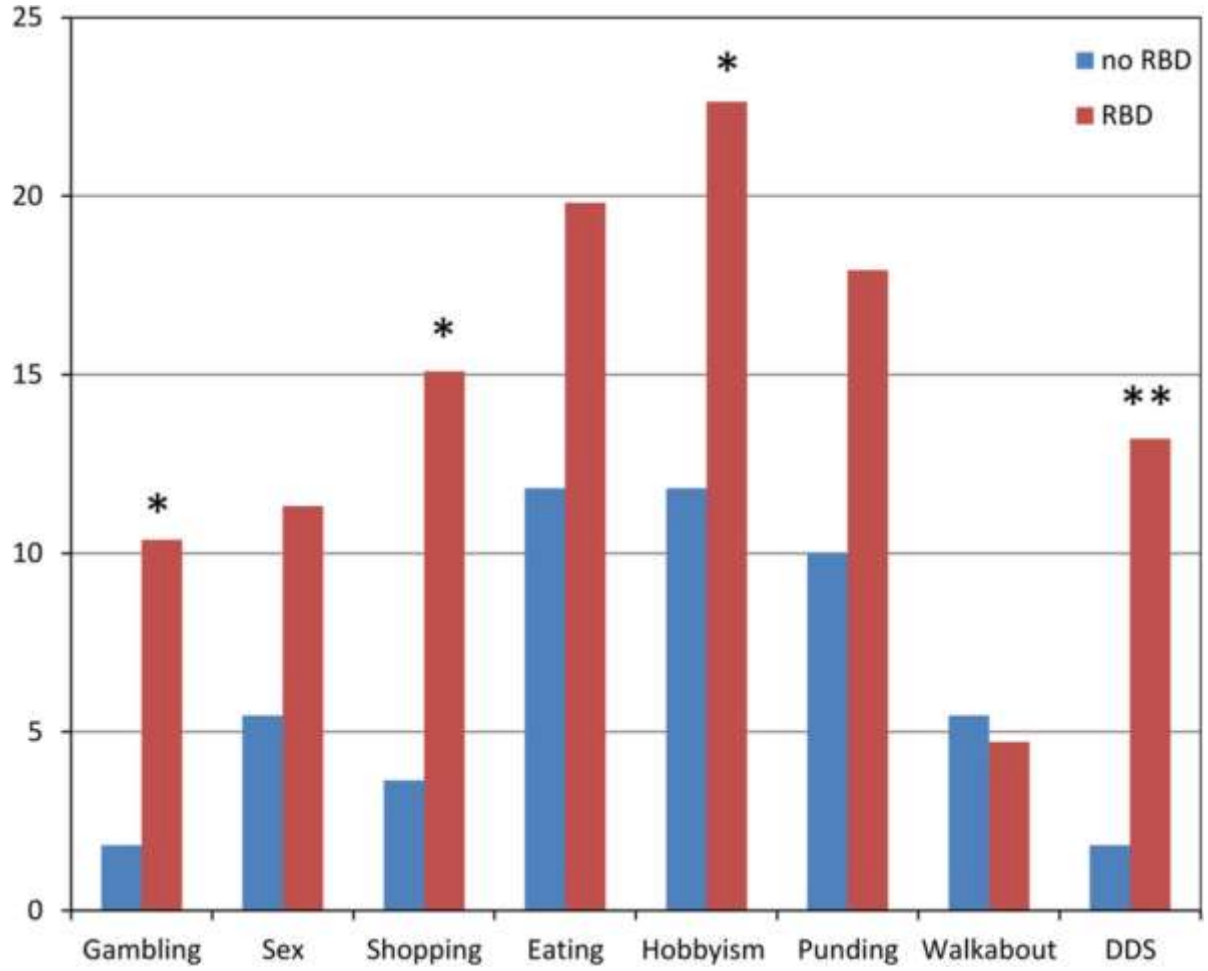

Figure 1. Frequencies of impulse control disorder (ICD) and related behaviour symptoms in patients with Parkinson's disease with and without probable REM sleep behaviour disorder. DDS, Dopa Dyregulation Syndrome. *p<0.05, **p<0.005.

The proportion of patients reporting symptoms of two or more concomitant ICDs or related behaviours was higher in PD-pRBD compared to PD-without pRBD (33/106 (31.3%) vs 11/110 (10.0%), χ^2: 14.861; p=0.0001). Results of univariate and multivariate analyses are illustrated in table 2.

Table 2. Relative risk for ICDs and related behaviours in PD-pRBD and PD-without pRBD (PD-noRBD).

	PD-pRBD (n=106)	PD-noRBD (n=110)	Unadjusted relative risk (95% CI)	p Value	Adjusted relative risk (95% CI)	p Value
Pathological gambling, n (%)	11 (10.4)	2 (1.8)	5.76 (1.31 to 25.38)	0.02	**4.87** (1.00 to 23.51)	**0.049**
Compulsive sexual behaviours, n (%)	12 (11.3)	6 (5.4)	2.09 (0.82 to 5.38)	0.12	2.15 (0.76 to 6.08)	0.15
Compulsive shopping, n (%)	16 (15.1)	4 (3.6)	4.19 (1.45 to 12.13)	0.008	3.03 (0.95 to 9.71)	0.06
Compulsive eating, n (%)	21 (19.8)	13 (11.8)	1.69 (0.89 to 3.20)	0.11	1.71 (0.78 to 3.74)	0.18
Any ICDs, n (%)	46 (43.4)	19 (17.3)	2.51 (1.58 to 3.99)	<0.001	**2.59** (1.45 to 4.64)	**0.001**
Hobbyism, n (%)	24 (22.6)	13 (11.8)	1.97 (1.06 to 3.66)	0.03	1.91 (0.90 to 4.02)	0.09
Punding, n (%)	19 (17.9)	11 (10)	1.74 (0.87 to 3.48)	0.12	1.77 (0.77 to 4.05)	0.18
Walkabout, n (%)	5 (4.7)	6 (5.4)	0.86 (0.27 to 2.72)	0.79	0.51(0.14 to 1.89)	0.31
Dopamine dysregulation syndrome, n (%)	14 (13.2)	2 (1.8)	7.26 (1.69 to 31.20)	0.008	4.40 (0.91 to 21.32)	0.07
Any ICDs or related behaviours, n (%)	56 (52.8)	31 (28.2)	1.87 (1.32 to 2.66)	<0.001	**1.84** (1.15 to 2.98)	**0.012**

Significant figures are shown in bold.
Parameters considered for adjustment: institution, age of onset, gender (male/female), Hoehn and Yahr score, duration of PD, HADS (Hospital Anxiety Depression Scale)-Depression sub-score, total Levodopa Equivalent Daily Dose (LEDD), dopaminergic agonist-LEDD.
ICDs, Impulse control disorders; PD, Parkinson's disease; RBD, REM sleep behaviour disorder.

A multivariate generalised-linear-model regression was performed including the following variables, namely: institution (Clermont-Ferrand/Turin), gender (male/female), age of PD onset, duration of PD, severity of PD (H&Y score), total LEDD and DA LEDD. After adjusting for all the aforementioned variables, the RR associated to RBD to have any ICDs or related behaviour symptoms was 1.84 (p=0.01), while the risk to develop any ICDs only was 2.59 (p=0.001). When looking at every single disorder, PD-pRBD patients showed an increased risk of developing pathological gambling symptoms (RR: 4.87; p=0.049) compared to patients with PD-without RBD, as well as a trend towards an increased risk for symtoms of compulsive shopping (p=0.06) and for dopamine dysregulation syndrome (p=0.07).

Discussion

The present study shows for the first time that the presence of RBD in PD is associated with an increased likelihood to have symptoms of ICDs and related behaviours. Indeed, RBD was associated with a more than twofold risk to develop symptoms of any ICDs, and to a more than fourfold risk for symptoms of pathological gambling.

ICDs imply the inability of a person to resist an impulse, drive or temptation to perform an act that may cause harm to himself or others, bringing obvious heavy consequences in a patient's personal

and social life. It has been estimated that around 14% of patients with PD suffer from one or more ICDs and related behaviours, and that 31% of patients with PD are affected by these disorders at any time during their PD. The development of ICDs in PD is thought to be closely related to the dopamine replacement therapy. Studies particularly highlighted the link between ICDs and the use of DAs especially at higher doses, whereas dopamine dysregulation syndrome has been associated with a greater dosage of levodopa.[27] Indeed, early untreated PD patients did not differ in ICD frequency from healthy controls in two different studies.[28,29] Similarly, ICDs occur in non-PD patients treated with dopaminergic medication, such as restless legs syndrome or progressive supranuclear palsy, suggesting that treatment per se, rather than the underlying pathological process, would be primarily responsible for the occurrence of ICDs.[28] In our study, patients with PD-pRBD were taking a higher total LEDD compared to PD-without pRBD, but a similar dose of DAs. Nevertheless, the RR to develop ICDs in PD-pRBD remained elevated even after adjusting for dopaminergic treatment.

Other factors that may predispose to ICDs in PD are male gender, younger age or younger age at PD onset, longer PD duration, a previous history of ICDs, a familiar or personal history of substance abuse or bipolar disorder.[27,30] In the present study, PD-pRBD patients did not differ from PD-without pRBD in terms of gender distribution, age and age of PD onset, while they showed a higher disease severity expressed by a higher H&Y score, a longer PD duration and higher doses of dopaminergic treatment. This finding is consistent with previous observations in several cohorts of Parkinsonian patients[5,7,13] reflecting the notion that RBD in PD would represent a more severe neurodegenerative process compared to PD-nonRBD. However, the risk associated with RBD remained elevated after adjusting for the abovementioned severity-related variables, suggesting that the higher frequency of ICDs in PD-pRBD is not solely explained by these measures. Results of the present study indicate that RBD should be considered as a risk factor per se for the development of ICDs symptoms in PD, and that its presence should be acknowledged in future epidemiological studies assessing risk factors for ICDs in patients with PD. The higher scores in depression found in PD-pRBD could reflect the different pattern of neurodegeneration inherent to these patients, it may be secondary to the higher functional impairment or it may be, at least in part, related to ICDs. Indeed, depression and other psychiatric symptoms tend to frequently coexist with ICDs, although the direction of such a relationship may be difficult to ascertain.[30]

The association between ICDs and RBD in PD is puzzling with respect to the age of patients. Patients with PD with ICDs are younger, while patients with PD with RBD tend to be older and to have a longer duration of PD than those with non-RBD.[6,30] However, most studies investigating cognitive performances in patients with PD with ICDs are concordant in reporting an impairment in executive functions, namely in visuospatial long-term memory, spatial working memory,[14] cognitive set shifting and visuoconstructional abilities,[31] compared to PD-noICDs. Interestingly, similar deficits have been demonstrated in PD with RBD compared to PD-without RBD, supporting the notion of an association between ICDs and RBD in PD.[9]

This is the first study specifically assessing ICD symptoms in PD with and without RBD. One recent study reported poorer sleep quality in PD-ICDs compared to PD-noICDs, but no between-group difference in percentage of pRBD sufferers.[32] However, sample size was smaller than the present study, and pRBD was identified in only 34% of the whole PD sample by clinical interview. Thus, the

lack of RBD screening questionnaires allowing a systematic symptoms assessment could have possibly led to underestimate RBD.

Pathogenesis of ICDs in PD is not fully elucidated. Mesocorticolimbic dopaminergic pathway is known to play a key role in reward, reinforcement learning, as well as in impulse control regulation. This includes the ventral striatum (namely the ventral tegmental area and the nucleus accumbens), the amygdala, the hippocampus, and the ventromedial and orbitofrontal regions of the prefrontal cortex.[14] Changes in dopamine transmission at presynaptic and postsynaptic levels, observed after chronic levodopa treatment as a result of neuroadaptation mechanisms in PD, may predispose to the emergence of ICDs via a sensitisation of an impaired ventral striatal circuitry.[14,33,34] Thus, it may be hypothesised that patients with PD with RBD would have more severe alterations in mesocorticolimbic pathway that would make them more susceptible to develop ICDs, compared to those without RBD.

Pathophysiology of RBD is complex and not entirely understood, but it is thought to be caused by a dysfunction within the brainstem neuronal circuitry involved in motor control during REM sleep.[2] There are some links between limbic areas implicated in reward and impulse control, and those involved in REM sleep and specifically in REM sleep motor control. Brainstem REM sleep modulatory area such as the pedunculopontine nuclei (PPN), via its connections with multiple basal ganglia and limbic structures, is also part of the reward system and may play a role in motivation, reinforcement learning, and response control.[35] On the other hand, cases of RBD occurring in concomitance with limbic lesions with a spared brainstem have been reported, suggesting a primary role of the limbic system in the pathophysiology of RBD, at least in those cases.[36] Limbic system regulates emotions during wakefulness and is intensely activated during REM sleep, particularly amygdala, probably in relationship with the emotional content of dreams.[37] Moreover, reciprocal strong anatomical connections exist between the amygdala and the pedunculo-pontine nucleus.[38] Thus, a damage of the limbic system could account at the same time for the vivid dreams and the impaired motor control occurring in RBD.[36] Furthermore, ventral tegmental area, a key region for reward and emotional functions, is particularly active during REM sleep, and its involvement in REM sleep regulation has been postulated via direct projections to the sublaterodorsal nucleus, a crucial area for REM sleep generation and REM sleep muscle atonia,[39] Thus, it may be conceivable that the neurodegenerative process inherent to the pathophysiology of RBD in PD would be associated with modifications in reward processing and/or impulse control, and that a dysfunction of the limbic system in PD may promote ICDs and may also contribute to RBD. Further studies are warranted to explore the pathophysiological link between the RBD and ICDs.

Several limitations have to be acknowledged. First, diagnosis of RBD was assessed by questionnaires and not confirmed by video-polysomnography (vPSG). The frequency of RBD in PD patients assessed by questionnaire or interviews is usually lower than that assessed by PSG,[40] since patients may be unaware of mild forms of RBD. It is also possible that some RBD behaviours reported by questionnaire may actually be a ‘pseudo-RBD’ (eg, motor behaviours occurring among patients with obstuctive sleep apnoea syndrome during arousals from NREM or REM sleep that mimic an RBD episode). In order to increase the sensitivity of the clinical diagnosis, two different screening tools were used to detect the presence of symptoms of RBD, namely the recently published RBD1Q[20] and

the RBDSQ.[21] The latter has shown fair internal consistency in patients with PD and a good validity for the screening of RBD in this population, with a recommended cut-off of six points[22] Indeed, its sensitivity in patients with PD, when compared to the diagnosis made according to ICDS-II criteria, ranges from 74% to 84%, while its specificity ranges from 63% to 96% in two different studies.[22,41] Sensitivity and specificity of RBD1Q, however, have not been formally assessed in patients with PD.

The present study is not intended to assess the frequency of ICDs in patients with PD as defined by standard criteria, but rather that of symptoms of ICDs or other compulsive behaviours at clinical and subclinical levels. Indeed, one has to keep in mind that, as a screening instrument, the QUIP is designed to be sensitive in detecting ICDs, but it has a poor specificity, as not all individuals positive to QUIP meet the diagnostic criteria for ICDs or related disorders. On the other hand, detecting subclinical ICD symptoms may be of valuable help in identifying patients at risk to develop ICDs.[15]

Unfortunately, no data were available on previous personal or familiar history of ICDs and related behaviours, as well as on previous history of substance abuse or bipolar disorders, that have all been associated with an increased risk to develop ICDs. Indeed, it is not known whether patients with PD and pRBD had an increased personal or familiar history of neuropsychiatric disorders predisposing to ICDs compared to those without pRBD.

In conclusion, this study showed, for the first time, that patients with PD with p-RBD have a higher risk of manifesting ICD symptoms compared to PD-without pRBD. Identifying a specific population of patients with PD who are at higher risk for ICDs or other compulsive behaviours may have an immediate impact on the clinical management. A systematic assessment of RBD symptoms, that include video-polysomnographic recording, might help the clinician to choose the best therapeutic option, such as tending to avoid DAs, and to set up strategies helping to prevent these invalidating disorders, such as promoting patient awareness about these symptoms. The study is preliminary. In order to confirm an association between RBD and ICDs in PD, further investigations assessing clinical ICDs and related behaviours by means of face-to-face semistructured interviews with gold standard criteria in PSG-confirmed PD-RBD patients, are warranted.

Acknowledgments

The authors wish to thank Dr Marco Bortolato, MD, PhD, from the University of Kansas (USA), for invaluable discussions that stimulated the conception of this research, and Miss Marie-Claire Guérinon and Mr Stéphane Bernard from the Neurology Department of Clermont-Ferrand, for their precious help in collecting data.

Contributors

MLF: study concept and design, acquisition of data, analysis and interpretation, writing the manuscript. LM: contribution to the study design, subjects recruitment, acquisition of data. MZ: recruitment of subjects, acquisition of data and critical revision of the manuscript for important

intellectual content. MS: recruitment of subjects and acquisition of data. TV: contribution to the study concept and design, critical revision of the manuscript for important intellectual content. BP: statistical analysis and interpretation of data, revision of the manuscript for technical and intellectual content. AM, PD, BD, MU, NV: recruitment of subjects and acquisition of data, critical revision of the manuscript for intellectual content. AC, LL and FD: study supervision and critical revision of the manuscript for important intellectual content.

Competing interests
None.

Ethics approval
Institutional Review Board (Comité de Protection des Personnes, CHU Clermont-Ferrand).

Provenance and peer review
Not commissioned; externally peer reviewed.

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